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Neuromodulatory Systems and Their Interactions: A Review of Models, Theories, and Experiments

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Neuromodulatory systems, including the noradrenergic, serotonergic, dopaminergic, and cholinergic systems, track environmental signals, such as risks, rewards, novelty, effort, and social cooperation. These systems provide a foundation for cognitive function in higher organisms; attention, emotion, goal-directed behavior, and decision-making derive from the interaction between the neuromodulatory systems and brain areas, such as the amygdala, frontal cortex, hippocampus, and sensory cortices. Given their strong influence on behavior and cognition, these systems also play a key role in disease states and are the primary target of many current treatment strategies. The fact that these systems interact with each other either directly or indirectly, however, makes it difficult to understand how a failure in one or more systems can lead to a particular symptom or pathology. In this review, we explore experimental evidence, as well as focus on computational and theoretical models of neuromodulation. Better understanding of neuromodulatory systems may lead to the development of novel treatment strategies for a number of brain disorders.

Keywords: neuromodulation, computational neuroscience, computational modeling, brain disorders, neuromodulatory systems

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INTRODUCTION

The mammalian neuromodulatory system consists of small pools of neurons (on the order of thousands in the rodent and tens of thousands in the human) located in the brainstem, pontine nucleus, and basal forebrain, which can have a powerful effect on cognitive behavior. Ascending neuromodulatory systems include noradrenergic, serotonergic, dopaminergic, and cholinergic projections from the brainstem and basal forebrain regions to broad areas of the central nervous system (Briand et al., 2007). Neuromodulators signal risks, rewards, novelty, effort, and social cooperation. These systems provide a basis for many higher cognitive functions; attention, decision-making, emotion, and goal-directed behavior result from the interaction between the neuromodulatory systems and brain areas, such as the anterior cingulate, frontal cortex, hippocampus, sensory cortex, and striatum (**Figure 1**). In this review, we explore experimental evidence, with a strong focus on computational and theoretical models of neuromodulation. We discuss how these models might increase our understanding of brain disorders.

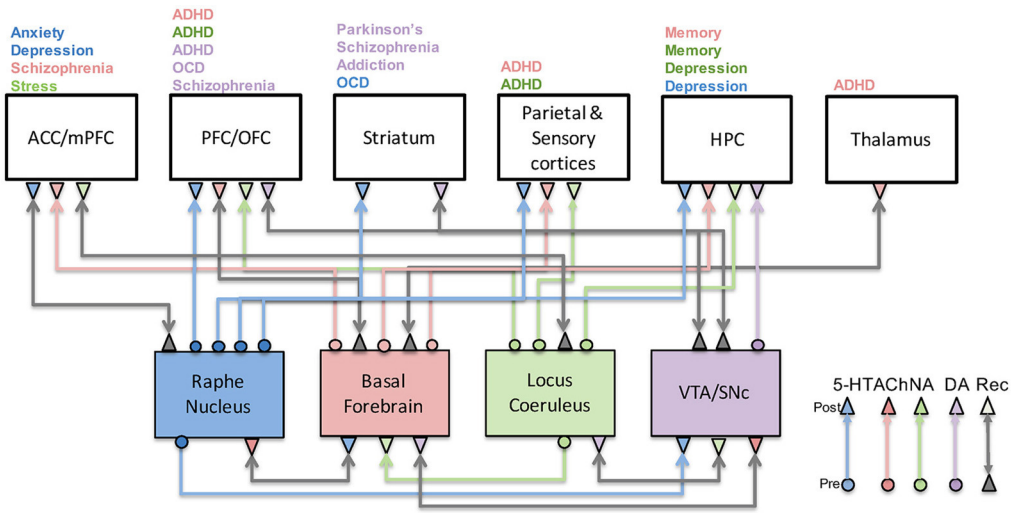


FIGURE 1 | Neuromodulatory system interactions and their role in disease. This figure illustrates how serotonergic (blue), cholinergic (red), noradrenergic (green), and dopaminergic (purple) systems are highly connected to one another as well as cortical and subcortical structures. Their malfunction has been associated with a host of neurological and psychiatric conditions as indicated above each brain region. Gray arrows denote recurrent connections.

DOPAMINERGIC SYSTEM

The dopaminergic neuromodulatory system has been extensively studied and is involved in nearly every aspect of brain function from cognition to behavior (Schultz, 1997; Schultz et al., 1997, 2000; Berridge, 2004, 2012; Hyman et al., 2006; Durstewitz and Seamans, 2008). Dopamine originates in either the ventral tegmental area (VTA) or substantia nigra pars compacta (SNc). A substantial amount of research has gone into understanding the circuits that regulate dopamine neuron firing as well as the downstream effects of dopamine release. In particular, we know that the VTA and SNc are strongly influenced by the striatum and subcortical structures such as the lateral habenula and pedunculopontine tegmental nucleus. It has been shown that the phasic increase and dip in dopamine response are due to the activation of the pedunculopontine tegmental nucleus and lateral habenula, respectively (Matsumoto and Hikosaka, 2007; Hong and Hikosaka, 2014). Phasic increases also may be due to collicular or other sensory or non-sensory inputs to VTA/SNc when a salient event is identified (Redgrave and Gurney, 2006).

Direct and indirect pathways in the striatum disinhibit and inhibit dopamine neuron firing, respectively, and are themselves modulated by cortical and limbic inputs. Prefrontal and hippocampal inputs to the striatum disinhibit the VTA leading to an increase in phasic and tonic activity, respectively (Takahashi et al., 2011; Murty et al., 2017). It has been hypothesized that an abnormal increase in glutamatergic input to striatum leads to excess dopamine in the striatum and may account for symptoms of schizophrenia (de la Fuente-Sandoval et al., 2011). Computational models of the basal ganglia have also shed light on the role dopamine plays in Parkinson's disease (Moustafa and Gluck, 2011; Moustafa et al., 2013; Balasubramani et al., 2015). Still, many questions remain regarding cortical and limbic inputs to the striatum, how they compete to drive striatum responses, and how phasic and tonic dopamine levels might regulate these brain regions. Understanding these upstream effects is a critical component as we develop a circuit-level understanding of brain disorders that are thought to result from abnormal dopaminergic activity.

Dopamine neurons, in turn, send projections to the striatum, thalamus, amygdala, hippocampus, and prefrontal cortex, demonstrating the "feedback" nature of this circuit. Dopaminergic neurons originating in the SNc project to the dorsal striatum. Abnormalities in this pathway can lead to motor disorders including Parkinson's disease. Two distinct areas in the VTA project to either the ventral striatum (mesolimbic) or to the prefrontal cortex (mesocortical). The effect that dopamine has on its downstream target depends on the post-synaptic receptor and the firing mode of the DA neuron. Phasic release of dopamine in the striatum, for example, preferentially activates D1 receptors on striatal Medium Spiny Neurons (MSNs) and increases their activity (direct pathway). Increases in tonic dopamine, on the other hand, are thought to activate D2 receptors (D2R) in the striatum, which inhibit MSNs in the striatum (indirect pathway). It has recently been shown, however, that phasic DA can also lead to increases in inhibitory post-synaptic currents in D2R-MSN neurons (Marcott et al., 2014), suggesting the role of tonic and phasic dopamine may be more complex than originally thought. Increases in both phasic and tonic activity would, therefore, lead to an increase in the direct pathway and a decrease in the indirect pathway, which would ultimately cause a strong release of inhibition on the thalamus.

The effects of tonic and phasic dopamine in the prefrontal cortex appears to be opposite of the striatum. D1 receptors in the prefrontal cortex are preferentially activated by tonic dopamine and have an inverted-U dose-dependent response

on superficial neurons (discussed below), whereas D2 receptors are activated by phasic dopamine and increase the activity of subcortically-projecting neurons in deep layers. This suggests that D2 receptors play a preferential role in behavior and reward processing, whereas D1-expressing neurons are involved in working memory and attentional modulation of visual cortices (Noudoost and Moore, 2011; Gee et al., 2012; Puig and Miller, 2014). Interestingly, the temporal dynamics of the phasic responses of dopaminergic cells resemble those found in a machine learning method known as reinforcement learning (Schultz et al., 1997). As we discuss below, this gives us a more rigorous understanding of the function of dopaminergic neurons in the brain and helps to understand the important components of dopamine responses for normal and abnormal brain function.

MODELS OF DOPAMINERGIC FUNCTION

The responses of dopaminergic neurons during behavioral conditioning experiments closely resemble temporal difference reward prediction error variables found in reinforcement learning. This has led to the prediction error hypothesis of dopamine signaling, which connects dopamine signaling to reinforcement learning models and indicates that dopamine neurons play an important role in human decision-making. It has also been hypothesized that dopaminergic neurons respond to and broadcast uncertainty and/or novelty related signals. The circuits involved in these computations are shown in **Figure 2**. We discuss these circuits and theoretical models below, together with several computational, network-based models that propose mechanisms for how dopamine-related computations are implemented in the brain.

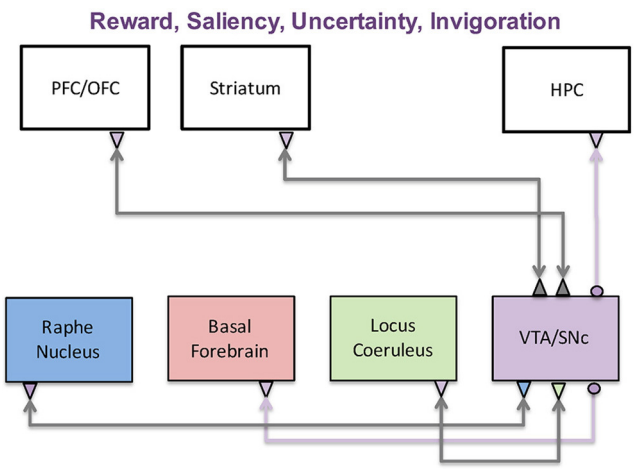


FIGURE 2 | The dopaminergic system and its functions. The dopaminergic system, which originates in the VTA and SNc, has been implicated in a wide variety of functions including reward, saliency, uncertainty, and invigoration. These functions are achieved through interactions with the prefrontal cortex, striatum, and hippocampus. It is also reciprocally connected with the three other neuromodulatory systems, further complicating its role in disease states.

REINFORCEMENT LEARNING MODELS

Reinforcement learning is a machine learning method that concerns itself with finding the appropriate actions that maximize future reward. Formally, the theory aims to find an optimal function, or policy, (P) for mapping states (S) into actions (A) that maximize the sum of future reward. Temporal difference learning methods, such as the actor-critic model, solve this problem by computing a reward prediction error signal (δ), which is used in the updating of a value function (reward expectation) and policy as shown in the equations below.

$$\begin{aligned} \delta_t &= r_{t+l} + \gamma V(s_{t-1}) - V(s_t) \\ V(s_{t+1}) &= V(s_t) + \alpha \cdot \delta \\ P(a|s_{t+1}) &= P(a|s_t) + \alpha \cdot \delta \end{aligned} \quad (1)$$

where r_{t+1} is the observed reward at time $t+1$, $V(S_t)$ is the value of state S at time t, γ is a discounting factor, and α is the learning rate. The algorithm works by sampling the environment, making predictions, and then adjusting the predictions based on the error signal. The ability to use the prediction error signal to update value estimates and behavioral policies is what gives this algorithm (and organisms) the flexibility to adapt to a dynamic environment. The temporal dynamics of the δ term closely resembles responses seen in dopaminergic cells *in vivo*, suggesting a prediction error hypothesis of dopamine function (Schultz, 1997; Schultz et al., 1997).

Doya extended the temporal difference equations to other neuromodulatory systems (Doya, 2002, 2008). In his view, dopamine signals the error in reward prediction (δ in Equation 1), serotonin controls the discounting of reward prediction (γ in Equation 1), and acetylcholine controls the speed of memory update (α in Equation 1). More recent theoretical models have extended the temporal difference rule to other neuromodulatory systems and have attributed the α parameter, which controls the rate of learning, to the serotonergic (Balasubramani et al., 2015) or noradrenergic systems (Nassar et al., 2012).

Abnormalities in dopaminergic responses have been linked to a host of disorders, including schizophrenia, attention and mood disorders, and Parkinson's disease (Wise, 2004; Björklund and Dunnett, 2007; Schultz, 2007; Sillitoe and Vogel, 2008). Within the context of the reinforcement-learning framework, these disorders are thought to arise from a failure of dopaminergic cells to properly compute reward prediction errors and communicate them to downstream structures. For example, depressive symptoms would result from a reduction in reward sensitivity within the reinforcement-learning framework (Huys et al., 2013; Chen C. et al., 2015). Abnormalities in reward prediction errors could also induce positive symptoms of schizophrenia (delusions/hallucinations) through the construction of unusual associations and abnormal internal models of the world (Maia and Frank, 2011). As discussed below, different hypotheses of dopamine function can lead different conclusions regarding the manifestation of a particular disease.

DOPAMINE, UNCERTAINTY, AND NOVELTY

Although theoretical and experimental evidence suggests that dopamine neurons encode reward prediction error (Schultz et al., 1997), several lines of evidence suggest that this hypothesis is incomplete. First, dopaminergic neurons not only respond to reward and reward prediction, but also respond to any salient or novel input in the environment regardless of its reward value (Bromberg-Martin et al., 2010). Second, the response of dopamine neurons to reward predicting stimuli is too fast to be mediated by a "predictive" input that would likely originate in prefrontal cortices (Redgrave and Gurney, 2006). Third, dopamine depletion primarily impacts task performance and learning is left intact (Berridge and Robinson, 1998; Cannon and Palmiter, 2003; Berridge, 2012).

This has led to several alternative hypotheses regarding dopaminergic function. The two we describe below are the saliency and uncertainty hypotheses. The saliency hypothesis suggests that dopamine neurons respond to salient or novel environmental events to discover novel actions (Redgrave and Gurney, 2006). This directly contrasts with the prediction error hypothesis in which reward prediction errors were used to update the weights of a set of defined actions. Within this framework, abnormal dopaminergic responses would lead to abnormalities in processing salient information. This is consistent with the aberrant salience hypothesis of schizophrenia (Kapur, 2003), which suggests that positive symptoms in schizophrenia originate and evolve from an improper allocation of attentional resources to what normally would be non-salient events.

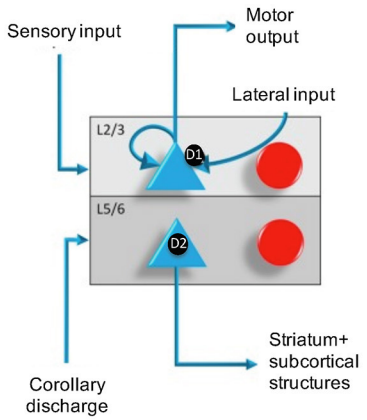
It has also been suggested that dopamine encodes the precision, the inverse of uncertainty, of alternative actions beliefs (Friston et al., 2012). This hypothesis is rooted in Bayesian inference models and is able to reconcile the prediction error hypothesis and incentive salience hypothesis, which accounts for the fact that dopamine is not necessary for learning. If dopamine encodes precision values, abnormal dopamine responses would lead to false inferences about the world as a result of an improper balance of sensory and prior information. False inferences could ultimately manifest as positive symptoms of schizophrenia, including delusions and hallucinations (Adams et al., 2013).

The uncertainty and salience hypotheses predict that dopamine plays an important role in regulating the information that gains access to conscious perception. The mechanism by which this is achieved, however, is unknown. Previous theoretical and computational models, as well as experimental studies have suggested several mechanisms that could support such computations, including: dopaminergic projections to the prefrontal cortex/basal ganglia, balance of excitation/inhibition in prefrontal cortex, D1/D2 receptor activation, and NMDA/GABA receptor activation. In particular, Cohen and colleagues developed a model that suggests that dopamine acts as a gate to regulate information that can enter prefrontal cortex (Braver and Cohen, 1999). In this model, dopamine acts on both the afferent excitatory and local inhibitory input in the prefrontal cortex, leading to a disruption in the maintenance and updating of information in the prefrontal cortex. They suggested that cognitive symptoms in schizophrenia arise from increasing the variability of dopamine inputs to the prefrontal cortex, which would destabilize working memory traces (Braver and Cohen, 1999; Rolls et al., 2008). This model was extended to include the basal ganglia as part of the gating mechanism (Hazy et al., 2006).

More recently, we developed a circuit-based model that shows how D1 and D2 receptors could balance the relative weight of information from different brain regions (Avery and Krichmar, 2015). This computational model suggests that activation of D1 receptors allows information from the thalamus to take precedence within the prefrontal cortex by blocking interference from lateral excitation in superficial layers (see **Figure 3**). Optimal D1 activation results in one column of the PFC being active, which represents holding a stimulus in working memory. Low D1 activation results in inter-columnar interference within the PFC. This can lead to a noisy representation of an object in working memory via lateral input from other regions of the PFC, which might manifest as cognitive symptoms in schizophrenia. A similar mechanism is proposed for attention disorders (Arnsten et al., 2012). Our model also suggests that activation of D2 receptors on deep layers 5 neurons in the prefrontal cortex disinhibits thalamic inputs to the prefrontal cortex via interactions with the basal ganglia (Avery and Krichmar, 2015). Improper activation of D2 receptors in the prefrontal cortex may lead to non-specific activity from the thalamus, potentially contributing to positive symptoms observed in schizophrenics. We also suggest that improper activation of D2 receptors on subcortically projecting layer 5 neurons leads to abnormalities in reward processing, resulting in negative symptoms of schizophrenia.

A model based on a dynamical systems framework suggests that D1 and D2 receptors influence the stability of persistent and spontaneous cortical attractor states by increasing and decreasing NMDA and GABA conductances, respectively (Durstewitz and Seamans, 2008). If a network is in a stable regime (high D1, low D2), the pattern of neuronal activity in the network will remain unchanged until a sufficiently strong input can push the network into a different state. If the network is in an unstable regime (low D1, high D2), however, even weak inputs impinging on the network will cause neurons to randomly shift from spontaneous to persistent states. This is related to the gating hypothesis in the sense that a highly stable state would effectively block incoming information (closed gate), whereas an unstable state would allow inputs to drive the network into a different state (open gate). The dynamical systems model predicts that instabilities in cortical attractor states, which arise from an improper balance in D1 and D2 receptor activation, might lead schizophrenia symptoms (Loh et al., 2007; Durstewitz and Seamans, 2008). In particular, cognitive and negative symptoms result from reduced NMDA (reduced D1), which leads to a reduction in firing rate in the prefrontal cortex. A reduction in both NMDA and GABA, on the other hand, leads to instabilities in the network that produce positive symptoms.

Each of these computational models offers insight into understanding the role of the dopaminergic system in the healthy and diseased brain and alludes to possible treatment strategies. The dynamical systems model, for example, suggests that NMDA and GABA receptors are important for maintaining



Normal	-Task-related ↓ in lateral input (reduces noise) -Normal D2 activation → proper gating of info into PFC (via striatum) and PFC regulation of reward structures
Cognitive	↓ D1 causes an ↑ in noise in PFC from lateral inputs
Positive	↑ D2 causes ↑ in noise in PFC from improper gating of thalamic input via striatum
Negative	↑ D2 also leads to improper timing/strength of activation of L5 neurons that project to or regulate reward centers

FIGURE 3 | Within a column in the PFC, neuromodulators were modeled by changing the strength of inputs from non-preferred directions (D1 receptors) between layer 2/3 neurons in different columns and the strength layer 5 neuronal responses (D2 receptors). This architecture also shows how layer 5 neurons in each column received input from the MD/SC and output to a non-specific inhibitory group and the basal ganglia in order to clear working memory and update other columns, respectively. In this model, Positive and negative symptoms arise from abnormalities in layer 5 outputs to subcortical structures and cognitive symptoms arise from a "leaky" spread of excitation of lateral excitatory inputs within the PFC.

stable working memory representations and may be important targets for drug therapies. Network-based models, on the other hand, point to regions of interest for deep brain stimulation or pharmacological intervention and could also make predictions regarding downstream effects of manipulation of a particular region of the brain. These models will become even more important as we begin to develop experiments that connect different levels of investigation of the brain and will allow us to generate more refined hypotheses regarding disease mechanism and treatment strategies.

SEROTONERGIC SYSTEM

Serotonergic projections, which originate in the raphe nuclei of the brainstem, extend to almost all forebrain areas (Barnes and Sharp, 1999), including the cortex, ventral striatum, hippocampus, and amygdala (Harvey, 2003; Meneses and Perez-Garcia, 2007). The raphe receives strong connections from the prefrontal cortex and the anterior cingulate cortex (Briand et al., 2007). Through interactions with these brain regions and other neuromodulatory systems, serotonin influences a broad range of decision-based functions such as reward assessment, cost assessment, impulsivity, harm aversion, and anxious states (Asher et al., 2013). The circuits involved in these functions are shown in **Figure 4**. Impairments to the serotonergic system have been linked to anxiety disorders and depression (Craske and Stein, 2016), as well as Parkinson's disease (Bédard et al., 2011).

SEROTONIN AND IMPULSIVITY

Several studies have investigated serotonin's involvement in impulsivity, which is the tradeoff between taking an immediate reward, or else waiting for a future, potentially larger reward. In the temporal difference learning rule, this term is called temporal discounting or gamma (see γ in Equation 1). Kenji Doya suggested that serotonin levels may be related to temporal discounting level (Doya, 2002). His group has confirmed this prediction in rodent and human experiments (Tanaka et al., 2007; Miyazaki et al., 2011). In addition, it has been shown that forebrain serotonin depletion the steepens discounting of delayed rewards, which leads to impulsive actions (Winstanley et al., 2003). In another study, it was observed that higher serotonin firing activity causes a rat to wait longer for upcoming rewards, as predicted by temporal discounting (Miyazaki et al., 2011). Wait errors associated with lower serotonergic neural activity suggest that 5-HT can affect choice involving delayed rewards.

The link between serotonin and temporal discounting has been explored using the Acute Tryptophan Depletion (ATD) procedure. 5-HT requires the amino acid tryptophan, which only can be acquired through diet. In ATD, subjects temporarily have a low-protein diet and drink an amino acid supplement that omits tryptophan. In essence, ATD acts as a temporary serotonin lesion. Altering 5-HT levels via ATD influences a subject's ability to resist a small immediate reward over a larger delayed reward (Tanaka et al., 2007, 2009; Schweighofer et al., 2008). As such, subjects that underwent ATD had both an attenuated assessment of delayed reward and a bias toward small reward, which were indicative of impulsive behavior and higher temporal discounting.

SEROTONIN AND HARM AVERSION

Serotonin (5-HT) has been linked to predicting punishment or harm aversion (Cools et al., 2008; Crockett et al., 2008, 2012; Seymour et al., 2012). ATD caused subjects to be aggressive and risk taking by rejecting more monetary offers in the Ultimatum Game (Crockett et al., 2008). In a reversal-learning task, Cools and colleagues demonstrated that ATD subjects made more errors for harmful than rewarding stimuli (Cools et al., 2008). Crockett and colleagues showed that lowering 5-HT levels with ATD resulted in decreased punishment-induced inhibition in a

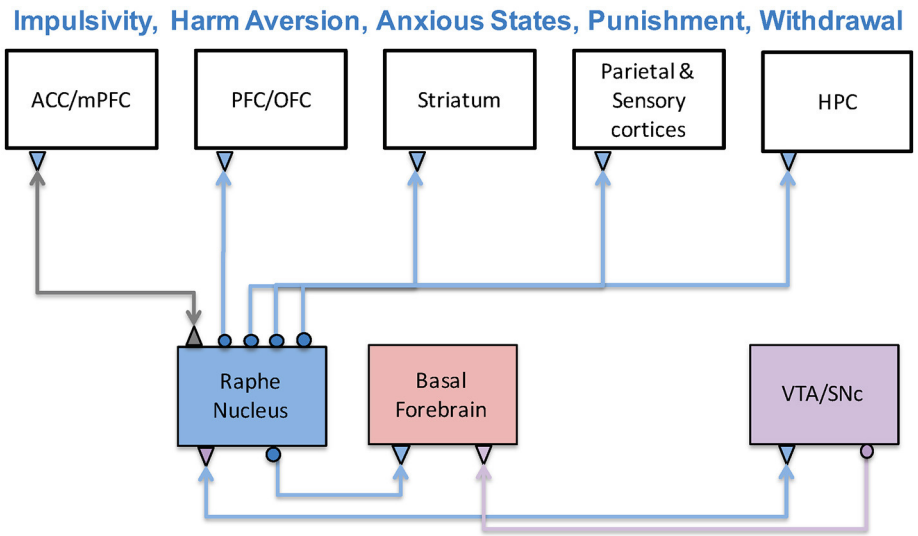


FIGURE 4 | The serotonergic system and its functions. The serotonergic system originates in the Raphe Nucleus of the brainstem and is connected to prefrontal, sensory, limbic, and striatal structures. Serotonin has been associated with a variety a functions including impulsivity, harm aversion, anxious states, punishment, and withdrawal. Experimental and theoretical studies have suggested it has an antagonistic relationship with the dopaminergic system.

Go/No-Go task to Crockett et al. (2009). In a follow up ATD study, they investigated the mechanisms through which 5-HT regulated punishment-induced inhibition with their Reinforced Categorization task (Crockett et al., 2012). Furthermore, recent evidence suggests that enhancing serotonin function through serotonin specific reuptake inhibitors (SSRIs) increased harm aversion, while enhancing dopamine through levodopa reduced altruism (Crockett et al., 2015). Together, these results suggest that 5-HT influences the ability to inhibit actions that predict punishment and to avoid harmful circumstances.

SEROTONIN AND ANXIETY

In addition to punishment and impulsivity, 5-HT affects stress and anxiety (Millan, 2003; Jasinska et al., 2012). It has been proposed that environmental impact factors and genetic variations of the serotonin transporter (5-HTTLPR) can be linked to stress (Jasinska et al., 2012). Furthermore, 5-HT function has been tied to an organism's anxious states triggered by conditioned or unconditioned fear (Millan, 2003). This suggests a functional role for 5-HT in the control of anxious states. These anxious states and behavioral responses were modeled in neurorobot experiments, which will be described in more detail in the Dopamine and Serotonin Opponency section. In brief, a stressor caused the robot's simulated serotonin level to increase, which in turn caused the robot to hide (Krichmar, 2013). In the model, artificially decreasing the rate that serotonin returned to base levels had a similar effect to the short allele variant of 5-HTTLPR discussed above, where serotonin reuptake is impaired. Under these conditions, the neurorobot showed longer-lasting hiding responses to a stressful sensor event (e.g., a bright light). These responses are similar to those seen in mice, where manipulations of 5-HT1A and 5-HT2A receptors resulted in the mice avoiding the center of an open arena and exploring novel objects, suggesting that these manipulations of serotonin led to higher anxiety levels (Heisler et al., 1998; Weisstaub et al., 2006).

MODELS OF SEROTONIN NEUROMODULATION

Using an Actor-Critic model, Asher et al. (2010), Zaldivar et al. (2010) constructed a neural network where a reward critic represented the dopaminergic system and a cost critic represented the serotonergic system (see **Figure 5**). In these experiments, the neural network model played the socioeconomic game of Hawk-Dove against other agents. In the Hawk-Dove game, players must choose to either take a resource (escalate) or share a resource (display). If both players escalate, a fight ensues, resulting in a penalty. If only one player chooses to escalate, then that player gets the resource, and the other player get nothing. If both players display, then the resource is shared. The reward critic tracked the expected value of obtaining the resource, and the cost critic tracked the expected punishment from fighting for the resource.

The simulations showed that the model was sensitive to the other player's strategy and the game environment (i.e., the likelihood of receiving a serious injury). The adaptive neural agent was more likely to escalate over the resource when activity of the reward system (VTA) exceeded the activity of the cost system (Raphe). Conversely, when the reward activity did not exceed the activity of cost, the adaptive neural agent tended toward display actions. The simulations also predicted that impairment of the serotonergic system would lead to perseverant, uncooperative behavior. A simulated lesion of the serotonergic system resulted in the agent almost always engaging in risk taking

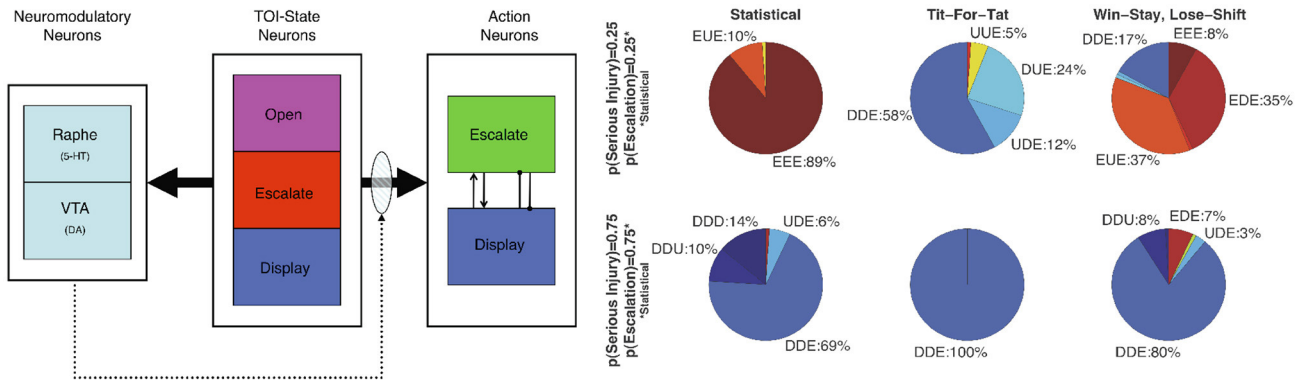


FIGURE 5 | Neuromodulation effects in simulation of the Hawk-Dove game. **(Left)** Architecture of the neural model (Neuromodulatory: Raphe and VTA; TOI-State: Open, Escalate, and Display; and two Action: Escalate and Display). Solid arrows from the TOI-State neurons denote all-to-all connections. The shaded oval and dotted arrows denote plastic connections. Within the Action neurons, the arrowhead denotes an excitatory connection, and the line with the dot at the end denotes an inhibitory connection. **(Right)** Proportion of actions taken by the Neural agent. Open, Escalate, and Display are states the Neural agent observes, and Escalate (E), Display (D), and Undecided (U) are actions the Neural agent can take. U represents random choice between "E" and "D". Labels denote the Neural agent's response to the three states. Dove-like strategies are displayed in blue, Hawk-like are displayed in red, and the lack of a strong bias is displayed in yellow. Reproduced from Asher et al. (2010) with permission.

(or lack of harm aversion) behavior, which was similar to behavior seen in human studies where serotonin levels were lowered via ATD while subjects played games such as Prisoner's Dilemma and the Ultimatum game (Wood et al., 2006; Crockett et al., 2008).

Following the simulation studies, human robot interaction experiments were performed to test the model's performance against human players, as well as the influence of embodied agents on game play (Asher et al., 2012). These experiments involved ATD; the dietary manipulation described above that temporarily lowers serotonin levels. Overall, subjects demonstrated aggressive behavior when playing against an aggressive version of the model with a simulated 5-HT lesion, which tended to escalate more. This resulted in subjects altering their strategy from Win-Stay-Lose-Shift (WSLS) against agents, to a retaliatory Tit-For-Tat (T4T) against an aggressive version of the model. A Bayesian analysis revealed two types of subjects; one in which subjects were more aggressive when tryptophan-depleted, and one in which they were less aggressive. In addition, some of the subjects were more aggressive toward robots than simulations, and vice versa (Asher et al., 2012). These results highlight the importance of taking individual variation into consideration in serotonin studies.

In a model inspired by serotonergic neuromodulation related to punishment or harm, Weng and colleagues constructed a neural model where artificial serotonin levels regulated stress or pain in two different tasks (Weng et al., 2013). The first was a visual recognition task that investigated how such a system can learn visual cues via a teacher that only provides punishments and reward signals. The second task had an agent wander in the presence of a friend and a foe. In both tasks, the interplay between reward and pain led to high performance and the emergence of internal representations without the need of a supervisory signal.

These computational models show how simulating serotonergic effects, even in fairly simple neural models, explain how altering serotonin modulation of neural activity can affect harm aversion and altruistic behavior. Moreover, embodying these models in robots highlights these behaviors and leads to the possibility of using human robot interaction as a means to study these disorders.

At the neuronal level, detailed computational models that include ionic currents can investigate receptor specific effects of serotonin to drug treatments (Wong-Lin et al., 2012; Cano-Colino et al., 2014). In a model of prefrontal cortex, it was shown that serotonin modulates spatial working memory performance via 5-HT1A and 5-HT2A receptors (Cano-Colino et al., 2014). Performance followed an inverted-U relationship, that is, both increases and decreases in serotonin concentrations, [5-HT], led to random choice errors. In their model, 5-HT suppressed pyramidal cell activity via the 5-HT1A receptor by increasing a K^+ and excited pyramidal cells via 5-HT2A receptors by increasing the Ca^{2+}-dependent K^+ current, which increased intracellular Ca^{2+}. The effects of 5-HT on GABAergic interneurons were modeled by inhibiting passive leak currents via 5-HT2A receptors. Another modeling group constructed an efficient spiking neural network model of the dorsal raphe nucleus, which included both serotonergic and non-serotonergic neurons (Wong-Lin et al., 2012). They simulated dorsal raphe nucleus recording experiments from a non-human primate performing a simple perceptual decision task for both rewarding and unrewarding trials (Nakamura et al., 2008; Bromberg-Martin et al., 2010). In addition, to observing the different firing patterns that were found in the primate, the model showed theta band oscillations, especially among the non-5-HT inhibitory neurons, during the rewarding outcome of a simulated trial. In summary, these detailed computational models can allow an investigation of the neural dynamics of serotonergic neuromodulation and its effects on specific receptors. Models at this level may be informative on possible treatments for serotonergic related disorders.

MODELS OF DOPAMINE AND SEROTONIN OPPONENCY

It has been suggested that the serotonergic and dopaminergic systems primarily activate in opposition, but at times in concert for goal directed actions (Boureau and Dayan, 2011). Opponency between these systems has been proposed behaviorally and in theoretical models (Daw et al., 2002; Tops et al., 2009). In this notion, dopamine triggers invigorated, reward seeking behavior, and serotonin triggers withdrawn and punishment avoiding behavior. Whether the anatomy supports unidirectional (i.e., the raphe inhibiting dopaminergic areas) or bidirectional inhibition (i.e., raphe inhibiting and being inhibited by dopaminergic areas) is an open issue (Boureau and Dayan, 2011). But there is evidence that projections from raphe serotonin cells to DA areas oppose the actions of DA and mediate avoidance of threats (Deakin, 2003). Interestingly, there is evidence in the striatum that under certain conditions dopamine transporters are able to transport significant amounts of 5-HT into DA terminals (Zhou et al., 2005). These studies suggest that the dopamine and serotonergic systems are highly interactive.

Computational models have been used to investigate these interactions between dopamine and serotonin. One model had tonic serotonin tracking the average reward rate and tonic dopamine tracking the average punishment rate, and that phasic serotonin responses carry a prediction error signal for punishment (Daw et al., 2002). However, it has been difficult to find empirical evidence supporting these roles for tonic and phasic neuromodulation. Modeling has shown that direct opponency between these systems is unnecessary for behavioral opponency (Asher et al., 2010; Zaldivar et al., 2010). In many cases, an environmental tradeoff between expected rewards and costs can lead to opposition between active reward-seeking and withdrawn behavior. Indeed, by having different neuromodulatory systems handle different sensory events, this type of opponency emerged in the present model.

A neurorobot model explored the idea of dopaminergic and serotonergic opponency by having the serotonergic system directly inhibit the dopaminergic system (Krichmar, 2013). In this study, he behavior of an autonomous robot in an open-field test paradigm was controlled using a neural network algorithm (see **Figure 6**). The open-field test is often used in animal models of anxiety (Heisler et al., 1998; Lacroix et al., 2000; Lipkind et al., 2004; Fonio et al., 2009). Similar to mice in the open field test, the robot demonstrated withdrawn, anxious behavior, such as wall following and finding its nest (i.e., the robot's charging station) when serotonin levels were high, and risky, reward seeking behavior, such as moving to the center of the arena or investigating a novel object when dopamine levels were high. Furthermore, the algorithm tested the idea that top-down signals from the frontal cortex to neuromodulatory areas are critical for an organism to cope with both stressful and novel events. As described above, it has been suggested that the mPFC inhibited the serotonergic raphe nucleus after handling a stressful event (Jasinska et al., 2012). This feedback loop prevented the raphe from being overly active after the stressor had been handled. Indeed, when the model's mPFC was lesioned, the robot withdrew to the outer wall or its charging station in response to a stressor such as a bright light or collision. The model further suggested that projections from the OFC to the dopaminergic VTA have a similar function when responding to a positive value event. When the simulated OFC was lesioned, the robot obsessively explored the center of the room and objects in the room. By using a neurorobot experiment that mimics an animal model of anxiety and depression, we can readily observe the behavior in a controlled environment, while also being able to make manipulations that would be difficult in the real animal.

In addition to the studies of serotonin and dopamine in the frontal cortex, interactions between the dopaminergic and serotonergic systems have been observed in the basal ganglia, which may have implications for Parkinson's disease treatments (Bédard et al., 2011). Moustafa and colleagues constructed a neural network model of the basal ganglia, including nuclei such as striatum, subthalamic nucleus and globus pallidum, which were controlled by dopamine and serotonin neuromodulation (Balasubramani et al., 2015). They predict that the modulatory effects of 5HT on dopamine D2 receptors on medium spiny neurons relate to risk sensitivity and reward-punishment learning in the basal ganglia. This may explain risky decision making impairments observed in Parkinson's patients. Moreover, the model suggests that optimizing 5HT levels along with DA medications may improve Parkinsonian deficits in reward-punishment learning.

NORADRENERGIC SYSTEM

With the exception of the basal ganglia, noradrenergic neurons, which originate in the locus coeruleus (LC), project to nearly every cortical and subcortical region (Berridge and Waterhouse, 2003). The LC receives inputs from brainstem structures, but is also highly regulated by the prefrontal cortex, highlighting its role in integrating low-level autonomic and cognitive information and broadcasting this signal throughout the brain. Traditionally the noradrenergic system was thought to mediate arousal levels through slow changes in tonic levels of activation. Phasic activation of the LC, however, characterized by short bursts of activity, has taken on an important role in behavioral adaptation and task performance (Aston-Jones et al., 1994; Aston-Jones and Cohen, 2005).

Phasic activation of the LC typically occurs in response to salient or novel inputs (Sara et al., 1995; Vankov et al., 1995) as well as task-relevant conditioned stimuli. If a reward is not associated with the novel stimulus, the response will eventually attenuate, which is likely important for transitions between phasic and tonic states. Interestingly, the ability of the LC to fire phasic bursts depends on the LC's tonic mode of activation. When tonic activity is either too low or too high, phasic bursts are not present (Aston-Jones and Cohen, 2005). Task performance is optimal when LC neurons can be phasically activated and declines with increasing or decreasing tonic activity. Therefore, an inverted-U relationship between tonic LC activity and task performance exists that resembles the Yerkes-Dodson relationship between arousal levels and

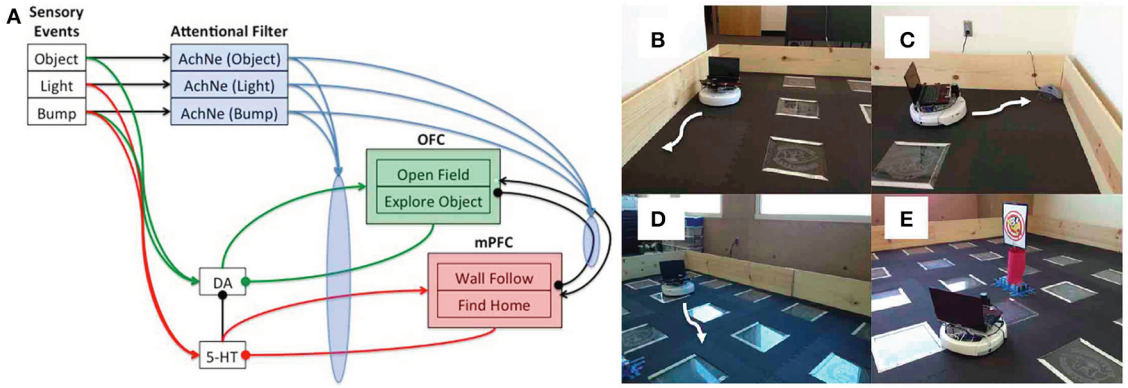


FIGURE 6 | Embodied model of neuromodulation in an open-field test experiment. Experiments were run on an iRobot Create, equipped with a laser range finder and a netbook that contained the neural model and controlled the robot's behavior. **(A)** Neural model architecture. Sensory events were handled by three binary neurons. These neurons projected to the attentional filter neurons (AchNE) and the dopaminergic and serotonergic neurons (DA and 5-HT). The DA and 5-HT neurons projected to the OFC and mPFC neurons. The most active OFC or mPFC neuron dictated the robot's behavioral state. The AChNE neurons had a modulatory effect on the projection from the DA and 5-HT to OFC and mPFC (see blue ellipse and arrows). OFC and mPFC projected to 5-HT and DA neurons with inhibitory connections. Excitatory and inhibitory connections within and between OFC and mPFC neurons were all-to-all. **(B)** Wall following behavior. **(C)** Find home behavior. Finding home consisted of locating the robot's docking station. **(D)** Open-field behavior. The robot moved toward open spaces in the environment based on laser range finder readings. **(E)** Explore object. The robot approached narrow objects based on laser range finder readings. Reproduced from Krichmar (2013) with permission.

task performance. This inverted-U nature of noradrenergic function in terms of signal detection and task performance has also been shown in working memory in the prefrontal cortex (Vijayraghavan et al., 2007; Wang et al., 2007; Avery et al., 2013). That is, too little or too much noradrenaline will likely impair working memory. This, in turn, could lead to attention disorders, stress-related disorders, and obsessive-compulsive disorders.

In the past decade or so, two important theories of noradrenergic function have been developed: (1) The "adaptive gain theory" suggests that the noradrenergic system mediates the switch between exploration and exploitation behaviors (Aston-Jones and Cohen, 2005). (2) The "network reset" theory, on the other hand, suggests that the noradrenergic system is critical for functional reorganization of cortical activity when environmental contingencies change to allow for behavioral adaptation (Bouret and Sara, 2005). A schematic depicting the brain regions involved in these computations is shown in **Figure 7**. We will discuss each of these below as well as recent studies in humans and rodents that have demonstrated an important connection between the noradrenergic system and pupillary responses and how these might be related to cortical states and internal model updating in the brain. Finally, we will discuss a neural network model we recently developed that investigates how varying levels of dopamine and noradrenaline influence working memory and behavior.

EXPLORATION-EXPLOITATION TRADEOFF

Reinforcement learning theory suggests that at each moment we should act in a way that maximizes reward. The problem with this is that sometimes the algorithm can get stuck in local minimums. The agent may become restricted to a subset of states within the entire space without knowing more rewarding states are possible. In this case, it is advantageous to make locally "non-optimal" actions in order to determine if there are surrounding states that will yield larger rewards. This idea is known as "exploration-exploitation" tradeoff. It has been hypothesized that the noradrenergic system is vital in resolving this computation.

In particular, Aston-Jones and Cohen (Aston-Jones and Cohen, 2005) suggest that exploration and exploitation modes are mediated by tonic and phasic LC activity, respectively. High phasic and low tonic activity is indicative of an exploitive phase in which an animal is task engaged. High tonic modes, however, put the animal into a highly distractible state, allowing them to explore the state space. They propose that the anterior cingulate and orbitofrontal cortices mediate transitions between tonic and phasic LC activity. It is thought that the anterior cingulate plays a role in evaluating cost and conflict, and that the orbitofrontal cortex plays a role in evaluating reward. However, both these regions are implicated in the representation of goal directed behaviors, uncertainty, and outcome expectancies (Schoenbaum et al., 2009; Stern et al., 2010; Gremel and Costa, 2013). More recent work looking at pupillary responses (discussed below) may allow further avenues to test and reshape this theory.

NETWORK RESET, CORTICAL STATES, AND BELIEF UPDATES

The noradrenergic system responds strongly to unexpected changes in the environment as well as task-relevant stimuli, which signal a change in behavior. This has led researchers to hypothesize that phasic activation of the LC is important for a "network reset" that induces a large-scale reconfiguration of neuronal activity across the brain to allow for changes in behavior and cognition (Bouret and Sara, 2005). This has been linked, for example, to the switching between the dorsal attention network,

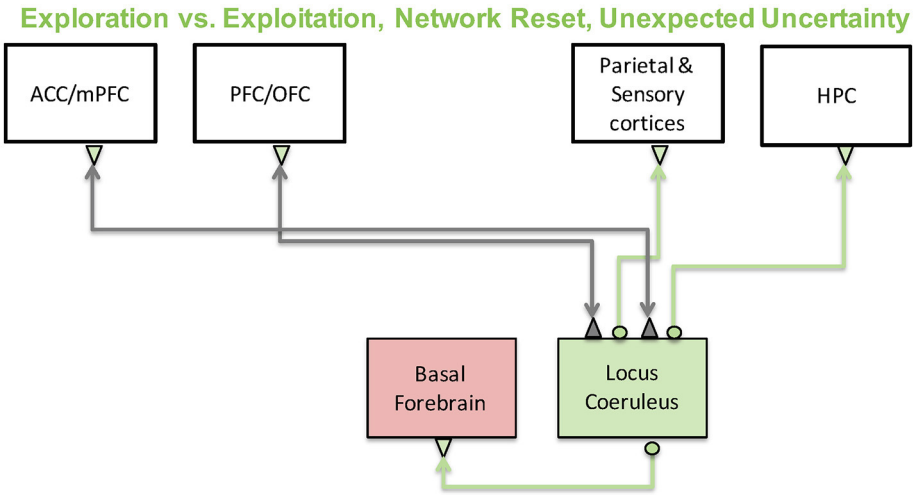


FIGURE 7 | The noradrenergic system and its functions. The noradrenergic system, which originates in the locus coeruleus, has been implicated in exploration-exploitation trade-off computations and large-scale reorganization of networks in the brain in response to surprise. Locus coeruleus activity is regulated by prefrontal and cingulate cortices and sends its projections throughout the cortex as well as to other neuromodulatory regions such as the basal forebrain.

which directs attention to expected stimuli, and the ventral attention network, which attends to novel stimuli (Corbetta et al., 2008). It has also been shown that stress, which directly involves the noradrenergic system, can similarly induce a large-scale reconfiguration of functional activity in the brain and that the reconfiguration is dampened when subjects are given a drug to block adrenergic receptors (Hermans et al., 2011).

The function of the LC in network resetting suggests that it may play a role in internal model updating, which is a well understood computation in a Bayesian framework. Interestingly, pupillary responses, which are strongly correlated to LC activity, are indicative of internal model updating based on Bayesian modeling of human responses. In particular, pupil diameter, in *human experiments*, correlates with learning rates and Bayesian belief updating in a task incorporating predictive inference and uncertainty (Preuschoff et al., 2011; Nassar et al., 2012; Lavín et al., 2014). When a change occurred in the inference task (unexpected uncertainty), pupil diameter increased and correlated with learning rates in their model. This suggests that this new information opened a "gate" to allow new sensory information to affect currently stored priors. More formally, this implies that locus coeruleus may affect the learning rate in Bayesian models as given by the following equation:

$$P_{t+1} = P_t + \alpha \cdot \delta \tag{2}$$

where P is the prior probability at time t, α is the learning rate and δ is the prediction error as described by reinforcement learning. When the environment is unstable, α will increase to allow for learning and reduce uncertainty. As stability increases, α will decrease so that priors are not updated. The circuit-level mechanism behind this is unknown, however, recent work in the mouse suggests that activation of somatostatin or vasoactive intestinal peptide (VIP) inhibitory interneurons, which disinhibit the cortical or limbic circuit, could gate learning (Letzkus et al., 2015). The noradrenergic and cholinergic systems strongly activate these interneurons, further solidifying their role in uncertainty-related computations. Taken together, these results suggest that the LC may disinhibit circuits to facilitate learning and, simultaneously, improve signal to noise ratios and to allow information to flow smoothly from one region to another when environmental uncertainty is high. Given the LC's link with pupillary responses, it is important to point out that abnormalities in pupillary responses have been associated with a host of disorders including negative symptoms and attentional allocation in schizophrenia (Granholm and Verney, 2004; Granholm et al., 2014), social reward in autism (Sepeta et al., 2012), and reward computations in Parkinson's disease (Manohar and Husain, 2015; Muhammed et al., 2016). Therefore, the LC and pupillary responses may provide a link between investigations of brain disorders and theoretical models of brain function.

Internal model updating may be realized in the brain through cortical state changes, which are also strongly linked to pupillary responses. Cortical states are often associated with oscillatory behavior. For example, low frequency synchronous oscillations are seen in resting states, and asynchronous patterns of activity are seen in active states. Cortical membrane potential recordings show that the transitions between these states occur on the order of seconds and are precisely correlated with pupil fluctuations (Reimer et al., 2014). Moreover, there is an inverted-U relationship between neuronal responses in cortex to sensory cues and behavior that corresponds with pupil diameter (McGinley et al., 2015). When pupil diameter is small, low frequency oscillations exist in the network and there is a high degree of variability in neuronal responses and animal behavior. As the pupil diameter increases, task performance increases concomitantly with sensory-evoked responses while neuronal

variability and slow oscillations decrease. Beyond the peak, pupil diameter continues to increase and task performance decreases as gamma oscillations begin to emerge in neurons. Amazingly, much of the variability seen in the membrane potential is directly correlated with pupil fluctuations. These results suggest that sensory information is largely dampened by the brain, however, there is an optimal "window" in which internal "noise" is silenced and sensory events can strongly and reliably drive cortical responses.

The above studies suggest that optimal sensory processing occurs when noradrenergic (NA) levels are neither too high nor too low. This "inverted-U" performance trend is also seen in the prefrontal cortex when primates perform working memory tasks (Vijayraghavan et al., 2007; Wang et al., 2007; Avery et al., 2013). This coincides well with the notion that attention disorders result from the prefrontal cortex being in a "non-optimal" working memory state. Drugs that treat attention disorders, such as guanfacine, which acts on adrenergic α2A receptors, are thought to push the system into an optimal working memory state. We developed a network model of working memory that incorporated this inverted-U feature for dopamine (DA) and noradrenaline (NA) neuromodulation (Avery et al., 2013). The model was of a cortical column with spiking neurons, synaptic conductances, and simulated D1, α2A, and α1 receptors. We simulated the oculomotor delay response task, in which a subject must remember the location of a brief visual cue during a delay period, and then saccade to that location. We explored how changing dopamine and noradrenaline concentrations simultaneously impacts performance and found that working memory is impaired in non-optimal zones, but for different reasons. When NA levels were high and DA levels were low, working memory impairments resulted from excess noise, however, when NA was low and DA was high, impairments resulted from an overall reduction in prefrontal activity. An overall reduction in prefrontal activity is thought to happen during high stress situations and is evolutionarily beneficial in fight or flight situations when "instictual" behaviors need to come online (Arnsten, 2009). If left unchecked, however, stress can ultimately lead to depressive symptoms (Gold et al., 2015). Non-optimal levels in NA may, therefore, play a role in depression and should further be investigated along with the more classic neuromodulators such as dopamine and serotonin. This study highlights the important point that neuromodulatory systems are interconnected and manipulating one system may be useful experimentally, but might not be valid in a real-world setting.

The model described above suggests that optimality in terms of prefrontal processing exists in a higher dimensional space and understanding how multiple neuromodulators interact in different modes (i.e., tonic vs. phasic) could help to expand upon our understanding of attention disorders and cognitive symptoms found in other diseases. Given that frontal regions shape sensory responses, these studies also suggest that different "non-optimal" zones of neuromodulatory activity, which may be associated with unique brain disorders, could manifest as unique changes in sensory processing. In the future it will be interesting to explore how sensory processing and working memory, which are simultaneously shaped by multiple neuromodulatory systems, interact in both healthy and diseased states.

CHOLINERGIC SYSTEM

The cholinergic system originates in the basal forebrain and affects essentially every system in the brain including sensory, prefrontal and limbic systems. Research on sleep-wake cycles suggests that a main function of acetylcholine (ACh) plays a major role in memory consolidation (Hasselmo, 1999; Hasselmo and McGaughy, 2004). Hasselmo and colleagues suggested that when ACh levels are low, recurrent connections are stronger and memories are retrieved. But, when ACh levels are high sensory inputs are enhanced, recurrent inputs are reduced, and memory is encoded. **Figure 8** shows a schematic of the brain regions and neuromodulators thought to be involved in these memory and sensory functions with the basal forebrain at its center. In particular, it was shown that during slow wave sleep, reduced ACh levels in the hippocampus lead to an increase in recurrent activity relative to cortical inputs, facilitating memory consolidation. While subjects were awake or in REM sleep, however, ACh levels are elevated, leading to an enhancement of cortical input to the hippocampus and stimulating memory encoding. In the following sections, we will mostly discuss conceptual and computational models focused on cholinergic effects on cortical processing. For a recent review discussing modeling cholinergic effects on hippocampus, see Newman et al. (2012).

Attention is strongly modulated by acetylcholine through its projections to sensory cortices (Sarter et al., 2001, 2005). Interestingly, research suggests that the same underlying principle seen in the hippocampus may also hold in sensory cortices. In particular, it is suggested that cortical acetylcholine enhances sensory input relative to recurrent inputs and feedback, leading to an overall improvement in the signal to noise ratio. Cholinergic inputs to visual cortex, for example, have been found to enhance the gain of sensory inputs by stimulating nicotinic receptors located presynaptically on thalamocortical inputs to layer 4 (Disney et al., 2007). Muscarinic receptors have been shown desynchronize population responses and reduce cortical noise by activating somatostatin neurons, which primarily target apical dendrites (Goard and Dan, 2009; Chen N. et al., 2015). Interestingly, muscarinic receptor stimulation has also been shown to enhance attentional signals in the macaque (Herrero et al., 2008), suggesting that the general role of "increasing sensory drive" in the cortex may need to be adapted.

Cholinergic projections to the prefrontal and parietal cortices also seem to play an important role in attention. Cholinergic inputs to these areas play an important role in cue detection (Parikh and Sarter, 2008; Howe et al., 2010) especially when increased attentional effort is required (Bucci et al., 1998; Dalley et al., 2001). Interestingly, prefrontal projections to the basal forebrain can regulate acetylcholine levels in the parietal cortex (Nelson et al., 2005) and may therefore affect the relative salience of targets and distractors (Broussard et al., 2009). A recent study has also implicated decreased nicotinic

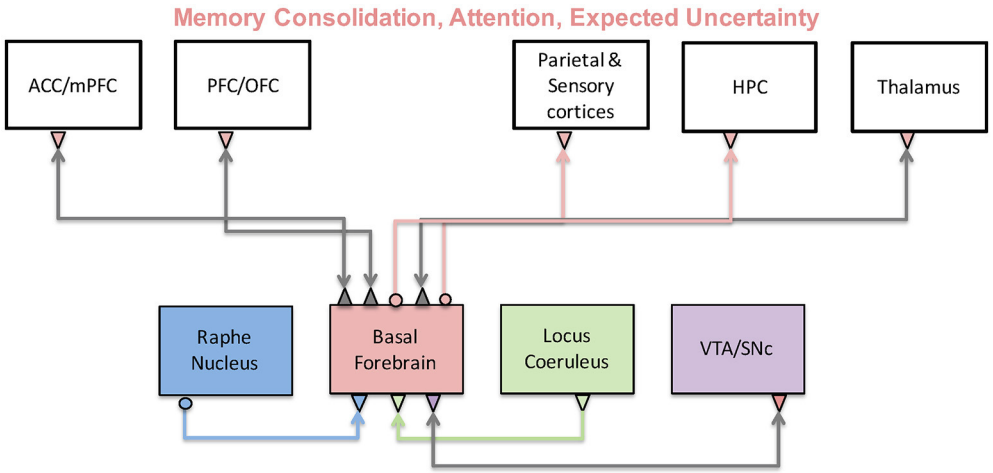


FIGURE 8 | The cholinergic system and its functions. The cholinergic system originates in the basal forebrain and sends projections to many cortical and subcortical regions. As a result, it has been implicated in a variety of functions including memory, attention, and uncertainty computations. Activity of the basal forebrain is thought to be regulated by prefrontal cortices, as well as other neuromodulatory brain regions.

stimulation to a reduction in frontal lobe activity, termed hypofrontality (Koukouli et al., 2017), which is often associated with the pathophysiology of schizophrenia. This study showed that introducing a single nucleotide polymorphism (SNP) into nicotinic receptors leads to hypofrontality in mice. Moreover, they showed that hypofrontality is alleviated by nicotine administration. This is one of the first studies that establishes a mechanistic link between schizophrenia and nicotine addiction and suggests an important role for the cholinergic system in the pathophysiology and treatment of schizophrenia.

In contrast to cholinergic projections from the substantia innominata to the prefrontal and parietal cortices, which increase attention to salient objects, cholinergic projections from the medial septum to the cingulate and hippocampus are important for decreasing attention to irrelevant stimuli (Chiba et al., 1995; Baxter and Chiba, 1999). In the Baxter and Chiba study, rats with lesioned cholinergic projections to the hippocampus disrupted the animal's ability to decrement attention away from a conditioned stimulus. This pathway for decrementing attention is far less studied than the cholinergic pathway to the cortex and the mechanism behind this is not well understood. It is possible that the decrementing of attention depends on the hippocampus' ability to encode novel information (Hasselmo and Stern, 2006). If attention to a conditioned stimulus should be decremented due to lack of reward, it requires the hippocampus to encode the fact that a reward wasn't present. It is interesting to note that working memory requires interaction between prefrontal cortex and hippocampus, perhaps especially of novel information, suggesting that the incremental and decremental pathways work together to orient behavior in order to learn the value of information in the environment. The importance of ignoring irrelevant information and focusing attention on relevant information is observed in learning disorders such as attention deficit hyperactivity disorder, mild cognitive impairment that lead to dementia, and schizophrenia (for review, see Lubow and Weiner, 2010).

CHOLINERGIC AND NORADRENERGIC COMPUTATIONS OF UNCERTAINTY

The ability to enhance sensory information, decrease recurrent activity, and regulate learning and memory suggests that acetylcholine may have a unique role in uncertainty-mediated inference computations in the brain. A Bayesian statistical theory developed by Yu and Dayan (2002, 2005), indeed, proposes that acetylcholine and noradrenaline levels encode expected and unexpected uncertainty, respectively. These systems, in turn, modulate perceptual inference by balancing sensory and prior information and influencing learning. In a Bayesian statistical framework, the posterior distribution (i.e., perception) is determined by likelihood and prior distributions, which can be thought of, in the context of the Yu and Dayan model, as sensory inputs and top-down expectations, respectively:

$$p\left(h|d\right) = \frac{1}{Z}p\left(d|h\right)p\left(h\right) \tag{3}$$

Where $p(h|d)$ is the posterior distribution of hypothesis given the data, $p(d|h)$ is the likelihood function (sensory inputs), $p(h)$ is the prior, and Z is a normalizing factor. Uncertainty is critical in this model as it determines the relative weight we should assign to priors vs. sensory inputs when making inferences. When prior uncertainty is high, optimal inference entails that sensory inputs should be preferentially weighted and learning should be enhanced so that priors may be updated (also, see discussion in Noradrenergic System section). The same principle also holds when weighting information from different modalities, such as visual and haptic information (Körding and Wolpert, 2006).

The posterior distribution is traditionally solved through exact inference or naïve inference, however, each has its own disadvantages computationally (Yu and Dayan, 2002, 2005). Exact inference requires representing and computing over all possible contexts, making it unlikely to be implemented

in neuronal circuits given our current understanding how information is represented in the brain, which is thought to be distributed and inexact (Loftus, 1996; Wixted et al., 2014). Naïve inference does not store prior information over time, making it cheaper computationally than exact inference. Naïve inference, however, leads to poor performance when prior uncertainty is low. The Yu and Dayan model takes a more balanced approach by computing a single state and attaching an uncertainty estimate to this state, which they attribute to the cholinergic signal in the brain. This overcomes the computational disadvantages of the exact inference model and outperforms the naïve model by allowing for use of prior information when uncertainty is low.

The Yu and Dayan model also hypothesizes that phasic bursts of LC activity encode unexpected uncertainty, which can be thought of as a large change in the environment that evokes a "surprise" response. This is consistent with the network-reset theory discussed above in the section on the noradrenergic system. Unexpected uncertainty acts to inform the model that a significant change has happened and priors need to be updated. Inabiltiy to recognize these changes, which can be demonstrated with noradrenergic antagonists, leads to impairments in behavioral flexibility (Caetano et al., 2013). This model assesses reliability in a broader context than the cholinergic encoding of expected uncertainty, which assigns reliability values to individual cues.

In order to understand how Bayesian computations of expected and unexpected uncertainty are realized in the brain, we developed a neural network model (Avery et al., 2012) that incorporated cholinergic and noradrenergic modulation (**Figure 9**). In particular, we were interested in identifying a mechanism that supports the generation of the noradrenergic surprise response from afferent inputs to the LC and expected uncertainty response through afferent inputs to the BF. Moreover, we hoped to gain insight into how noradrenaline and acetylcholine influence downstream targets to perform Bayesian computations (Avery et al., 2012).

We found that the response of locus coeruleus neurons to novel stimuli and BF neurons to expected uncertainty could be realized in the brain through short-term synaptic depression (**Figures 9B,C**, blue connections). Short-term plasticity was incorporated into prefrontal projections to the LC and BF. The LC neurons in turn enhanced feedforward input and updated priors by modulating the learning rate of plastic afferent and efferent prefrontal projections. LC neurons also increased the gain of BF neurons as has been shown experimentally (Zaborszky and Duque, 2003). BF neurons, on the other hand, balanced the weight of sensory and prefrontal inputs on decision neurons such that high BF responses favored sensory information. This computational model is unique from many other models of neuromodulation in that it attempts to model both the downstream effects of neuromodulatory input as well as the afferent projections that shape the responses of neurons within neuromodulatory brain regions.

The Bayesian model discussed above suggests that acetylholine computes expected uncertainty in the brain and therefore plays a central role in balancing sensory and prior information. Although we know a great deal about the effects of acetylcholine at the cellular and synaptic levels, this balance of information is likely realized in cortical circuits composed of many neurons of different types in multple brain regions. Deco and Thiele offer insight into this by developing a spiking neural network model that proposes several important mechanisms that mediate the muscarinic enhancement of top-down attention (Deco and Thiele, 2011). Their model incorporated key cellular and synaptic changes resulting from cholinergic modulation including reduction in firing rate adaptation, enhanced thalamocortical input, reduction in lateral connectivity strength, and an increase in inhibitory drive. They show that muscarinic enhancement of attention is mediated by suppression of intracortical connections and an increase in inhibitory drive. Again, this highlights the importance of acetylcholine in suppressing a very specific set of connections (intracortical) and potentially enhancing a broader class of behaviorally relevant inputs, which may include emotional, cognitive or memory.

More recently, we developed a model (Avery et al., 2014) that took a slightly different approach from Deco and Thiele and suggested that local and global activation of the cholinergic system might account for attentional and sensory enhancement, respectively. In this model, stimulation of the basal forebrain has a global effect on the brain and enhances sensory input by disinhibiting the sensory thalamus via inhibitory projections from the basal forebrain to the thalamic reticular nucleus. The model dissociates this enhancement of sensory input from the cholinergic enhancement of top-down input, which suggests that sensory enhancement is mediated by a local release of acetylcholine and activation of muscarinic receptors on inhibitory neurons in the visual cortex. Similar to the Deco and Thiele model, this model stresses the importance of muscarinic receptors on inhibitory neurons. The model demonstrates that activation of muscarinic receptors is primarily involved in reducing noise correlations between neurons, which have been shown to influence information processing capabilities in the cortex. Whether there is local acetylcholine release with attention is still not known. However, (Chen N. et al., 2015) has recently shown the importance of cholinergic activation of somatostatin inhibitory neurons for improving information processing.

The models discussed above aim to understand how sensory and prior knowledge are integrated in the brain. These models, however, do not incorporate learning, which is a key component of cholinergic function and Bayesian models. As discussed earlier, learning to attend toward an object of interest (incrementing attention) and attend away from another stimulus (decrementing attention) is thought to be realized through cholinergic projections to the neocortex and hippocampus/cingulate, respectively. In a neural network model, Oros and colleagues tested the different contributions made by the ACh projections from the substantia innominata/nucleus basalis region (SI/nBM) to the neocortex and the medial septum/vertical limb of the diagonal band (MS/VDB) in incrementing and decrementing attention. The neural simulation was tested in a range of behavioral paradigms that require both attending to a salient stimuli and ignoring an irrelevant stimuli (Oros et al., 2014). The model exhibited behavioral effects such

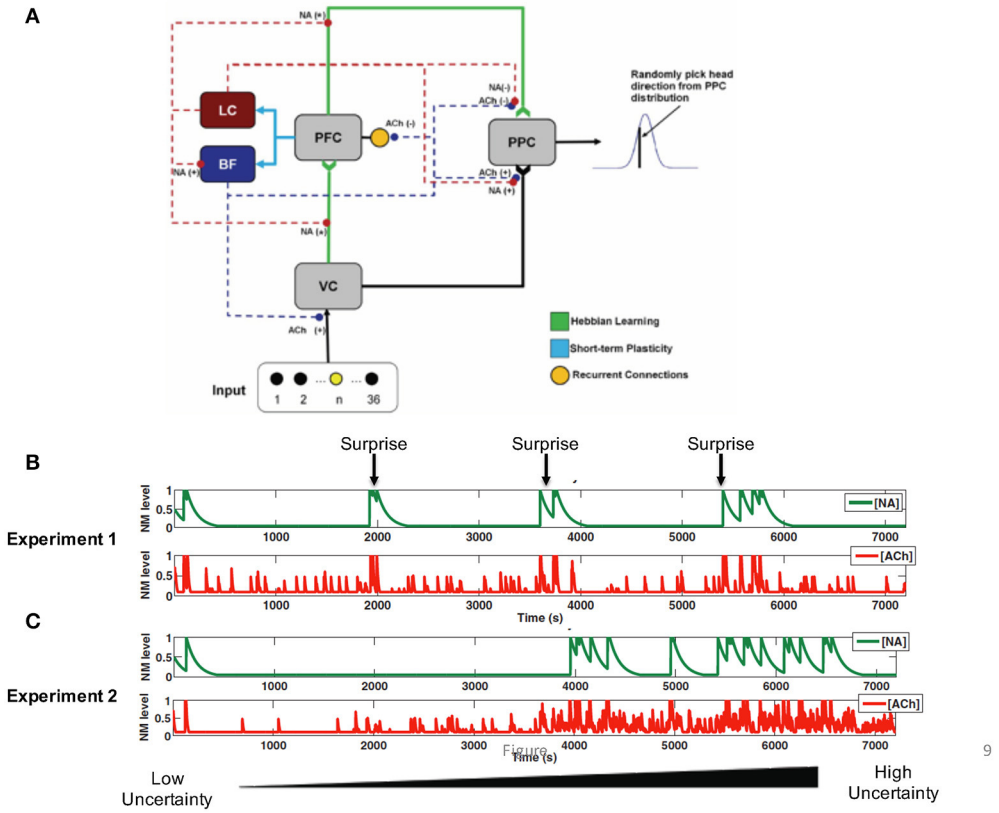


FIGURE 9 | Neural network model incorporating noradrenergic and cholinergic systems that adapt to uncertainty. **(A)** The visual input group drives activity in the VC (visual cortex). VC and PFC (prefrontal cortex) provide input to the PPC (posterior parietal cortex). The noradrenergic system, LC (locus coeruleus), enhances the depression of weights ("forgetting") between VC and PFC, and PFC and PPC [indicated by NA(−)]. The noradrenergic system increases the gain in the BF (basal forebrain) and the input to the PPC from VC [shown by NA(+)] and suppresses input to the PPC from the PFC [shown by the NA(−)]. The cholinergic system, BF, enhances input to VC and PPC [indicated by the ACh(+)] and suppresses recurrent activity in the PFC and input to the PPC from the PFC [indicated by the ACh(−)]. **(B)** In Experiment 1, the uncertainty level was constant and a surprising stimulus was occasionally presented. NA levels rapidly increased in response to the unexpected stimulus (green), whereas ACh levels rose more gradually. **(C)** In Experiment 2, surprise was kept constant, but expected uncertainty gradually increased. The figure shows that ACh levels increase as expected uncertainty increases (red). Reproduced from Avery et al. (2012) with permission.

as associative learning, latent inhibition, and persistent behavior. The model suggests that the neuronal projection from the MS/VDB to the hippocampus and cingulate is important for: (1) Decreasing attention to a cue that previously predicted a reward. (2) Preventing perseverative behavior when reward contingencies change (e.g., in extinction or reversal learning tasks). (3) Showing latent inhibition to previously uninteresting cues. Lesioning the MS/VDB disrupted latent inhibition, and drastically increased perseverative behavior. Taken together, the model demonstrated that the ACh decremental pathway originating in the MS/VDB is necessary for appropriate learning and attention under dynamic circumstances and suggests a canonical neural architecture for attention that includes both an incremental and a decremental pathway.

CONCLUSIONS

The present article reviewed experimental evidence, as well as computational and theoretical models of neuromodulation. It is difficult to pinpoint a specific function for each neuromodulator. It has been suggested that dopamine is related to positive value, serotonin to risk aversion, noradrenaline to vigilance, and acetylcholine to attentional effort (Krichmar, 2008). Another theory posits that dopamine is related to reward prediction, while serotonin is related to temporal discounting, and that noradrenaline regulates the exploration/exploitation tradeoff, while acetylcholine controls learning rate (Doya, 2002, 2008). These functions can be mapped to elements of temporal difference learning. However, in neither case are things this simple. The same neuromodulator can have different effects on their target brain areas. For example, dopamine has different functional implications depending on whether it targets D1 or D2 receptors (Durstewitz and Seamans, 2008; Avery and Krichmar, 2015). Acetylcholine increments attention in sensory cortex, but decrements attention in the cingulate and hippocampus (Chiba et al., 1995; Baxter and Chiba, 1999; Oros et al., 2014). Interestingly, all neuromodulators are involved to some degree in attention and novelty detection. This suggests that no matter

what the specific function, neuromodulators in all cases signal important events for the organism and shape behavior.

In this review, we highlight studies that focus on the interactions within and between neuromodulatory systems. Still, most of the experiments, computational models and theoretical models described here focused on one or two neuromodulators. There are strong interactions between all of these systems. An exploratory survey of cholinergic, dopaminergic, noradrenergic, and serotonergic receptor expression using the Allen Mouse Brain Atlas showed that the substantia innominata of the basal forebrain, which is a source of cholinergic innervation, and the VTA, which is a source of dopaminergic innervation, displayed high receptor expression of all four neuromodulators (Zaldivar and Krichmar, 2013). Since the nuclei of these neuromodulatory systems are thought to be the source of specific neurotransmitters, the projections from these nuclei to target regions may be inferred by receptor expression and suggest that neuromodulatory systems are highly interactive. It should be noted that many of these nuclei, in which neuromodulatory neurons originate, also have GABA-ergic and glutamatergic neurons (Zaborszky, 2002; Barker et al., 2016). Moreover, there is evidence that multiple neurotransmitters and neuromodulators are co-released at the axon terminals of these neurons (Trudeau, 2004; Sarter et al., 2005; Zhou et al., 2005). We have a limited understanding of how these interactions affect the functionality of the nervous system. Therefore, more computational, theoretical and disease models that focus on these interactions are needed. Theoretical models are important and can help us reduce and simplify these complex interactions in terms of a single overarching computation, such as computing uncertainty.

Computational models of neuromodulation and its effects can contribute to our understanding of a number of neurological diseases and disorders. Dopamine's involvement in schizophrenia has been modeled many times (Braver and Cohen, 1999; Loh et al., 2007; Durstewitz and Seamans, 2008; Rolls et al., 2008; Arnsten et al., 2012; Avery et al., 2012), as well as Parkinson's disease (Moustafa and Gluck, 2011; Moustafa et al., 2013). Serotonin is thought to be involved in anxiety disorders (Millan, 2003; Tops et al., 2009; Jasinska et al., 2012) and depression (Deakin, 2003; Weisstaub et al., 2006; Gold et al., 2015). Models of anhedonia, anxiety, and withdrawal can provide mechanistic underpinnings for these disorders (Wong-Lin et al., 2012; Huys et al., 2013; Krichmar, 2013). The cholinergic and noradrenergic systems play a significant role in allocating attention, and models of these systems may have implications on how imbalances in these neuromodulators can contribute to ADHD (Yu and Dayan, 2005; Cohen et al., 2007; Deco and Thiele, 2011; Avery et al., 2013, 2014). Many of the current drug treatments for these disorders target neuromodulators. Thus, understanding how these drugs can disrupt the fine balance in neural circuits through computational modeling is of the utmost importance.

Detailed computational models will be important for understanding the complexity of neuromodulation including how neuromodulatory responses are generated (e.g., short-term plasticity Avery et al., 2012), the result of influencing multiple targets simultaneously, how neuromodulatory systems interact with each other directly, and how these systems interact in target sites. We hope that computational and theoretical models may work hand in hand with experimental research to drive discovery of the underlying mechanisms a large set of multifaceted and complex disorders.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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BRAIN RESEARCH REVIEWS

The emergence of the volume transmission concept [1]

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Abstract

Interneuronal communication in the central nervous system (CNS) have always been of basic importance for theories on the cerebral morphofunctional architecture. Our group has proposed that intercellular communication in the brain can be grouped into 2 broad classes based on some general features of the transmission: wiring (WT) and volume (VT) transmission. WT occurs via a relatively constrained cellular chain (wire), while VT consists of 3-dimensional diffusion of signals in the extracellular fluid (ECF) for distances larger than the synaptic cleft. Both morphological and functional evidence indicates that dopamine (DA) synapses in striatum are 'open' synapses, i.e., synapses which favor diffusion of the transmitter into the surrounding ECF and observations are compatible with the view that DA varicosities can synthesize, store and release DA for VT. The DAergic mesostriatal transmission has, therefore, been examined by several groups to give experimental support to VT. Moreover, due to its minor structural requirements, VT may become prevalent under some pathological conditions, e. g. Parkinson's disease. In animal models of DAergic pathway degeneration, it has been shown that a compensatory activation of surviving DA terminals may lead to a preferential potentiation of VT. WT and VT favor different and complementary types of computation. VT is markedly slower and less safe than WT, but has minor spatial constraints and allows the reach of a large number of targets. Models of neuronal systems integrating classical neuronal circuits and diffusible signals begin to show how WT and VT may interact in the neural tissue.

Keywords: Intercellular communication; Dopamine; Striatal lesions

Contents

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1. Modes of intercellular communication in the central nervous system: the concept of wiring and volume transmission

As beautifully discussed in Jacobson's book Foundations of Neuroscience [47] and Shepherd's book Foundations of the Neuron Doctrine [73], connectivity and communication between the cellular elements building up the central nervous system (CNS), have always been of basic importance for theories on the morphofunctional architecture of the brain. At the turn of this century two main opposing views on these issues were competing with each other: Cajal's neuron doctrine and Golgi's reticular theory. One aspect of the dispute between Cajal and Golgi that has not been sufficiently considered is the basic tenant of Cajal and Sherrington that a structurally defined intercellular connection (the synapse) was a prerequisite for interneuronal communication. In contrast, Golgi maintained that the two concepts could be, in some instances, unrelated. In fact, he stated that ''The structural contact or fusion between two nerve fibers is not a necessary condition to have functional relationship between different neurons [...] since, studies on electricity show that electrical currents can link two conductors not in direct contact'' [35a,35b]. This specific hypothesis has been subsequently demonstrated since intercellular communication via electrotonic currents takes place in the CNS [48]. Furthermore, Golgi's position may have an even broader meaning, since, nowadays, most neuroscientists, in a more or less explicit way, believe that there exists in the brain some kind of non-synaptic, hormone-like, modulatory transmission besides synaptic transmission. Indeed, data on new transmitter substances, like gases, give a strong support to this view. For instance, it has been estimated [32] that nitric oxide (NO), once released, can affect the electro-metabolic state of a huge number of neurons not in synaptic contact with the neuron source of the signal.

In the mid 80's our group has proposed that intercellular communication in the brain can be grouped into 2 broad classes based on some general features of the transmission [1–4,31,84]: wiring transmission (WT) and volume transmission (VT). Initially, they were differentiated on an intuitive basis. Thus, WT was defined as a mode for intercellular communication which occurs via a relatively constrained cellular chain (wire), while VT was defined as the 3 dimensional diffusion of a signal in the extracellular fluid (ECF) volume for a distance larger than the synaptic cleft.

VT basic elements are:

- a cell source of the VT signal, which may be a presynaptic terminal but also any other portion of neuronal or non-neuronal cells from which a signal can be released into the ECF;
- a VT signal diffusing in the ECF for a distance larger than the synaptic cleft. The chemical nature of the VT signal varies from gases to ions to complex peptides and its chemical characteristics (for instance, molecular size, electrical charge, lipophilicity) affect diffusion in the ECF [58,59,78];
- a communication channel in the ECF [77];
- a cell target of the VT signal, that is, a cell possessing molecules capable of detecting and decoding this message. Therefore, the spatial uncoupling between the source of the VT signal and the biochemical machinery capable of its detection and decoding is a necessary (although not sufficient, see Ref. [4] for discussion) condition for the existence of VT. Accordingly, chemical neuroanatomy has provided a large amount of evidence for transmitter/receptor mismatches in the CNS [1,4,41,42,52].

2. The dopaminergic mesostriatal pathway as a model system for VT

From the list of VT basic elements reported above, it is evident that this type of intercellular communication may be present in many central neural systems and have very different features according to the cell structures (sources and targets) and chemical nature of VT signal involved in the communication process as well as the characteristics of the ECF pathways. Model systems for VT are the highly divergent monoaminergic pathways of the brain, e.g., the dopaminergic mesostriatal system. Both morphological and functional evidence indicates that dopamine (DA) functions as a VT signal in striatum [22,33,37,84] (Fig. 1).

The mesostriatal DAergic terminals form en passant symmetrical synapses (located in the thin intervaricose portions, and more uncommonly in varicosities, of the axons) on dendritic spines and shafts of medium spiny neurons [28,39]. These synapses show the classical features of a synapse, e.g. a presynaptic active zone and a postsynaptic density separated by a narrow (about 15 nm) synaptic cleft. However, only a small fraction of DA D1 (around 7%) and D2 (around 4%) receptors detected in dendritic spine membranes are associated with symmetrical synapses [72,82]. Synaptic vesicles are also present, although at lower concentration, in the intersynaptic segments of the axon terminal [39].

Release of DA is principally dependent on arrival of action potentials [36]. Studies of this pathway in awake unrestrained rats have shown that DAergic neurons have two main modes of discharge, single spikes and small trains of spikes (2–6 action potentials at 15 Hz) [27,38]. The latter causes a much larger increase in ECF DA (around 0.5 μM, a concentration close to the EC_{50} for D1 receptors) [16,37]. In both rats and monkeys, appetitive stimuli cause the switch from single to burst discharge of DA mesencephalic neurons [27,68] and marked increases in DA ECF levels in striatum [12,64]. Once released, DA is cleared primarily through reuptake, as its enzymatic

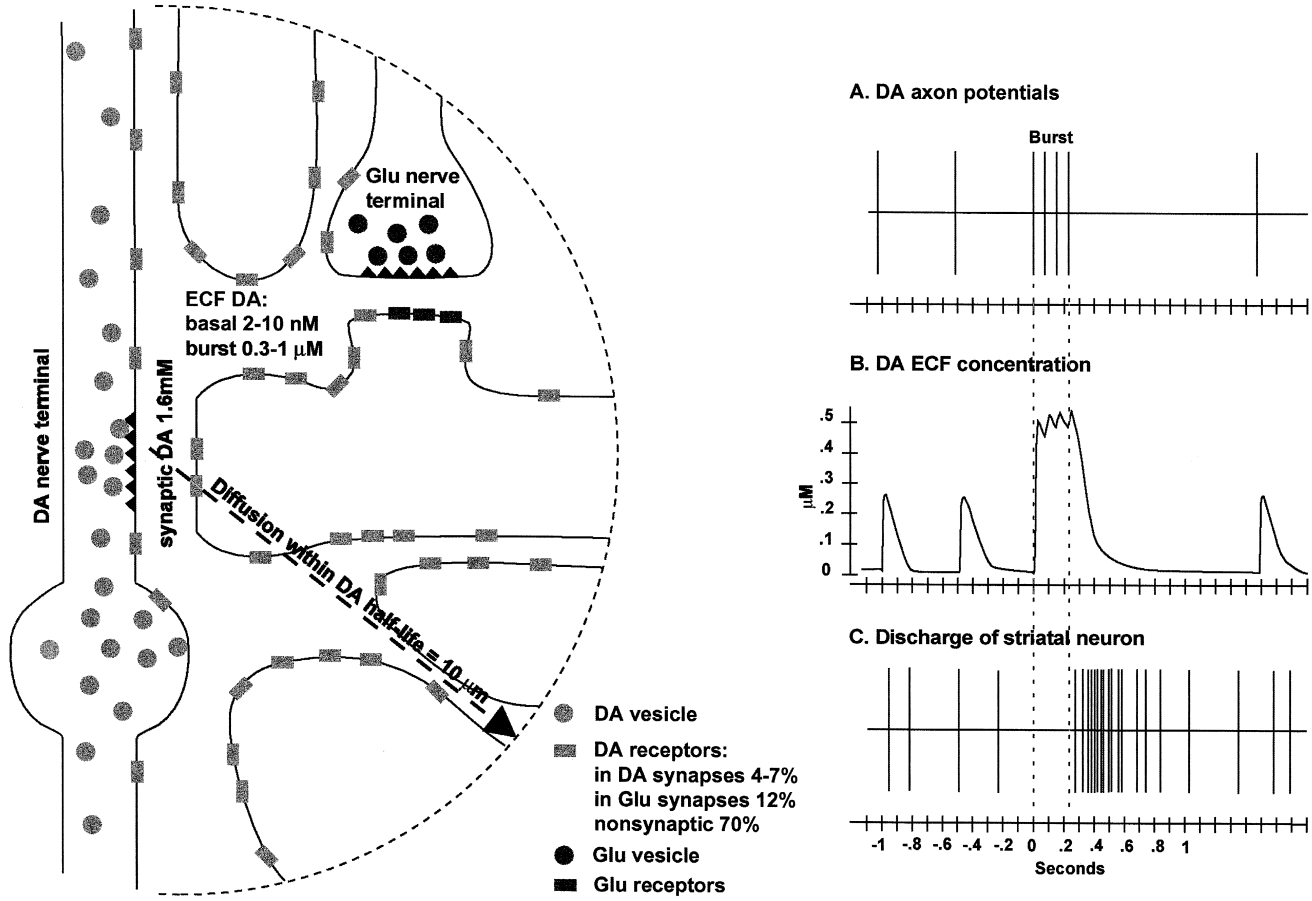

Fig. 1. Schematic representation of the DAergic open synapse of the striatum. Quantitative figures are taken from refs. [16,33,36,37,82]. For discussion, see text.

degradation is relatively slow [55,80]. However, blockade of either synaptic receptors or uptake sites does not markedly influence diffusion of DA outside the synaptic cleft [33]. This implies that neither buffered diffusion due to synaptic receptor occupancy [7,49] (see also Ref. [84]) nor synaptic uptake are effective in this type of synapse. In addition, it indicates that DA uptake sites are principally effective outside the synaptic cleft (see also Refs. [15,60]) and may regulate ECF rather than synaptic DA concentration. The crucial role of DA uptake sites in DA transmission and diffusion is underlined by recent data showing a 100-fold increase in the permanence of DA in the ECF in mice with genetic inactivation of the DA transporter [34].

The result of this morphofunctional arrangement is that DA may have synaptic effects but can also efficiently diffuse into the extrasynaptic space (more than 10 μm from the source synapse within 1 half-life of DA, which means that it can affect around 200 other DA synapses, so called 'sphere of influence') to reach DA receptors located in extrasynaptic membranes or other synapses (for a thorough discussion, see Ref. [33]). Accordingly, the concentration of DA in the local ECF after stimulation of the DAergic terminal is in the high nanomolar range [33,16]. This hypothesis received further support in a recent paper by Gonon [37], who simultaneously studied DA ECF levels and activation of D1 receptors in rat striatum. This author showed that a physiological (see above) burst of 4 pulses at 15 Hz (i.e., spaced 66 ms) in the medial forebrain bundle causes in striatal neurons either 4 discharges, each one temporally related to the arrival of a spike, or a single delayed excitation, which starts after the end of the burst and lasts for up to 1 s. The latter effect was mimicked by D1 agonists and blocked by D1 antagonists or DA denervation. Interestingly, the extent of the postsynaptic excitation was not linearly related to the peak concentration of DA but rather to the overall DA overflow [37].

In conclusion, the mesostriatal DA synapse is a prototypical 'open' synapse (see Ref. [84] and below), i.e., a synapse which favors diffusion of the transmitter into the surrounding ECF. In addition, DA varicosities may represent preferential sites for synthesis, storage and release of DA for VT [29] (see also Section 2.1). Accordingly, much functional evidence has accumulated for non-synaptic actions of DA in striatum, for instance, on striatal cholinergic interneurons (for review, see Ref. [79]).

This transmission has, therefore, been examined by several groups to give experimental support to VT. Since the signal DA diffusing out from synaptic clefts is highly

diluted into the ECF volume, at the beginning our group took advantage of in vivo bioassay systems. A means to detect DA in striatal ECF was to transplant pituitary cells into the striatum of an adult rat and evaluate the rate of prolactin (PRL) secretion by measuring the extent of PRL immunoreactivity (IR) spread from the transplanted cells. The spread of PRL is inversely related to the DA levels in the ECF, since DA inhibits PRL secretion by the pituitary cells. In fact, increased (obtained by injecting amphetamine) or decreased (obtained by lesioning DA terminals with 6-hydroxydopamine, 6-OHDA) DA concentration in the ECF decreases or increases the halo of PRL IR, respectively. These experiments show that DA concentration present in the ECF under basal conditions is capable of inhibiting PRL secretion. Hence, DA diffuses out of striatal synapses in functionally relevant concentrations to activate D2 receptors in the PRL gland cells [5].

Another means of studying DA diffusion in striatum is to perform partial or total lesions of the mesostriatal DAergic system with selective neurotoxins and to study the morphological features of surviving DA terminals as well as DA ECF levels or DA-induced responses in surrounding striatal tissue.

2.1. Partial lesions of the dopaminergic mesostriatal pathway

It has been shown that, after partial DA denervation (an animal model of Parkinson's disease), a releasing stimulus administered to the intact portion of striatum causes a local increase in DA ECF concentration and, with a delay, in the denervated portion [67]. The same stimulus applied directly to the denervated part of striatum has no effect, which confirms that DA stores are not present in the denervated area. After partial lesion of the DA pathway, increased activity has been demonstrated in spared DA cells. This phenomenon has been interpreted as an attempt of the system to compensate for the lesion. Given the fact that VT poses much less structural constraints than WT, it has been hypothesized that increased function in lesioned neuronal systems will result in preferential potentiation of VT. Some preliminary data from our group (Zoli, Torri, Agnati, in preparation) show that DA terminals surviving in lesioned portions of striatum increase production and release of DA.

Striatal DA nerve terminals were lesioned with local administration of 6-OHDA (2.5μg/μl, 3.5 μl) and visualized for their content of tyrosine hydroxylase (TH) and DA transporter (DAT, the main regulator of DA ECF diffusion). In the caudate–putamen area, 3 fields were chosen corresponding to total (intralesional), partial (perilesional) or no lesion (extralesional). Double immunofluorescence experiments were carried out using an anti-TH mouse monoclonal antibody (detected with Cy3) and an anti-DAT rabbit polyclonal antibody (detected with FITC) and analyzed by confocal laser microscopy, followed by computerised image analysis. The analysis showed that around 2.5%, 20% and 100% of DA terminals (with respect to intact side) were present in the intra-, peri- and extra-lesional regions, respectively. A marked increase of both TH (200%) and DAT (300%) content as well as the size (400%) of DA-varicosities was observed in intra- and peri-lesional fields (Fig. 2). Increased TH may provide DA to these hyperactive terminals and DAT may work, under these conditions, in a reverse fashion [25]. Thus, the present data are in good agreement with previous results demonstrating a compensatory activation of surviving DA cells after partial lesion of the pathway [17,30,74,83]. Furthermore, TH-containing varicosities (which are known to be almost devoid of synaptic contacts and may be preferential release sites for VT [82]) become hypertrophic and may represent the morphological counterpart of increased extrasynaptic DA release. Overall, these neurochemical and structural data support the notion that enhanced VT occurs in surviving DA nerve terminals in a rat model of Parkinson's disease.

2.2. Total lesions of the dopaminergic mesostriatal pathway

Partial denervation models have been used to study local VT, since remaining DA terminals are spaced a few μm away from each other, a distance similar to the radius of the physiological sphere of influence of a DA synapse (see above). On the other hand, total DA denervation is aimed at testing a different type of DA spread, i.e., long distance VT. Under these conditions, less than 5% of DA remains in the entire striatum (including nucleus accumbens and tuberculum olfactorium). Therefore, increased extracellular DA in the lesioned striatum has in principle to stem from either extraordinarily hyperactive, sparse, surviving DA terminals in the lesioned side or far located DA terminal fields such as the contralateral striatum, which are not hit by the toxin. In the latter case, DA should travel for a distance of mm in order to reach the denervated striatum. In this model, amphetamine administration caused DA-related electrophysiological (inhibition of firing) and neurochemical (increase in c-fos expression) effects in the totally denervated striatum [10]. One possible explanation for these effects is that DA, released by intact contralateral DA terminals, diffuses into the close by lateral ventricle and reaches the lesioned striatum through the cerebrospinal fluid (CSF). In order to test this hypothesis, DA was administered into the contralateral ventricle and DA-related inhibition of neuron firing was studied in the lesioned side. Preliminary data (Strömberg, Jansson, Fuxe, in preparation) indicate that only pharmacological concentrations of DA are effective, suggesting that other pathways besides the CSF are likely to be involved in the interstriatal migration of DA. In previous experiments, interstriatal migration of substances in rat brain has been evaluated by injecting fluorescent dextran into one striatum and detect-

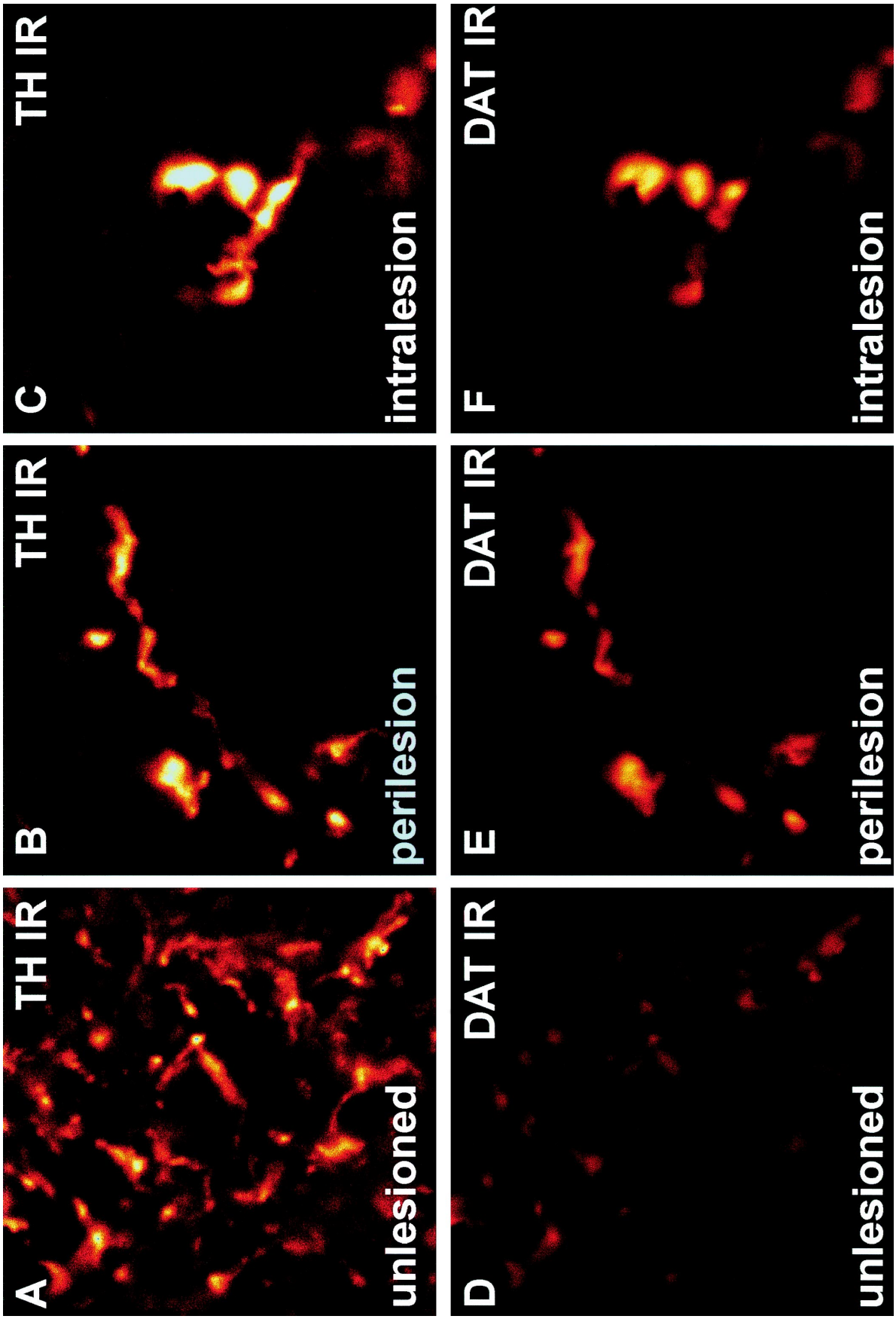

Fig. 2. Confocal images of tyrosine hydroxylase (TH) and dopamine transporter (DAT) immunoreactive (IR) terminals in three regions (unlesioned, perilesional and intralesional) of the partially 6-hydroxydopamine denervated caudate–putamen. Double immunocytochemistry was performed using FITC and Cy3 fluorochromes to detect TH and DAT IR, respectively. For further details, see text.

ing the marker on the contralateral side [11]. After about 30 minutes, fluorescent dextran could be detected on the contralateral side and was particularly enriched within fiber bundles, such as the corpus callosum and the anterior commissure. Fiber bundles may, therefore, represent the anatomical links allowing the fast migration of DA from intact to lesioned striatum.

It has been shown by our and other groups [11,20,45,63] that fiber bundles and, especially, paravascular spaces are preferential pathways for fast migration of substances in the CNS. In these structures fast migration of substances is dependent on the existence of convective forces, at least in part caused by vascular pulsatility [63]. Recent magnetic resonance imaging (MRI) studies on water self-diffusion give further support to this view [62]. In fact, while water self-diffusion is almost isotropic in the gray matter, diffusion along the axis parallel to that of axons in the white matter is up to 8 times higher than diffusion along the other axes.

3. Classification of intercellular communication modes in the frame of the WT and VT concepts

Besides the few examples reported above, a wealth of data support the existence of VT in the mammalian brain (see Refs. [4,84] for recent reviews). They comprise evidence of transmitters released by non-neuronal cells (such as glial GABA and glutamate), transmitters which are not limited by cell barriers (such as gases), transmitters released by extrasynaptic sites (e.g., most neuropeptides), etc. An attempt to classify the different classes of VT has been recently made in the frame of a conceptual refinement of the initial intuitive definitions of WT and VT. The basic distinction in two classes mirrors the Cajal's proposal of a point-to-point transmission (WT) and the Golgi's proposal of a diffuse mode of transmission (VT). Recently, objective criteria to differentiate these two classes of intercellular communication modes have been proposed [84]. A crucial parameter is the source (S) vs. target (T) ratio. We mean by S/T ratio the relationship between the number of source structures and the number of target structures in the transmission. It must be noted that this does not refer to the source cell–target cell link but rather to the link between the subcellular structure which releases the signal and that which recognizes the signal, i.e., in the case of synaptic transmission, the presynaptic terminal-postsynaptic density link. All the WT modes of transmission are characterized by a $S/T = 1$, all the VT are characterized by a $S/T < 1$ (usually $\ll 1$). Other quantitative parameters can be used to further subdivide these two classes into subclasses, that are highly relevant for the neurochemical description of intercellular communication in the brain. Known modes of intercellular communication can be classified according to these criteria (Table 1).

3.1. Open and closed synapses

In the classification proposed above, we distinguish two categories of synapses, i.e., closed and open synapses. Historically, the neuromuscular cholinergic synapse has set a standard for synaptic transmission. However, a growing

Table 1
Different types of intercellular communication in the central nervous system

Transmission type	S/T ratio	S/T distance	S/T delay
Wiring transmission			
1. Quasi-continuity			
Gap-junction	1:1	2–3 nm	μs
2. Contiguity			
Membrane juxtaposition	1:1	2–10 nm	ms
Closed synaptic transmission	1:1	20–50 nm	ms
Volume transmission			
1. Diffusion-based			
Local ion currents	1:n, $n > 1$–$n \gg 1$	100 nm–mm	ms–s
Paracrine transmission			
Open synaptic transmission	1:n, $n > 1$–$n \gg 1$	100 nm–mm	ms–min
Non-synaptic source[a]	1:n, $n \gg 1$	μm–mm	s–min
Para-axonal transmission[b]	1:n, $n \gg 1$	mm	min
2. Convection-based			
Para-vascular transmission[c]	1:n, $n \gg 1$	mm–cm	min
Intra-CSF transmission	1:n, $n \gg 1$	mm–cm	min

Abbreviations: CSF = cerebro-spinal fluid, S/T = source/target.
[a] Note that all transmitters of nonneuronal (e.g., astroglial) origin acting on neighboring cells belong to this transmission type.
[b] See Refs. [11] and [20].
[c] See Refs. [45] and [63].

body of evidence indicates that a wide spectrum of synaptic types is likely to exist [33,75,84]. The present classification of synaptic transmission is based on the distinction between the one-to-one ('closed' state) and one-to-many ('open' state) synapse, which assure the WT and VT, respectively (see Table 1 and Ref. [84]). Thus, the main feature of the VT-type synapse is the capability of permitting transmitter diffusion outside the synaptic cleft at biologically relevant concentrations.

Recent studies have shed some light on the kinetics of transmitter diffusion in central synapses [8,19,23,33,37]. Hippocampal glutamatergic synapses are an example of central synapse which mostly functions in a closed state [84]. While extrasynaptic diffusion of glutamate is hindered by glial ensheathment of the synapse [18,54], its fast clearance is assured by specific carriers especially concentrated in the astroglia [19]. However, in certain physiological states [8,54] glutamate can diffuse outside active synapses and reach a concentration in the ECF sufficiently high to activate glutamate receptors outside the source synapse. This phenomenon, called 'spill-over' has also been observed in other amino acidergic synapses [8,26,46].

On the other hand, extra-synaptic diffusion of the transmitter may be a common phenomenon in many central synapses (for a thorough discussion, see Refs. [8,84]). The possibility that DA synapses function as open synapses is discussed above (see Section 2). Many features of peptidergic synapses (e.g., preferential extrasynaptic location of releasing sites, absence of reuptake mechanisms, preferential extrasynaptic location of high affinity receptors [14,43,51,65,66,76]) indicate that they also often work as open synapses.

It must, however, be considered that a synapse can switch from a closed to an open state, and vice versa, in different functional states. In addition, a synapse containing several transmitters can work as an open synapse for one transmitter and as a closed synapse for another (see e.g., the case of ATP and noradrenaline in sympathetic synapses [75]).

4. Differential functional features of WT and VT: models of VT-based computation

As pointed out in this and previous papers [1–5,29–31,84] intercellular transfer of information via WT or VT is clearly different. At first sight, VT has several drawbacks over WT, since it is markedly slower (Table 2) and less safe (as it can be influenced by many sources of noise present in the ECF). However, a more penetrating analysis shows that VT and WT are in fact complementary and suited for different functions (Table 3). For instance, VT is not dependent on the existence of encumbrant intercellular links and has no space limitations. In a WT circuit, a source cell must send a process (a dedicated line) to close proximity of every target cell. Thus, every communication channel occupies some space. The structural and energetic cost of communication lines is a problem which has to be faced by telephonic communication, too. The common solution in telephonic networks is to avoid connection of all sources with all targets but rather to create a few long distance lines connecting nodes in turn connected with local networks. In nodes a high degree of switching is required. Neuronal networks working via WT may be build according to similar principles. Instead, VT communication has no space requirement and may connect every source with every target (indeed in a bidirectional fashion) with no need of switching (Fig. 3).

4.1. Retrograde signals and volume learning

A physiological role for diffusible signals has been recently proposed in several models of neuronal circuits. Diffusible (VT) signals can be released by post-synaptic cells to modify as retrograde messengers the pre-synaptic cell function. This functional arrangement have been proposed to occur in several neural systems (see e.g., adenosine in striatum and ventral tegmental area [13,40]). Much work have been done on retrograde signals in hippocampal glutamatergic transmission, namely on the development of long term potentiation (LTP). Several studies have shown that some retrograde signals (nitric oxide, carbon oxide, arachidonic acid, platelet activating factor) contribute to the establishment of, at least some forms of, hippocampal LTP [6,53,81]. Among them NO has received particular attention.

NO is generated from L-arginine by NOS, which is highly enriched in nervous tissue. The prevalent forms of NOS in the neural cells are type I and III (so called neuronal and endothelial NOS, respectively), which are Ca^{2+}-calmodulin dependent [50]. A main stimulus for these enzymes is calcium increase induced by neuronal excitation, in particular by NMDA receptor activation. Once formed upon activation of NOS, NO diffuses outside the source cell and enters the target cell where it can activate a soluble form of guanylate cyclase [21]. Due to these properties, NO can work as a retrograde signal in glutamatergic synapses where it increases the release of glutamate from the presynaptic terminal [71].

A theory, termed 'volume learning' [32,56], has been proposed to model the action of VT signals, such as NO, in neuronal computation. A VT signal, through its diffusion in a local volume of tissue, forms a transient domain in which synaptic strengths can be modified. Interestingly, the rules for synaptic strength modification in the transient domain may be different from the standard hebbian rules. Hebbian rules hold that a synapse is strengthened when there is a temporal coincidence between pre- and post-synaptic activity. Montague and Sejinovski [56] propose a more complex scheme based on predictive learning rules

Table 2
Differential properties of WT and VT communication channels

	WT	VT
1. Type of signal	Ions (e.g., Ca^{2+}) and neurotransmitters (e.g., amino acids)	Ions (e.g., K^{+}, H^{+}), neurotransmitters (e.g., monoamines), neuropeptides, gases, neurosteroids
2. Chemical signal concentration at receiver	Usually high (μM)	Usually low (nM)
3. Receiver affinity for chemical signal	Usually low (high nM–μM)	Usually high (pM–low nM)
4. Transmission code[a]	Rate and temporal code	Rate code
5. Transmission delay	Low (ms)	High (s–min)

For a discussion, see text and Refs. [4,84].
[a] Rate code models hold that changes in the firing rate signal an event (a train of impulses) and in the VT can be equated to the arrival of the VT-signal at the receptor at suprathreshold concentration. The average rate of impulses in the train codes the strength of the stimulus and in the VT can be equated to the VT-signal concentration at the target receptor level. Temporal codes hold that information is encoded by the precise occurrence of spikes over time. This constraint makes it unlikely that this type of code is used in VT.

Table 3
Differential properties of WT and VT circuits

	WT	VT
1. Cell composition	Usually only neurons or only astrocytes	Any cell type
2. Divergence[a]	Low	Potentially high
3. Type of connectivity[a]	Preferentially serial	Preferentially parallel
4. Space filling[a]	High	Low
5. Time scale	ms–s	s–min
6. Biological effect	Typically phasic	Typically tonic

For a discussion, see text and Refs. [4,84].
[a] In a WT circuit, a source cell must send a process (a dedicated line) to close proximity of every target cell. Thus, every communication channel occupies some space (space filling). Indeed, the number of targets of a single cell (i.e., divergence) is relatively limited (an average neuron is supposed to have 10^2–10^3 synaptic contacts). On the contrary, VT-signals released in the ECF by a single cell can, in principle, reach any cell in the brain practically without any space filling. Finally, the difference in single cell divergence makes WT and VT circuits more suited for serial and parallel treatment of information, respectively.

which are sensitive to the temporal order of input activities: synapses are strengthened if active during phases of high local concentration of a diffusible substance, but weakened if active during phases of low concentration.

Synaptic learning related to diffusible signals may further differ from classic hebbian learning. In fact, synaptic specificity can also be lost as the molecule diffuses from active to inactive target cells, and may influence synaptic strengths therein [69]. Some evidence for this phenomenon has been obtained for NO-dependent LTP [70]. In these experiments, LTP was elicited in CA1 pyramidal neurons by pairing Schaeffer collateral activation with depolarization of the target (paired) neuron and blocked by injecting an NOS inhibitor in the paired neuron. Intracellular recording of non-paired neurons located around 150 (but not 500) μm from a paired neuron, showed that LTP was also

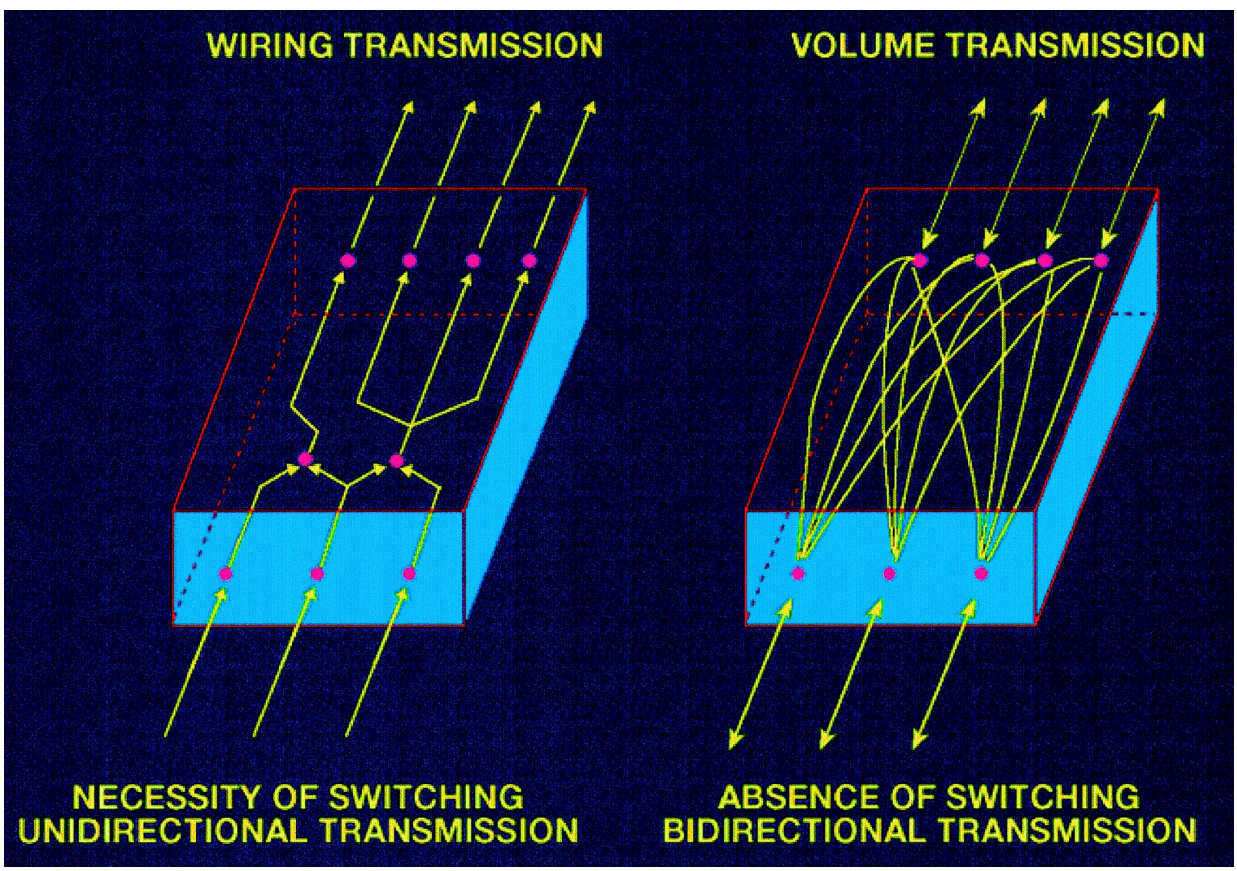

Fig. 3. Schematic representation of some features of the connectivity of WT-based and VT-based cellular circuits.

present in synapses contacting non-paired neurons. The absence of synaptic specificity in LTP has been confirmed by other groups (see e.g., Ref. [24]), although no attempt was made to identify the extracellular or intracellular mediator of the effect.

4.2. Reinforcement learning

Another paradigm in which diffusible signals have been implicated is reinforcement learning [9,44,61]. In this type of models, feedback from environment is assured by a 'critic' which sends to the circuit a global error (or reinforcement) signal whose value is a measure of the overall 'goodness' of the circuit outcome. Differently from the models incorporating retrograde VT signals described above, reinforcement learning models assume the presence of a third pathway besides the pre- and post-synaptic cell populations, which can vehiculate the environmental feedback onto the pre- and post-synaptic units. The feedback signal can transmit the reward itself (e.g., in associative reward–penalty algorithms) or the error in reward prediction (e.g., in temporal difference learning algorithms) [9,61]. In both cases, the global error signal must be delivered homogeneously to all modifiable synapses of the system (requirement of 'equal access', see Ref. [61]). It is obvious that this requirement is implemented with difficulty in a WT-based circuit, but can be easily met by VT signals. Accordingly, the best candidate transmitter for reward signals is DA in the mesostriatal system [44,57].

In this context it is interesting to notice that chemical neuroanatomy has given evidence for chemical compartments in striatum (called striosomes/matrisomes, patch/matrix etc. [2,5]) in which VT seems predominant. This brain structure contains a complex array of overlapping or complementary compartments characterized by high densities of specific transmitter releasing sites and/or receptors. Several lines of evidence, including the presence of transmitter–receptor mismatches in these compartments ([2,4,41,42] and see above), indicate that they may mainly function via the delivery of VT signals.

Much work is still needed to understand the relative importance of WT vs. VT for the function of transmitter-identified neural systems. The formal models summarised above (see Section 4.1 and Section 4.2) are starting to give us some hints on how VT-systems may interact with WT-systems. Notably, a common feature of the proposals regarding diffusible signals concerns their possibility of prolonging the narrow time window and disregarding the strict spatial relations between pre- and post-synaptic elements typical of WT. Again, WT and VT appear highly complementary as the absence of spatial (synaptic) and temporal (coincidence) specificity is compensated by the possibility of influencing in a homogeneous fashion a large number of targets (see e.g., problem of equal access) and the easier implementation of complex learning rules (e.g., temporal difference learning).

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Review

Neuromodulation of Spike-Timing-Dependent Plasticity: Past, Present, and Future

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Spike-timing-dependent synaptic plasticity (STDP) is a leading cellular model for behavioral learning and memory with rich computational properties. However, the relationship between the millisecond-precision spike timing required for STDP and the much slower timescales of behavioral learning is not well understood. Neuromodulation offers an attractive mechanism to connect these different timescales, and there is now strong experimental evidence that STDP is under neuromodulatory control by acetylcholine, monoamines, and other signaling molecules. Here, we review neuromodulation of STDP, the underlying mechanisms, functional implications, and possible involvement in brain disorders.

1. Introduction

Synaptic plasticity and neuromodulation are two brain mechanisms that together allow animals to adapt to environmental demands. However, these two mechanisms operate at different timescales. Whereas synaptic plasticity is the ability to make experience-dependent long-lasting changes in the strength of neuronal connections, neuromodulation refers to reversible changes in the functional properties of neurons and synapses, induced by the momentary release of specific signaling molecules, such as acetylcholine or monoamines. Thus, with its rapid induction and long duration, synaptic plasticity is a strong candidate to mediate synaptic remodelling during development, learning, and memory. Conversely, neuromodulation can adjust the neural circuits to accommodate immediate behavioral requirements. Neuromodulation also sets the conditions for induction of synaptic plasticity; thus, these mechanisms act in concert to flexibly respond to behavioral demands.

Synaptic plasticity enables adaptive experience-based brain development, learning, and memory as well as response to brain injury and neurologic disease. Much research into synaptic plasticity is inspired by the ideas formulated by Donald Hebb. He postulated that "When an axon of cell A […] repeatedly or persistently takes part in firing [cell B], some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" (Hebb, 1949). Experimental support for Hebbian plasticity is strong. Repeated activation of a presynaptic cell A immediately *before* spikes in a postsynaptic cell B induces synaptic strengthening, known as timing-dependent long-term potentiation (t-LTP). Hebb did not explicitly propose a rule for the reverse spike ordering, but experiments indicate that, at many synapses, repeated activation of a presynaptic cell A immediately *after* a postsynaptic cell B leads to timing-dependent long-term depression (t-LTD). Together, these synaptic learning rules are known as spike-timing-dependent plasticity (STDP; Figure 1; Bi and Poo, 1998; Debanne et al., 1998; Markram et al., 1997; Song et al., 2000). Such STDP is "Hebbian" because synaptic inputs that contribute to postsynaptic firing are strengthened. Hence, STDP captures the concept of causality in determining the direction of synaptic modification (Bi and Poo, 1998; Masuda and Kori, 2007; Vogt and Hofmann, 2012). The temporal order of spiking activity is significant, as it provides a mechanism for storing sequences of neuronal activity, creating and stabilizing activity patterns in neural assemblies, and regulating total levels of synaptic drive (Paulsen and Sejnowski, 2000; Song et al., 2000). Spike-timing-dependent plasticity is now widely considered a biologically plausible model for synaptic modifications occurring *in vivo* (Caporale and Dan, 2008).

In its classic form, STDP is local in nature, involving only the presynaptic and postsynaptic neurons (and possibly supporting glial cells), detecting the timing of arrival of presynaptic action potentials at the bouton and backpropagating postsynaptic action potentials in the dendrite (Stuart and Sakmann, 1994), making it a computationally elegant model for investigating plasticity during naturally occurring behaviors. Indeed, STDP can be observed in response to natural patterns of spiking activity (Paulsen and Sejnowski, 2000; Froemke and Dan, 2002). STDP has been demonstrated *in vitro* and *ex vivo* at both excitatory (Markram et al., 1997; Bi and Poo, 1998; Debanne et al., 1998) and inhibitory synapses (Ormond and Woodin, 2009; Ahumada et al., 2013; Takkala and Woodin, 2013) across different brain regions in a range of species, from locust and *Xenopus* through rodents to non-human primates and humans (Zhang et al., 1998; Meredith et al., 2003; Testa-Silva et al., 2010; Huang et al., 2014; Verhoog et al., 2016). Moreover, its physiological relevance has been assessed *in vivo* (Zhang et al., 1998; Yao and Dan, 2001; Meliza and Dan, 2006; Jacob et al., 2007; Dahmen et al., 2008; Schulz et al., 2010; Cui et al., 2018). Beyond the initial characterization of the Hebbian STDP time windows, it has emerged that the quantitative rules governing STDP vary; synapses with anti-Hebbian STDP (where the sign of plasticity is reversed in comparison to Hebbian STDP) and with symmetric STDP (where the sign of plasticity is uniform across the entire STDP time window) have also been reported (Bell et al., 1997; Egger et al.,

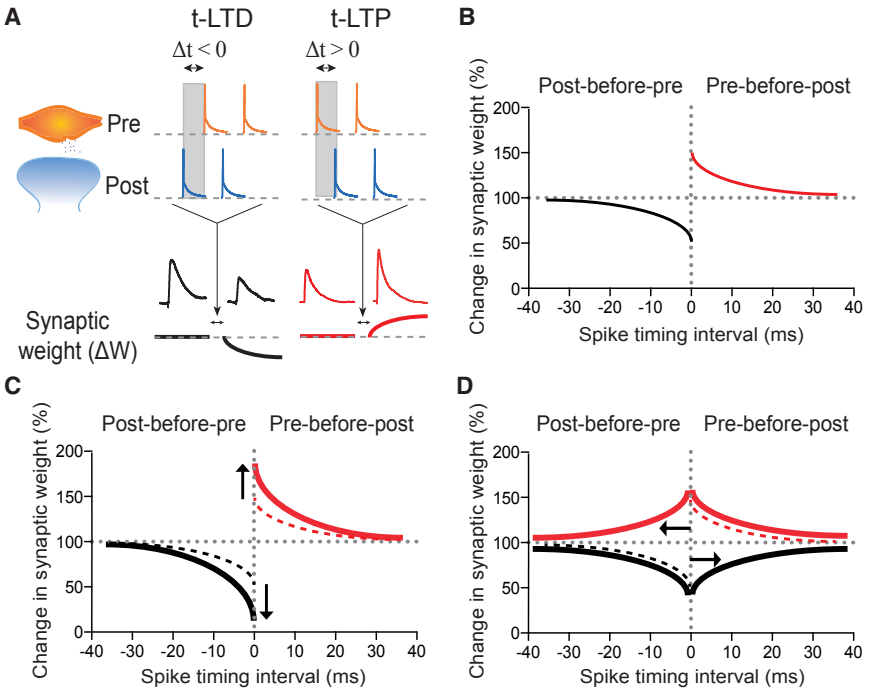

Figure 1. Induction and Expression of Spike-Timing-Dependent Plasticity (STDP)

(A) After a stable baseline period, STDP is typically induced by repeated pairings of single presynaptic and postsynaptic spikes. In its classic form, STDP depends on the order and millisecond-precision timing of spikes: multiple pre-before-post spike pairings induce timing-dependent long-term potentiation (t-LTP), whereas post-before-pre pairings induce timing-dependent long-term depression (t-LTD). The magnitude of change, as an indicator of synaptic plasticity, is defined as a percentage change in synaptic weight from baseline.

(B) The classic Hebbian STDP window: induction protocols with positive (pre-before-post) spike-timing intervals induce synaptic potentiation; protocols with negative (post-before-pre) spike-timing intervals induce synaptic depression.

(C and D) The relative spike timing is not the sole determinant governing timing-dependent plasticity. Instead, STDP is malleable. Both the magnitude (C) and the temporal requirements for STDP (D) can be modulated.

1999; Wang et al., 2000; Fino et al., 2005; Letzkus et al., 2006; Tzounopoulos et al., 2007; Mishra et al., 2016). Thus, STDP is a versatile mechanism with diverse properties allowing for flexible synapse-specific learning rules (Fino et al., 2008, 2010; Tzounopoulos et al., 2004, 2007).

However, the local nature and millisecond timescales for association of pre- and postsynaptic spikes in STDP raise two fundamental problems in understanding its relation to behavior. First, how can neural events preceding and following the plasticity-inducing event influence the outcome of synaptic plasticity, and, second, how can the millisecond timescales of STDP be reconciled with the much longer delays of behaviorally relevant signals? Neuromodulation offers an attractive solution to both these problems. Neuromodulator activity is different in sleep and wake, and different in different stages of sleep and different levels of vigilance in wakefulness (Lee and Dan, 2012). Moreover, the specific release of neuromodulators occurs in a wide range of behavioral situations, including during attention and arousal (Aston-Jones and Bloom, 1981; Aston-Jones and Cohen, 2005; Chamberlain and Robbins, 2013), during exposure to novelty (Wilson and Rolls, 1990), and when an unexpected reward is encountered (Schultz et al., 1993, 1997). Moreover, there is strong experimental evidence that STDP is under neuromodulatory control (Seol et al., 2007; Pawlak et al., 2010). An important reason why neuromodulation may be able to span the timescales is that modulation of STDP occurs not only during induction of plasticity but may precede it (act prospectively) or follow the induction period (act retrospectively).

Here, we review experimental evidence on the neuromodulation of STDP, the underlying mechanisms, and the possible functional and clinical relevance. We will restrict ourselves to reviewing neuromodulation of STDP and not other forms of plasticity, such as high-frequency and low-frequency stimulation-induced LTP and LTD, respectively (Bliss and Lomo, 1973; Dudek and Bear, 1992; Mulkey and Malenka, 1992), or various forms of homeostatic plasticity (Turrigiano et al., 1998). We will argue that STDP is controlled not only by the neuromodulatory state during spiking activity of pre- and postsynaptic neurons, but also by neuromodulation prior to or after the plasticity-inducing event. This places constraints on the possible underlying mechanisms. The striking versatility and state dependence of STDP rules make them particularly attractive synaptic mechanisms for learning and memory and may help explain synaptic dysfunction in neuropsychiatric, neurodevelopmental, and neurodegenerative disorders (Figure 2).

2. Neuromodulation of STDP

Spike-timing-dependent plasticity is shaped by various intrinsic and extrinsic factors including the history of activity at the synapse (Larsen et al., 2014), dendritic location (Froemke et al., 2005; Letzkus et al., 2006; Sjöström and Häusser, 2006), astrocytes (Valtcheva and Venance, 2016), activity at adjacent synapses (Harvey and Svoboda, 2007), and availability of neuromodulators (Seol et al., 2007). Although local signaling molecules, such as endocannabinoids (Sjöström et al., 2003; Bender et al., 2006; Tzounopoulos et al., 2007; Fino and Venance, 2010; Cui et al., 2015, 2016) and brain-derived neurotrophic factor (Edelmann et al., 2014, 2015; Lu et al., 2013), as well as blood-borne steroid hormones, can influence plasticity, here we focus on the neuromodulation of STDP by long-range neural projections, whose activity is associated with distinct behavioral states *in vivo* and play a pivotal role in mediating higher cognitive functions (Pawlak et al., 2010). These include the cholinergic, dopaminergic, noradrenergic, serotonergic, and histaminergic systems, mediated by neurons with cell bodies located in specific subcortical nuclei and with diffuse projections to the thalamus and cerebral cortex (Gu, 2002). Several of these neurons

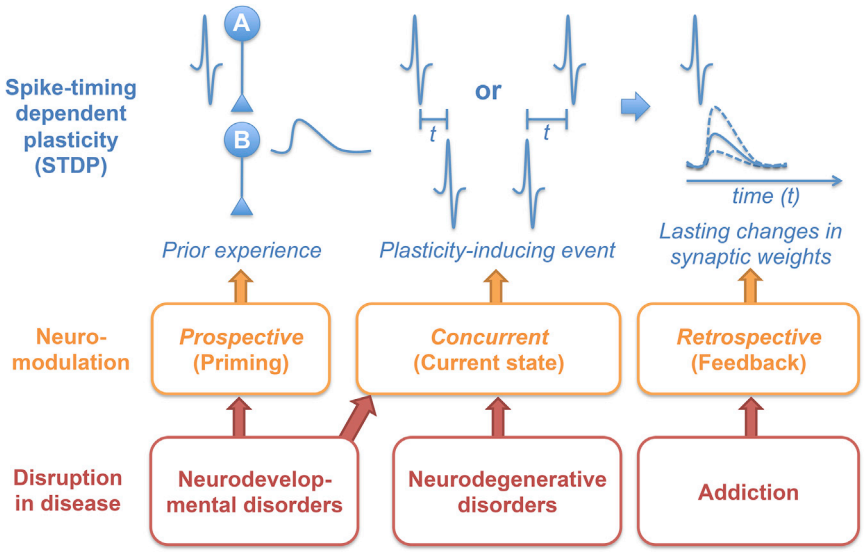

Figure 2. Neuromodulation of STDP in Behavior and Disease

STDP (blue) can be conceptualized in three stages: the neuronal activity prior to the plasticity-inducing event, the spiking-timing event that induces plasticity, and the expression of plasticity seen as a long-lasting change in synaptic weights. Neuromodulation of STDP (orange) occurs at all three stages leading to priming of synaptic plasticity by prior experience (prospective neuromodulation), modulation of STDP rules at the time of induction (concurrent neuromodulation), and modification—or even reversal—of synaptic weights based on behavioral outcomes after the plasticity-inducing event (retrospective neuromodulation). Altered neuromodulation of STDP may play a key role in neurologic and psychiatric disorders (red) and may serve a target for developing new treatments.

show co-transmission with glutamate (Trudeau and El Mestikawy, 2018) or GABA (Granger et al., 2016). The computational advantages of using neuromodulation as a third, global factor in Hebbian plasticity have recently been reviewed (Frémaux and Gerstner, 2016; Pedrosa and Clopath, 2017; Foncelle et al., 2018; Gerstner et al., 2018) and will not be explicitly discussed here.

2.1. Prospective Neuromodulation of STDP by Prior Neuronal Activity

STDP is a powerful mechanism for computation and information processing in the brain, in part because of the variation in induction requirements for STDP at different synapses on to the same cell, between different brain regions, and over postnatal development. Experience-induced plasticity during development as well as in the adult depends not only on the patterns of afferent input, but also on modulatory signals related to the behavioral and emotional state of the animal (Bear and Singer, 1986; Kilgard and Merzenich, 1998; Gu, 2002; Conner et al., 2003; Hu et al., 2007). Both previous synaptic activity and neuromodulatory events may influence subsequent induction of plasticity. This is known as "metaplasticity" (i.e., the plasticity of synaptic plasticity; Abraham and Bear, 1996), or priming of synaptic plasticity (Seol et al., 2007). Indeed, neuromodulatory inputs can prime synapses for the induction and expression of STDP (Seol et al., 2007; Edelmann and Lessmann, 2011; Sugisaki et al., 2011), and both cholinergic and adrenergic mechanisms have been reported to prime synaptic plasticity. The cholinergic agonist McN, acting on muscarinic acetylcholine receptors (mAChRs), was able to prime timing-dependent LTD, an effect that lasted for 30 min (Seol et al., 2007). The activation of nicotinic acetylcholine receptors (nAChRs) also leads to priming effects on STDP. While acute nAChRs activation in the medial prefrontal cortex (mPFC) of adolescent rats decreases the ability of layer (L)2/3 synapses to exhibit t-LTP shortly after nicotine exposure (Couey et al., 2007; Goriounova and Mansvelder, 2012), it facilitates t-LTP in adult rats that received nicotine treatment during adolescence (Goriounova and Mansvelder, 2012). Thus, nicotine's effect on the ability of cortical synapses to undergo subsequent plasticity depends on the time after exposure (Goriounova and Mansvelder, 2012). The beta-adrenergic receptor (β-AR) agonist isoproterenol similarly primes induction of timing-dependent LTP, an effect that lasts for at least 40–50 min (Seol et al., 2007). Conversely, in L2/3 of visual cortex, transient activation of α- and β-adrenergic receptors can suppress LTP and LTD, respectively, for up to an hour, leading to a push-pull mechanism for modulation of STDP, in which α-adrenergic receptor (α-AR) activation promotes subsequent induction of t-LTD and suppresses t-LTP, while β-AR activation promotes t-LTP and suppresses t-LTD (Huang et al., 2012). Thus, prior neuromodulatory events may enable or disable subsequent timing-dependent plasticity with a duration that can vary from short experience-dependent modulation (Huang et al., 2012) to lasting changes that occur during development (Banerjee et al., 2009; Goriounova and Mansvelder, 2012).

2.2 Concurrent Neuromodulation of STDP

Activation of neuromodulatory inputs at the time of presynaptic and postsynaptic spiking activity can strongly influence plasticity. Thus, both the induction requirements and the polarity of plasticity are controlled by neuromodulation.

2.2.1 Neuromodulatory Control of the Induction Requirements of STDP. The cholinergic system affects the induction of STDP via activation of ionotropic nAChRs and metabotropic mAChRs. In layer (L)5 pyramidal neurons of mouse mPFC, nicotine, a cholinergic agonist acting on nAChRs, elevates the threshold for STDP induction by increasing the amount of postsynaptic activity necessary to induce plasticity. This effect is likely mediated by activation of nAChRs on GABAergic interneurons (Couey et al., 2007). Activation of muscarinic M_1 receptors promotes t-LTD and suppresses t-LTP in slices from visual cortex (Seol et al., 2007) and the CA1 region of the hippocampus (Brzosko et al., 2017) and prevents the induction of postsynaptic disinhibition-mediated t-LTP (Ormond and Woodin, 2009; Takkala and Woodin, 2013). mAChRs are required for t-LTD at inhibitory GABAergic synapses (Ahumada et al., 2013). However, mAChRs have also been reported to facilitate t-LTP (Sugisaki et al., 2016) and other types of

potentiation, e.g., that induced by theta burst stimulation (Buchanan et al., 2010).

In contrast, noradrenaline (NA) promotes t-LTP in the hippocampus. Activation of β_2-ARs widens the time window for t-LTP induction in both CA1 hippocampal neurons (Lin et al., 2003; Liu et al., 2017) and L2/3 pyramidal cells of the rodent and primate visual cortex (Seol et al., 2007; Huang et al., 2012, 2014) as well as cortical interneurons (Huang et al., 2013). Moreover, since endogenous NA can act on both α- and β-ARs, with different affinities for NA, the outcome of such neuromodulation may be concentration dependent. While a high concentration of NA has been found to enable bidirectional STDP, a low concentration leads to a depression-only state (Salgado et al., 2012).

Endogenous dopamine acting on type 1 dopamine receptors (D_1Rs) is required for t-LTP at Schaffer collateral–CA1 synapses in acute hippocampal slices from juvenile rats (Edelmann and Lessmann, 2011). Evidence from dissociated hippocampal cell cultures suggests that the effect of dopamine on t-LTP may be due to a reduction in the threshold for induction of plasticity, as activation of D_1Rs reduced the number of spike pairings needed to induce t-LTP (Zhang et al., 2009). These effects appear to be specific to dopamine as activation of β-ARs, although acting via the same signaling cascade as D_1Rs (cAMP/PKA), could not restore t-LTP after dopamine depletion (Edelmann and Lessmann, 2011). Dopamine also dramatically widens the time window for detecting coincident spiking in the pre- and postsynaptic cells, facilitating the induction of t-LTP. Thus, D_1R activation in both L5 of the prefrontal cortex (Ruan et al., 2014; Xu and Yao, 2010) and hippocampal cultures (Zhang et al., 2009) allows t-LTP induction at substantially longer, normally ineffective, spike-timing intervals. In the prefrontal cortex, however, this D_1R-mediated effect occurs only at pharmacologically isolated excitatory synapses, and the cooperation between D_1-like and D_2-like receptors, acting in separate glutamatergic and inhibitory circuits, is needed to effectively broaden t-LTP window under intact inhibition (Xu and Yao, 2010). Dopamine, acting via D_2Rs, suppresses feed-forward inhibition to enable successful t-LTP induction in L5 of the prefrontal cortex (Xu and Yao, 2010). A similar mechanism was reported in the amygdala (Bissière et al., 2003). Also in the amygdala, at the synapses between the lateral nucleus and dorsal intercalated cell mass (ITC), t-LTD requires the activation of, most likely presynaptic, D_4Rs and a concomitant increase in inhibition from dorsal ITC neurons (Kwon et al., 2015).

In the striatum, the effect of dopamine is independent of GABAergic transmission (Pawlak and Kerr, 2008; Shen et al., 2008). In dorsal striatum under $GABA_A$ receptor blockade, inhibiting D_1Rs prevents t-LTP as well as t-LTD (Pawlak and Kerr, 2008). While blocking D_2Rs hastens the onset of the potentiation (Pawlak and Kerr, 2008), D_2Rs on cortical terminals are required for endocannabinoid-dependent (eCB)-t-LTP expression induced by few coincident pre- and postsynaptic spikes ($\sim$5 to 15 pairings; Xu et al., 2018). In the ventral tegmental area (VTA), endogenous dopamine acts via D_1-like receptors (most likely of the D_5 subtype) to permit t-LTP in the dopaminergic cells (Argilli et al., 2008).

2.2.2 Neuromodulatory Control of the Polarity of STDP. Perhaps the most striking demonstration of the effect of neuromodulation on STDP is how the neuromodulatory state can determine whether the same timing between the activity of the pre- and postsynaptic neurons strengthens or weakens the synaptic weights. This reversal in the sign of plasticity can be seen in dissociated hippocampal cell cultures, where application of exogenous dopamine during STDP induction leads to robust t-LTP with spike timing that would induce t-LTD in control conditions. This effect was mediated by D_1Rs, but not D_2Rs (Zhang et al., 2009). Similarly, in the CA1 region of murine acute hippocampal slices, endogenous dopamine, presumably released during the plasticity-inducing event, as well as exogenous dopamine applied during pairings of postsynaptic action potentials before presynaptic action potentials (post-before-pre pairing) also induced t-LTP rather than t-LTD (Brzosko et al., 2015). In the dentate gyrus, during inhibition of D_1Rs, both narrow post-before-pre and pre-before-post spike-timing intervals induced t-LTD, while activation of D_1Rs with the same pairing protocols induced t-LTP instead (Yang and Dani, 2014). A similar effect was observed in L5 of the prefrontal cortex, where dopamine application enabled t-LTP with spiking timing that would otherwise induce t-LTD (Ruan et al., 2014). Unlike dopamine-enabled t-LTP with a pre-before-post protocol (Xu and Yao, 2010), this dopamine-enabled t-LTP with post-before-pre pairings occurred under intact inhibitory transmission and only required D_1R activation in the excitatory prefrontal circuitry (Ruan et al., 2014). In contrast, inhibition of D_2Rs, but not D_1Rs, during a protocol for induction of eCB-dependent t-LTP at synapses on striatal medium-sized spiny neurons resulted in t-LTD instead (Cui et al., 2015).

Both adrenergic and cholinergic stimulation can also change the sign of STDP. Application of a β-AR agonist restored the classical STDP window by changing pre-before-post pairing-induced t-LTD into t-LTP in L2/3 of the prefrontal cortex (Zaitsev and Anwyl, 2012). Conversely, activation of nAChRs using nicotine during STDP induction changed t-LTP into t-LTD in L5 of prefrontal cortex (Couey et al., 2007). A similar effect occurs with activation of mAChRs in the dorsal cochlear nucleus; synaptic or pharmacological activation of postsynaptic M_1/M_3 mAChRs changes postsynaptic Hebbian t-LTP to presynaptic anti-Hebbian t-LTD (Zhao and Tzounopoulos, 2011). Activation of mAChRs also changes pre-before-post spike pairing-induced t-LTP into t-LTD at the Schaffer collateral–CA1 synapses in mouse hippocampus (Brzosko et al., 2017). Remarkably, activation of mAChR (Adams et al., 2004; Sugisaki et al., 2011, 2016), or nAChR (Sugisaki et al., 2016), can also change t-LTD into t-LTP at the Schaffer collateral–CA1 synapses in rat hippocampus (Sugisaki et al., 2016), as in L2/3 of the rat prefrontal cortex (Zaitsev and Anwyl, 2012). Thus, cholinergic stimulation appears to be capable of bidirectional modulation of plasticity at CA3-CA1 hippocampal synapses.

Layer-specific cholinergic modulation is seen in neocortical STDP. Brief light-evoked cholinergic signals prevent t-LTP in L2/3 while facilitating t-LTP in L6 in mice (Verhoog et al., 2016). Interestingly, similar cholinergic modulation of STDP was also observed in human neocortex from surgically resected brain tissue from epilepsy patients (Verhoog et al., 2016). The bidirectional effects of cholinergic modulation on STDP depend on the concentration of agonist and the specific cholinergic receptor

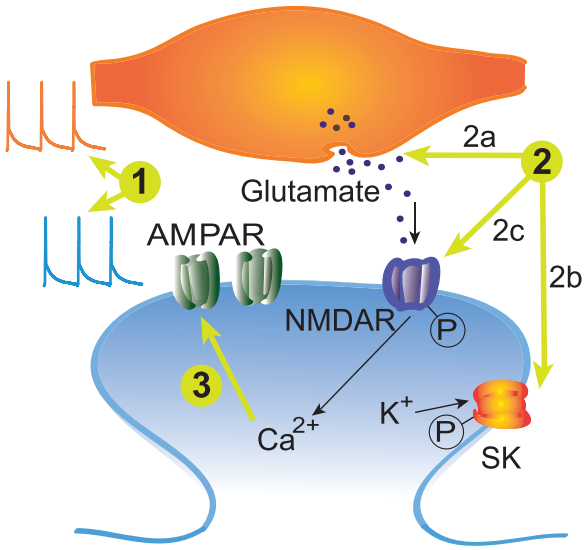

Figure 3. Cellular Mechanisms Underlying Neuromodulation of STDP
Neuromodulatory inputs at synapses can alter STDP rules via three classes of mechanisms: (1) alteration of neuronal excitability and spiking dynamics; (2) gating of synaptic function, including control of presynaptic glutamate release (2a), regulation of postsynaptic membrane potential via potassium channels (SK; 2b), and availability of co-agonist at NMDA receptors (2c); and (3) regulation of intracellular signaling cascades involved in synaptic plasticity.

subtypes activated (Auerbach and Segal, 1996; Sugisaki et al., 2011; Dennis et al., 2016). Cholinergic modulation of STDP also exhibits a remarkable temporal precision (Ge and Dani, 2005; Gu and Yakel, 2011). Single pulses of the septal cholinergic input can directly induce either potentiation or depression of the Schaffer collateral–CA1 synaptic plasticity depending on the millisecond-range timing of cholinergic input relative to the Schaffer collateral input (Gu and Yakel, 2011). Thus, the precise timing of neuromodulator action can be critical for the action of neuromodulators on STDP.

2.3 Retrospective Neuromodulation of STDP

One of the challenges to understanding learning at the cellular scale is that mechanisms for inducing changes in synaptic weights depend on spike-timing in milliseconds, while the change in synaptic weights occurs more slowly (over minutes to tens of minutes) and may need to be modified based on further information, for example behavioral outcome evaluation. Dendritic plateau potentials can extend the time window of activity between pre- and postsynaptic neurons to a few seconds (Bittner et al., 2017), but behavioral outcomes are often not available until several seconds or minutes after the initial experience. Neuromodulation provides a mechanism for making adjustments to the synaptic weights up to several minutes after the STDP-inducing event. This may be particularly important for biological reinforcement learning (4.2. Reinforcement Learning).

Previously, neuromodulators acting within a delay time window of up to 2 s were shown to affect timing-dependent plasticity, first in the locust (Cassenaer and Laurent, 2012), and later in rats (Fisher et al., 2017) and mice (Yagishita et al., 2014; Shindou et al., 2019). In locust, at the synapses between the Kenyon cells and the β-lobe, delivery of a brief injection of the reinforcement signal octopamine after spike pairings alters the outcome of STDP such that the synapses invariably become weaker, even under conditions in which they would normally have grown stronger. Crucially, the action of octopamine was shown to be specific to synapses that had undergone associative changes, even though its release is diffuse and delayed relative to the conditioned stimuli (Cassenaer and Laurent, 2012). Similarly, a recent study in mouse striatal medium spiny neurons tested the effects of a physiologically relevant phasic release of dopamine induced by the optogenetic stimulation of dopaminergic fibers from the VTA. The authors found that dopamine promotes robust spine enlargement when acting immediately after the induction of STDP (Yagishita et al., 2014).

STDP is modulated *in vivo* by physiologically relevant, visually evoked activation of afferent networks following a pairing protocol with a delay of 0.25 s in striatal neurons (Schulz et al., 2010). Similarly, sensory experience (light flash to a rat's contralateral eye) applied 1 s after STDP pairings, followed by electrical stimulation in substantia nigra pars compacta after a further 1 s, resulted in significant bidirectional corticostriatal synaptic plasticity. Pre-before-post pairings followed by conditioned light stimulus induced synaptic potentiation while post-before-pre pairings followed by the same reinforcement protocol induced synaptic depression. Conditioned light was shown to modulate STDP via dopamine (D_1) and adenosine (A_{2A}) receptors (Fisher et al., 2017). Phasic dopamine release at different time points before and after the STDP protocol induced t-LTP, even up to 2 s after the cessation of presynaptic cortical and postsynaptic striatal pairing activity given a period free of glutamatergic excitation (Shindou et al., 2019). In the mPFC—another important projection area of the dopaminergic system, which is involved in detecting reward—dopamine induced synaptic potentiation within a delay on the scale of seconds following the normally ineffective pre-before-post pairing protocol at L2/3 synapses (He et al., 2015). STDP can also be retrospectively modulated by other neuromodulators. At L2/3 synapses in the visual and prefrontal cortices, the application of distinct and specific monoamine neuromodulators following normally ineffective STDP pairing protocols results in robust t-LTP or t-LTD (He et al., 2015). While NA retrospectively enables the pre-before-post-conditioned pathway to express t-LTP, serotonin enables the post-before-pre-conditioned pathway to express t-LTD with otherwise ineffective pairing protocols (He et al., 2015).

The timing rules for modulation vary depending on neuromodulator, brain region, and species. The narrow temporal detection window of up to 2 s (Yagishita et al., 2014; Fisher et al., 2017) cannot account for behavioral studies of response acquisition with an extended reinforcement delay of 1–40 s in rats and pigeons (Lattal and Gleeson, 1990; Sutphin et al., 1998), rhesus monkeys (Galuska and Woods, 2005), and humans (Okouchi, 2009). Longer delays, on the order of minutes, however, were effective for dopamine in the hippocampus. It was demonstrated that dopamine can retroactively modulate STDP with an extended delay of at least 1 min (Brzosko et al., 2015). In the CA1 of acute hippocampal slices, activation of DARs after the pairing protocol converted both conventional t-LTD (post-before-pre pairing; Brzosko et al., 2015) and acetylcholine-facilitated LTD

(pre-before-post pairing protocol; Brzosko et al., 2017) into synaptic potentiation. This conversion of t-LTD into t-LTP was dependent on afferent synaptic activity, suggesting that the conversion can occur only at synapses that are reactivated following the initial pairing event (Brzosko et al., 2015).

Almost everything we know about neuromodulation of STDP originates from *in vitro* and *ex vivo* experiments. What will be important in the future is to investigate in what neuromodulatory state synapses are in the intact brain during different behavioral states. This is now possible due to the development of new techniques, in particular optogenetics, which enables cell-type-specific activation of afferent input to individual cells *in vivo* (González-Rueda et al., 2018).

3. Mechanisms of Neuromodulation

Multiple mechanisms contribute to the control of STDP by neuromodulation. First, at the network level, neuromodulation alters the excitability and spiking dynamics of neural circuits, thus determining whether the pre- and postsynaptic spiking requirements for inducing STDP are met or not. Second, at the synaptic level, neuromodulation gates the synaptic activation of glutamate receptors, including NMDA receptors, which are crucial for both timing-dependent potentiation and depression. Third, at the intracellular signaling level, neuromodulation directly activates, inhibits, or regulates intracellular signaling cascades involved in synaptic plasticity (Figure 3).

3.1. Excitability and Spiking Dynamics

Neuromodulation controls the network states of thalamocortical and hippocampal networks. Neuromodulation is involved both in setting a global network state, such as regulating sleep and wakefulness, and in controlling local circuit activity, such as during selective attention. Acetylcholine, for example, is important for shifting network dynamics from sharp wave-ripples to theta-gamma oscillations in the hippocampus and from slow oscillations to desynchronized states in the neocortex (Alger et al., 2014). Some effects on cortical networks are mediated indirectly through changes in thalamic networks, which are also strongly influenced by neuromodulators and show dramatically different activity during sleep and awake states (McCormick, 1992). The mechanisms of neuromodulation involve both changes in intrinsic membrane properties of individual cells and changes in synaptic transmission (Lee and Dan, 2012; Nadim and Bucher, 2014). In general, both acetylcholine and monoamines increase the excitability of principal neurons by modulating various ion channels, particularly through changing the phosphorylation state of potassium channels or associated proteins (Nicoll, 1988; Storm, 1990). They also alter excitability in GABAergic interneurons, which may control action potential timing in principal cells (Cobb et al., 1995), and shift the excitability of different subclasses of interneurons (Bacci et al., 2005), thus changing the balance between somatic and dendritic targeting interneurons. Dendritic inhibition is important for controlling the extent of dendritic backpropagation of action potentials (Meredith et al., 2003) and was recently shown to control branch-specific dendritic responses during development (Yaeger et al., 2019).

3.2. Synaptic Gating of Plasticity

NMDA receptors are crucial for both t-LTD and t-LTP (Shipton and Paulsen, 2013). Modulation of NMDA receptors can therefore gate plasticity at individual synapses. The activation of NMDA receptors requires synaptically released glutamate and membrane depolarization to relieve the NMDA receptor channel of its voltage-dependent Mg^{2+} block (Bliss and Collingridge, 1993). Thus, both presynaptic release probability and membrane excitability can modulate the activation of NMDA receptors during pre- and postsynaptic spiking. In addition, NMDA receptor activation requires binding of a co-agonist, either glycine or D-serine. Although the co-agonist site of the NMDA receptor was initially assumed to be saturated *in vivo*, there is now strong evidence it is not, and this opens the possibility for an interesting neuromodulatory gating mechanism of plasticity (Johnson and Ascher, 1987; Schell et al., 1995; Henneberger et al., 2010).

Astrocytes may mediate some of the gating functions of neuromodulation. In addition to the pre- and postsynaptic neuronal elements, astrocytes are an integral part of the "tripartite synapse" (Araque et al., 1999) and appear to be important for both t-LTP (Yang et al., 2003) and t-LTD (Min and Nevian, 2012). They are therefore in a prime position to mediate neuromodulation of STDP. However, although Ca^{2+} signaling in astrocytes is required for several forms of LTP and LTD (Henneberger et al., 2010; Min and Nevian, 2012), the mechanism of astrocytic regulation of STDP is not clear. They have been suggested to supply glutamate for mGluR-dependent presynaptic potentiation in the hippocampus (Perea and Araque, 2007) and NMDA receptor-dependent presynaptic depression in the neocortex (Min and Nevian, 2012). They have also been suggested to supply the co-agonist at NMDA receptors during hippocampal LTP (Yang et al., 2003; Henneberger et al., 2010) and t-LTD (Andrade-Talavera et al., 2016); however, the identity and source of this co-agonist remain controversial, and might be different between synaptic and extrasynaptic receptors (Papouin et al., 2012), different at different synapses (Le Bail et al., 2015), and vary with NMDA receptor subunit composition (Papouin et al., 2012; Le Bail et al., 2015) and synaptic activity level (Li et al., 2013). In particular, it is currently unclear whether D-serine originates from neurons and/or glia (Wolosker et al., 2016; Mothet et al., 2019). Nevertheless, irrespective of the origin of the co-agonist, there is good evidence that long-range neuromodulators mediate some of their effects through local astroglia; for example, acetylcholine requires astroglial α7 nicotinic receptors for controlling synaptic D-serine levels (Papouin et al., 2017). In addition to this external modulation of NMDA receptor activity, the NMDA receptor itself is also subject to direct neuromodulation by phosphorylation (Chen and Roche, 2007).

3.3. Intracellular Signaling Pathways

Whereas priming and concurrent neuromodulation of STDP could be explained by changes in spike patterns and synaptic gating, retrospective effects are more likely to involve modulation of the intracellular signaling pathways that mediate plasticity. There is strong evidence that synaptic potentiation is mediated by postsynaptic Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), and at least some forms of LTD rely on a signaling pathway in which the Ca^{2+}/calmodulin-dependent phosphatase calcineurin dephosphorylates and inactivates inhibitor-1, which in turn increases protein phosphatase 1 activity (Mulkey et al., 1994). This establishes a push-pull mechanism of kinase-phosphatase activity which ultimately controls the

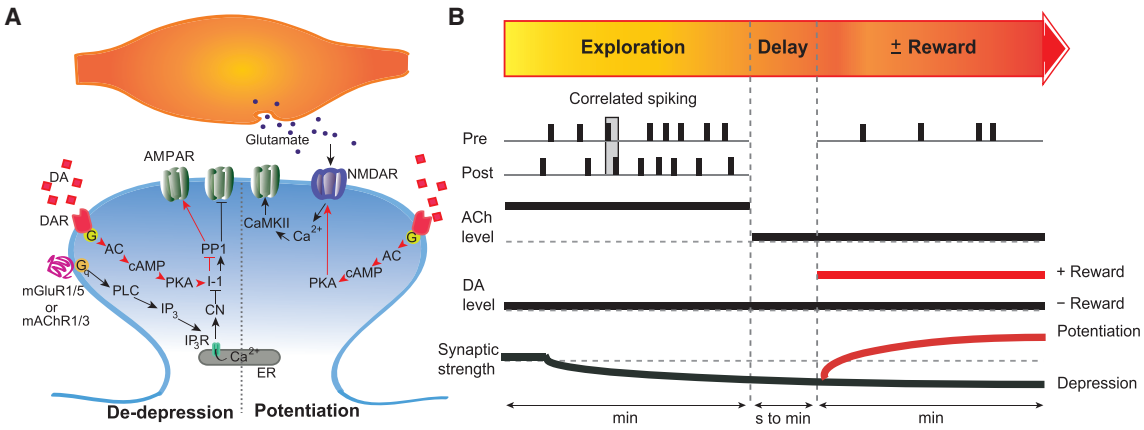

Figure 4. Retrospective Modulation of STDP at the Synaptic and Behavioral Level

(A) Schematic of the dopamine-induced conversion of t-LTD into t-LTP. De-depression (left of dotted line): Activation of dopamine receptors (DAR) stimulates adenylate cyclase (AC), increasing cAMP which activates protein kinase A (PKA). PKA phosphorylates inhibitor 1 (I-1), which reverses the PP1-induced dephosphorylation of synaptic AMPARs. Potentiation (right of dotted line): Activation of postsynaptic dopamine receptors stimulates AC, increasing cAMP, which activates PKA. PKA enhances Ca^{2+} influx leading to the insertion of AMPA receptors via Ca^{2+}-calmodulin-dependent protein kinase II (CaMKII). Arrows indicate activation/phosphorylation, blunt-ended lines indicate inhibition/dephosphorylation.

(B) Schematic of synaptic and behavioral timescales in reward-related learning. During exploration, the activity-dependent modification of synaptic strength due to STDP depends on the coordinated spiking between presynaptic and postsynaptic neurons on a millisecond timescale. The change in synaptic weights develops gradually on a scale of minutes. Increased cholinergic tone (ACh) during exploration facilitates synaptic depression. Reward, signaled by an increase in dopamine (DA), within a delay of seconds to minutes following exploration, converts synaptic depression into potentiation. (B) modified from Brzosko et al., 2017.

trafficking of postsynaptic AMPA receptors (Diering and Huganir, 2018). However, presynaptic forms of t-LTD have also been reported (Bouvier et al., 2018). A key insight from the specific receptor subtypes involved in neuromodulation of STDP reviewed in 2. Neuromodulation of STDP is that neuromodulators affect STDP induction and expression by acting on distinct signaling cascades involved in synaptic potentiation and depression (PKA pathway activated by stimulation of Gs-coupled receptors including D_1Rs and β-ARs, and PLC pathway activated by stimulation of Gq-coupled receptors including mAChRs and α1-ARs). A still-unresolved question is whether both potentiation and depression occur at the same synapses or at distinct ones. A detailed discussion of signaling pathways involved in neuromodulation of LTP and LTD is beyond the scope of this review, but a simple model to explain retrospective modulation of STDP is illustrated in Figure 4A.

4. Functional Implications

The release of neuromodulators occurs in a wide range of behavioral situations. Hence, the neuromodulatory influence on STDP can be associated with an equally extensive range of behavioral processes, including attention (Couey et al., 2007; Sugisaki et al., 2011; Sabec et al., 2018), reward-based learning (Pawlak and Kerr, 2008; Zhang et al., 2009; Hamilton et al., 2010; Xu and Yao, 2010; Ruan et al., 2014; Yang and Dani, 2014; Brzosko et al., 2015), and fear-conditioning (Bissière et al., 2003), as well as pathological states (Shen et al., 2008), such as addictive behaviors (Argilli et al., 2008). Despite the conceptual attractiveness of a link between behaviorally relevant neuromodulatory inputs and the cellular process of STDP, there is a scarcity of experimental data directly testing the relationship between neuromodulated-STDP and behavior. Here, we briefly discuss some examples of how neuromodulation of STDP may relate to specific cognitive processes.

4.1. Attention

Attention can refer to level of alertness, or vigilance, as well as the ability to focus on a particular stimulus or task, termed selective attention (Lee and Dan, 2012). Acetylcholine is essential for both vigilance and selective attention, and the release of acetylcholine is dynamically modulated to improve performance on tasks requiring sustained attention (Hasselmo, 2006; Wallace and Bertrand, 2013). One of the key features of selective attention is the ability to filter stimuli based on their relevance (Kirszenblat and van Swinderen, 2015). While behaviorally we associate improved performance due to selective attention with increased sensitivity to salient stimuli, this is achieved at the circuit level by suppressing activity from non-relevant stimuli (Kirszenblat and van Swinderen, 2015). This suppression of response to irrelevant stimuli can occur through modulating neuronal firing rates in target areas (Herrero et al., 2008) and decreasing the correlation of firing from non-salient stimuli (Kirszenblat and van Swinderen, 2015; Lee and Dan, 2012).

Early studies of cholinergic modulation of hippocampal LTP using frequency-based induction protocols suggested that acetylcholine may improve performance by facilitating LTP (Boddeke et al., 1992; Huerta and Lisman, 1995; Ovsepian et al., 2004; Shinoe et al., 2005; Buchanan et al., 2010; Connor et al., 2012; Digby et al., 2012; Dennis et al., 2016). However, STDP studies (reviewed in 2. Neuromodulation of STDP) revealed that activation of cholinergic receptors may instead play a role in suppressing the response to non-relevant stimuli, critical for selective attention. Acetylcholine biases neocortical and hippocampal STDP toward t-LTD (Seol et al., 2007; Brzosko et al., 2015), thus providing a mechanism for enhancing the

signal-to-noise ratio in cortical information processing and improving task-specific performance (Couey et al., 2007).

The prospective and concurrent effects of cholinergic modulation on STDP may be particularly relevant for understanding how selective attention improves performance on memory tasks. First, the pattern of acetylcholine release is finely tuned to specific aspects of learning and memory. Tonic levels of acetylcholine, coordinated between the prefrontal cortex and hippocampus, are maximal during training on a rewarded working memory task, while phasic acetylcholine release occurs only during retrieval and is localized to reward delivery areas without being contingent on trial outcome (Teles-Grilo Ruivo et al., 2017). Second, the polarity of acetylcholine-modulated plasticity can also depend on the concentration and specific cholinergic receptor subtype activated (Müller et al., 1988; Auerbach and Segal, 1996; Dennis et al., 2016). Distinct functions of nAChR subtypes, for example, allow bidirectional modulation of STDP at hippocampal-prefrontal synapses during different stages of long-term associative recognition memory tasks. Activation of $\alpha7$ nAChRs, which gate t-LTP, is required for encoding of associative recognition memory, while activation of $\alpha4\beta2$ nAChRs, which gate t-LTD, is critical for memory retrieval (Sabec et al., 2018). Third, the synaptic depression bias induced by acetylcholine can also be modulated retroactively. Subsequent application of dopamine after acetylcholine-induced t-LTD can retroactively convert synaptic depression into potentiation (Brzosko et al., 2017). This sequential neuromodulation of STDP may yield flexible learning, surpassing the performance of other reward-modulated plasticity rules (Zannone et al., 2018).

Noradrenergic neurons from locus coeruleus also play a key role in vigilance, attention, and emotional arousal, with low firing rates during drowsiness and slow-wave sleep, regular firing at quiet wakefulness, and burst-firing in response to arousing stimuli (Aston-Jones and Bloom, 1981). Hence, the finding that adrenergic signaling biases STDP toward t-LTP (Seol et al., 2007) and increases dendritic excitability to facilitate t-LTP induction (Liu et al., 2017) may provide an additional mechanism for how arousal facilitates learning.

Neuromodulation of STDP also provides a paradigm for future studies of cellular and circuit mechanisms underlying improved performance with attention. In particular, further *in vivo* STDP studies are needed in rodent models to examine the state-dependent cholinergic and adrenergic modulation of t-LTP and t-LTD. Using head-fixed rodents within virtual reality environments, it may also be possible to directly test the possible role of attention in neuromodulation of STDP for task performance.

4.2. Reinforcement Learning

By connecting the different timescales of the induction of plasticity (milliseconds) and behavioral outcomes (seconds or longer), studies of neuromodulation of STDP may also yield new insights into the cellular basis of learning, in particular biological reinforcement learning, which depends on the activity of reward-linked neuromodulators, in particular dopamine (Schultz et al., 1997; Suri and Schultz, 1999; Pan et al., 2005). One of the key outstanding questions—at the cellular level—is how neural networks, despite the temporal gap, identify which past network activities led to reward and which are irrelevant. This problem is referred to as the *distal reward problem* (Hull, 1943; Izhikevich, 2007) or *credit assignment problem* as it is known in machine learning literature (Minsky, 1963; Sutton and Barto, 1998). Reinforcement learning theory postulates the existence of a slowly decaying eligibility trace (Klopf, 1982) marking the memory parameters associated with an event or episode as eligible to undergo learning changes (Sutton and Barto, 1998). Neuromodulators including dopamine may then act on this eligibility trace produced by the spiking activity. Most studies on the effect of dopamine on STDP manipulated dopamine during the entire experiment (Pawlak and Kerr, 2008; Shen et al., 2008) or during the induction of STDP (Zhang et al., 2009) and did not investigate the effect of dopaminergic modulation on pre-existing synaptic plasticity. The finding that dopamine can retroactively convert depression to potentiation in the hippocampus provides evidence for dopamine as a positive reinforcement signal (Brzosko et al., 2015). Additionally, the effects on STDP of neuromodulators other than dopamine (e.g., NA and serotonin) suggest the existence of distinct eligibility traces for LTP and LTD in the cerebellum (Wang et al., 2000; Sarkisov and Wang, 2008) and cortex (He et al., 2015). The difference observed in the maximum time delay between the STDP induction protocol and the application of the neuromodulators for modulation to occur (5 s for t-LTP and 10 s for t-LTD) may impact the temporal dynamics and play a role in generating stable learning (He et al., 2015).

The activity dependence of the retroactive modulation of STDP is interesting in terms of credit assignment to the relevant synapses. In this scenario, it is not enough for the synapse to have been active during the behavioral episode, but the synaptic weights are updated only if the neurons are reactivated following the event (Brzosko et al., 2015). Interestingly, the reward signal dopamine does not only update the synaptic weights following reactivation of the synapse, but it also increases the frequency of reactivation events themselves, making them an interesting biological solution to the credit assignment problem. In the hippocampus, the signature of a reactivation event is the sharp-wave ripple, during which event-related spike sequences are replayed in forward or reverse order (O'Neill et al., 2010; Foster, 2017). Both reward itself (Singer and Frank, 2009) and optogenetic activation of dopaminergic neurons in the VTA (McNamara et al., 2014), which project to the hippocampus, increase reactivation events. Interestingly, reward appears to selectively increase reverse order replay events (Ambrose et al., 2016), and thus may potentiate those synapses that have undergone t-LTD during previous behavior. In this way, the combination of dopamine and reactivation may strengthen a trace of multiple synapses in a network if a reward is encountered, possibly converting a repellor network induced by cholinergic depression, which would favor exploration, into an attractor induced by dopaminergic potentiation, which would favor exploitation (Figure 4B). A next step could be to investigate whether retrospective modulation of STDP can alter the synaptic efficacy based on behavioral outcome *in vivo*. It would be interesting to test whether the combination of reactivation and dopamine release could switch the polarity of synaptic plasticity only at synapses relevant to the previous few minutes of experience.

4.3. Memory Consolidation

Sleep is critical for memory consolidation (Kandel, 2014; Dudai et al., 2015); however, the precise mechanisms remain unknown.

Consolidation can be considered at the synaptic and systems levels, and there is debate as to what plasticity rules underlie memory consolidation in the sleeping brain (Timofeev and Chauvette, 2017; Tononi and Cirelli, 2019). Sleep is under neuromodulatory control and is classified into different stages. During slow-wave sleep (SWS), the levels of ACh and monoamines are low, whereas rapid eye movement (REM) sleep is characterized by an increased level of ACh, which may explain the characteristic brain rhythms seen in different sleep stages (Krishnan et al., 2016). Neural reactivations, assumed to be important for memory consolidation during sleep, are seen primarily during SWS (Kudrimoti et al., 1999; Dudai et al., 2015). Since the neuromodulatory state is different in sleep and during wake and different in different stages of sleep, one may expect the rules of synaptic plasticity to differ as well. Unfortunately, there are very few studies on STDP during sleep. SWS has been suggested to be associated with enhanced synaptic potentiation (Timofeev and Chauvette, 2017). On the other hand, a seminal study found evidence for net synaptic potentiation in wake, whereas synaptic strength, on average, appears to decrease during sleep in the cortex and hippocampus *in vivo* (Vyazovskiy et al., 2008). Whereas the wake potentiation has generally been attributed to Hebbian plasticity, the sleep-related synaptic depression could be due to global, homeostatic downscaling (Turrigiano et al., 1998) or specific activity-dependent synaptic depression, as recently reviewed (Tononi and Cirelli, 2019). A recent study in urethane-anesthetized mice revealed that cortical plasticity rules during slow-wave-sleep-like activity vary based on whether the pre- and postsynaptic activity occurs during Up-states or Down-states. Whereas conventional STDP was seen during Down-states, Up-states were biased toward depression such that presynaptic stimulation alone led to synaptic depression, while connections contributing to postsynaptic spiking were protected against this synaptic weakening (González-Rueda et al., 2018). Alternatively, the latter result has been considered as a potential mechanism for anesthesia-induced amnesia and not sleep-related plasticity (Timofeev and Chauvette, 2018). However, recent *in vitro* recordings in entorhinal cortex slices, without the addition of drugs, also showed weakening of subthreshold synaptic inputs during Up-states (Bartram et al., 2017). In the latter study, pairing synaptic input with postsynaptic spike bursts during Up-states induced synaptic potentiation, suggesting that postsynaptic bursting activity may have special significance for synaptic potentiation (Lisman, 1997; Pike et al., 1999) and supporting the idea that both potentiation and depression may occur during SWS. The activity-dependent and input-specific downscaling mechanism discussed here offers two important computational advantages over global downscaling: improved signal-to-noise ratio and preservation of previously stored information (González-Rueda et al., 2018). A similar role was recently suggested for hippocampal sharp-wave ripples in downscaling of synaptic weights during SWS (Norimoto et al., 2018). This downregulation of synaptic weights was input specific and NMDA receptor dependent, as in the neocortex, and could serve as a mechanism for refining memories and reducing responses to irrelevant activity (Norimoto et al., 2018). An important next step will be to investigate the plasticity rules and effects of neuromodulation during natural sleep *in vivo*.

5. Neuromodulation of STDP in Disease Models

Neuromodulation and STDP are two cellular mechanisms that enable adaptation to our environment; however, there is growing evidence that these mechanisms may also play an important role in the pathogenesis of brain disorders as well as provide novel pharmacologic targets for developing new therapies (Figure 2). Alterations in the conditions for LTP and LTD have been identified in animal models of multiple neurologic and psychiatric disorders; however, most studies have used non-physiological stimuli for inducing plasticity such as high- or low-frequency or theta-burst stimulation protocols. Thus, further studies using STDP protocols may reveal how neuromodulation of STDP before, during, and after the plasticity-inducing event is altered in these disorders and provide insight into how synaptic deficits lead to the cognitive dysfunction. One of the main challenges in studying STDP in neurologic and psychiatric disorders is the availability of animal models that share a common pathogenesis with the human disorder. This is particularly true for common psychiatric disorders including depression, schizophrenia, and obsessive-compulsive disorder, in which neither the genes nor the underlying neurobiology is known. There is growing evidence of deficits in STDP, however, from monogenic disorders of neurodevelopment and familial forms of neurodegenerative diseases, in which mouse models have been made with the human disease mutation that replicate many of the anatomical and behavioral features of the disorders. This section will review possible roles for altered neuromodulation of STDP in the pathology of neurologic and psychiatric disorders and the potential to use neuromodulation as therapeutic target for neuropsychiatric disorders. It should be noted that neuromodulation is often used with a different meaning in clinical neuroscience, namely the alteration of neural activity through delivery of electromagnetic or chemical stimulation with a therapeutic aim. Here, we discuss the involvement of physiological neuromodulation through long-range neural projections.

5.1. Addiction and Obsessive-Compulsive Disorder (OCD)

5.1.1. Role for Disruption of Neuromodulation of STDP in Addiction. Drugs of abuse increase dopamine in the VTA and its projections, leading to lasting changes in synaptic transmission (Lüscher and Malenka, 2011). Based on the studies of dopaminergic modulation of STDP, stimulants such as cocaine, which inhibits the reuptake of dopamine, would be predicted to lead to pathological over-strengthening of synaptic connections by "hijacking" the adaptive mechanisms for experience-dependent plasticity. Thus, mechanisms of cocaine addiction may directly involve alteration of the requirements for STDP. In the VTA, activation of D_5R is required for t-LTP (Argilli et al., 2008); thus, higher dopamine levels may increase the likelihood of potentiating inputs. Likewise in prefrontal cortex, activation of D_1R increases the time window for t-LTP (Xu and Yao, 2010). Thus, pathological dopaminergic stimulation would be predicted to allow t-LTP at normally ineffective spike-timing intervals. In addition, increased dopamine may impair t-LTD; blocking D_1Rs was necessary to see t-LTD in striatal D_1 medium spiny neurons (Shen et al., 2008). Further understanding of the net effect of dopamine on different circuits is needed to fully understand the relationship between cocaine use and possible pathological

neuromodulation of STDP, however, due to variation in the region-, layer-, and cell-type-specific effects of dopamine on STDP.

There is growing evidence for neuromodulation of STDP in the pathogenesis of drug addiction from rodent models. A single injection of cocaine potentiates dopaminergic cells in the VTA, occluding t-LTP in rats (Ho et al., 2012), suggesting that cocaine is acting through neuromodulation to promote t-LTP. Chronic, intermittent exposure extends the time window for t-LTP induction in L5 of the prefrontal cortex (Ruan and Yao, 2017) and D_1R-expressing medium spiny neurons of the nucleus accumbens, consistent with our prediction, while inhibiting t-LTP induction in D_2R-expressing medium spiny neurons (Ji et al., 2017). These effects of cocaine on STDP likely act not only through direct modulation of the induction by altering the behavioral state but also as a form of metaplasticity, as prior exposure to cocaine use has lasting effects on the regulation of synaptic plasticity in rodent models (Lee and Dong, 2011). Interestingly, this hijacking of normal STDP mechanisms by cocaine may also act through factors necessary for the maintenance of STDP. Cocaine facilitation of t-LTP requires a brain-specific isoform of protein kinase C—protein kinase Mζ (PKMζ)—which is critical for LTP maintenance (Ho et al., 2012). Administration of PKMζ inhibitor, myristoylated zeta inhibitory peptide (ZIP), restores t-LTP in cocaine-treated rats (with no effect on t-LTP in saline-treated rats) suggesting that cocaine may upregulate PKMζ synthesis after induction, leading to a pathological maintenance of cocaine-induced potentiation (Ho et al., 2012). Thus, the alteration in STDP rules may shift the balance of excitation and inhibition in these circuits, contributing to the persistence of addictive behaviors.

In contrast to the effects of cocaine, acute exposure to ethanol (5 mM to 50 mM) inhibited the induction of t-LTP at synapses onto medium spiny neurons in the nucleus accumbens in a concentration-dependent manner with no effect on t-LTD until a small increase was observed at higher concentrations (Ji et al., 2015). The loss of t-LTP may be due to an ethanol-induced enhancement of the large conductance calcium- and voltage-gated potassium (BK) channels on the medium spiny neurons (Ji et al., 2015). Chronic intermittent exposure to ethanol that induced dependency in mice, however, enhanced t-LTP in layer 5 pyramidal cells in orbitofrontal cortex, likely through the concomitant increase in the ratio of AMPA to NMDA receptors and the expression of GluA1/2-containing AMPA receptors (Nimitvilai et al., 2016). This highlights potential roles for STDP in both the acute depressive effects of ethanol and the addictive potential from repeated use.

5.1.2. Neuromodulation of STDP as a Potential Therapeutic Target in Addiction. Maladaptive dopaminergic function is likely not only a key contributor to addictive behaviors but may also provide an effective therapeutic target. A decrease in phasic release of striatal dopamine observed in rats that self-administered cocaine could be rescued with the indirect dopamine receptor agonist levodopa (L-DOPA; Willuhn et al., 2014). Treatment with L-DOPA increased dopamine release in the medial prefrontal cortex and decreased cocaine self-administration in the rats (Antinori et al., 2018). Future therapeutics may also target cholinergic modulation to dampen cocaine's potentiating effect on synaptic plasticity. Activation of nAChR in the prefrontal cortex increases the threshold for STDP in rodent models (Couey et al., 2007). Further studies will be necessary to identify the specific receptor subtypes and regions to target as drugs with broad cholinergic effects would likely also activate mAChRs, which has mixed effects on STDP (see 2. Neuromodulation of STDP). Serotonergic modulation may also hold potential as a future therapeutic, as activation of 5-HT_4 receptors promotes t-LTD in striatal neurons (Cavaccini et al., 2018) and activation of 5-HT_{1A} receptors can reduce dopamine release and synthesis (Renard et al., 2017). Key to new therapeutics will be to identify drugs with receptor subunit specificity. For example, the anxiolytic drug cannabidiol, unlike delta-9-tetrahydrocannabinol (THC), has no known psychoactive or dependence-producing side effects and is thought to reduce the effects of dopaminergic modulation via 5-HT_{1A} receptors (Renard et al., 2017).

5.1.3. Role for Neuromodulation of STDP in OCD Pathogenesis and Treatment? Obsessive-compulsive disorder is characterized by distressing repetitive thoughts, urges, or impulses and repetitive behaviors (or thoughts) that occur in response to the obsessions to reduce the distress (Hirschtritt et al., 2017; Richter and Ramos, 2018). Dysfunction of frontostriatal and frontotemporal circuits has been implicated, which is supported by the prevalence of OCD-like behaviors in neurodegenerative diseases including frontotemporal dementia, Huntington's disease, and Parkinson's disease (Richter and Ramos, 2018). Drug-induced OCD-like behaviors are often seen with dopaminergic drugs, suggesting both a role for dopaminergic modulation in the pathogenesis and a potential therapeutic target. Activating or blocking dopamine receptor subtypes show different effects on STDP in these brain regions; thus, maladaptive neuromodulation of STDP and other factors affecting the balance of excitation and inhibition in these circuits may contribute to the symptoms. In particular, activation of D_1Rs in the prefrontal cortex increases the time window for t-LTP, which could contribute to the pathological reinforcement of the intrusive thoughts and repetitive behaviors in these frontostriatal circuits.

Serotonergic dysfunction may also play a role. Serotonin gene variants have been the target of genetic studies in families with OCD (Sinopoli et al., 2017), and the first-line medications for OCD are selective serotonin reuptake inhibitors (SSRIs; Hirschtritt et al., 2017; Richter and Ramos, 2018). STDP at thalamocortical synapses is regulated by serotonergic tone; for example, t-LTD requires decreased activation of 5-HT_4 receptors (Cavaccini et al., 2018). Serotonergic modulation of STDP may also act indirectly through its regulatory effects on other neuromodulatory systems and specific inhibitory cell types within cortical circuits. There is also evidence from other SSRIs tested on frequency-based synaptic plasticity. Vortioxetine, which acts on multiple serotonin receptor subtypes, enhances frequency-based LTP at hippocampal CA1 synapses (Dale et al., 2014). Chronic treatment with fluoxetine impaired both frequency-based LTP and LTD in CA1 from Schaffer collateral, but not perforant path, stimulation in the hippocampus (Rubio et al., 2013).

Atypical antipsychotics, many of which have mixed effects on dopamine receptors, are also used as adjunct therapy with SSRIs for OCD; however, the efficacy has not been supported in randomized-control trials (Hirschtritt et al., 2017; Richter and

Ramos, 2018). Surgical approaches to OCD treatment have included ablation of the anterior cingular cortex and/or internal capsule and, more recently, deep brain stimulation in the anterior limb of the internal capsule, nucleus accumbens, thalamus, or sub-thalamic nucleus (Hirschtritt et al., 2017). It is important to note that while clinically these surgical (and non-surgical approaches including transcranial magnetic stimulation) are often referred to as "neuromodulation" therapies, their mechanisms are unknown and may or may not affect the neuromodulatory tone in the relevant brain regions.

5.2. Neurodevelopmental Disorders

5.2.1. Role for Disruption of Neuromodulation of STDP in Neurodevelopmental Disorders. Autism spectrum disorders (ASD) are characterized by childhood-onset and lifelong difficulties with social interaction, communication, and sensory perception (Brugha et al., 2016). There is growing evidence that widespread disruption of synaptic function during early postnatal development may underlie the core deficits in autism (Meredith et al., 2012; Johnson et al., 2015). Many of the genes identified in ASD and related monogenic neurodevelopmental disorders affect synaptic proteins (Peça et al., 2011; Pinto et al., 2014). Developmental changes at the synapse, primarily in the receptor composition, and in the local circuit, through changes in inhibition, alter the conditions for the induction of synaptic plasticity in the cortex and hippocampus. Alteration of NMDA receptor expression and maturation in multiple mouse models of autism and related disorders would predict perturbations of STDP rules, as NMDA receptors are critical for many forms of STDP throughout the brain (Shipton and Paulsen, 2013). Moreover, excitatory and inhibitory cell types may have different STDP rules even in the same area of cortex (Huang et al., 2013). Thus, any alteration in STDP time windows, for example, may contribute to the imbalance of excitation and inhibition during early postnatal development (Gogolla et al., 2009). Disruption of neuromodulatory circuits has also been identified in multiple developmental disorders, including Rett syndrome. Rett syndrome is a severe neurodevelopmental disorder caused by loss-of-function mutations in *MECP2*, which codes for MeCP2, a chromatin remodeler (Chao et al., 2007; Cohen et al., 2011). Selective deletion of *Mecp2* in different neuromodulatory cell types (dopaminergic, noradrenergic, or serotonergic) in mice reproduced different aspects of the clinical phenotype (Samaco et al., 2009). Thus loss of Mecp2 would predict disruption of synapse- and region-specific rules for STDP, which may contribute to the cognitive decline. For example, loss or impairment of dopaminergic modulation in the cortex would predict a loss of flexibility in the refinement of STDP rules over development and may favor facilitation- or depression-only states.

Although there are limited studies of STDP in models of neurodevelopmental disorders, evidence for deficits in STDP has been identified in monogenic mouse models, including fragile X syndrome (Meredith and Mansvelder, 2010). Loss of t-LTP occurs at L4/5-to-L5 synapses in primary somatosensory cortex (Desai et al., 2006), L2/3-to-L2/3 synapses in prefrontal cortex (Meredith et al., 2007), and medium spiny neuron synapses in the nucleus accumbens (Neuhofer et al., 2015). t-LTP is decreased in CA1 stratum-radiatum synapses in cultured hippocampal slices (Hu et al., 2008). The loss of t-LTP at multiple synapses in the *Fmr1* knockout (KO) mice is likely due to an increase in the threshold for induction (Meredith et al., 2007) through impairments in AMPA receptor trafficking (Hu et al., 2008), altered spine morphology leading to a decrease in synaptic AMPA receptor expression (Meredith and Mansvelder, 2010), and, in the nucleus accumbens, a decrease in synaptic NMDA receptors (Neuhofer et al., 2015). Interestingly, t-LTD is preserved in the somatosensory cortex (Desai et al., 2006) and prefrontal cortex of *Fmr1*-KO mice (Meredith et al., 2007); moreover, mGluR5-mediated LTD is actually enhanced in mouse models of both fragile X and Angelman syndromes (Meredith and Mansvelder, 2010). Thus, disrupted regulation of STDP may contribute to the excitatory-inhibitory imbalance underlying the cognitive dysfunction.

There is strong evidence that the balance of excitation and inhibition is altered by loss of Mecp2. NMDA receptor subunit composition is altered in homogenates of hippocampus (Asaka et al., 2006) and visual cortex (Durand et al., 2012). Importantly, cell-type-specific effects on the maturation of excitatory synaptic transmission in excitatory and inhibitory neurons (Mierau et al., 2016) may also affect the induction of STDP. The developmental delay of GluN2B to GluN2A subunit switch in pyramidal cells and the acceleration of the switch in parvalbumin-positive interneurons would predict deficits in NMDA receptor-dependent forms of STDP at the L4-to-L2/3 visual cortical synapses (Mierau et al., 2016). These deficits would be predicted to arise not only from the altered maturation of inhibition, but also from the NMDA receptor subunit composition, which affects the permissibility of STDP (Shipton and Paulsen, 2013). Although, notably, the only available study of STDP in Mecp2-deficient mice to date did not show any impairment of t-LTP at layer-5-to-layer-5 synapses in pyramidal cells in primary somatosensory cortex (Dani and Nelson, 2009), further studies of STDP in other cell types, cortical layers, and brain regions may reveal significant deficits in STDP that may be modulated in a receptor subtype- and region-specific manner.

5.2.2. Neuromodulation of STDP as a Therapeutic Target for Neurodevelopmental Disorders. Multiple mouse studies illustrate neuromodulation as a potential target to reverse the deficits observed in synaptic plasticity. In the *Fmr1* KO mice, co-activation of serotonin (5-HT_{2B}) and dopamine (D_1) receptors restored frequency-based LTP in cultured slices from CA1 hippocampus (Lim et al., 2014). Based on these findings, pharmaceutical trials in fragile X syndrome for the first disease-modifying therapy in a cognitive disorder are underway. In addition, activation of a different group of serotonin receptors ($5\text{-HT}_7\text{R}$) with a novel agonist (LP-211) was able to reverse the abnormal enhancement of mGluR-LTD in CA1 hippocampal pyramidal neurons from the *Fmr1* KO mice (Costa et al., 2012). Of note, increasing 5-HT_7 receptor activity may also be beneficial in Rett syndrome; LP-211 injections improved performance on several behavioral tests in Mecp2-deficient mice, although effects on synaptic plasticity have yet to be assessed (De Filippis et al., 2014). Modulating serotonergic release in the nucleus accumbens has also shown promise for ameliorating social deficits in the 16p11.2 autism mouse model (Walsh et al., 2018). Further studies of neuromodulation of STDP in ASD mouse are warranted to reveal a more detailed, synapse-specific mechanistic picture of how STDP is

differentially disrupted in these disorders and may be targeted with novel synapse- or cell-type-specific therapeutics.

5.2.3. Can Neural Circuits be Modulated Retrospectively? Targeting defects in synaptic plasticity identified in genetic mouse models offers a strategy for developing new therapies for neurologic and psychiatric disorders. However, given the developmental constraints on synaptic plasticity rules, a key question is whether these synaptic defects can be corrected retrospectively. For neurodevelopmental disorders, in particular, many of the synaptic deficits occur early in postnatal development either before or during critical periods in sensory development. Thus, treatments targeting synaptic plasticity deficits would either require introduction before the onset of symptoms or reopening critical periods of early development in adulthood.

Critical periods for induction of specific types of STDP have been identified in animal models. In humans, critical periods exist in early postnatal life in which sensory experience is required for the normal development of skills including vision, hearing, and language. The visual cortex requires input from both eyes during early life in order to acquire binocular vision. Misalignment of eyes, if not corrected prior to 8 years-of-age, will prevent the development of depth perception and impair visual acuity in the amblyopic eye. Until recently, this deficit was thought to be permanent; however, new studies suggest that it may be possible to re-open critical periods in adulthood (Gervain et al., 2013).

Neuromodulation of synaptic plasticity may be key to correcting developmental deficits. Increased cholinergic transmission may re-open critical period plasticity in adult visual cortex. Loss of input from one eye—such as in monocular deprivation—shifts the response of neurons in the contralateral visual cortex to the ipsilateral eye in young animals but this effect disappears by adulthood. Remarkably, this form of plasticity could be induced in adult mice through the deletion of *Lynx1*, a molecular break on critical period plasticity, which works through increased nicotinic cholinergic transmission (Morishita et al., 2010). Human trials are now underway to investigate whether acetylcholine esterase inhibitors, which also increase cholinergic transmission, might improve vision in the amblyopic eye in people over the age of 8 years (NIH Clinical Trial, NCT01584076). Serotonergic modulation may also allow modification of visual circuits later in development. Modulation of layer 1 5-HT_{3A} receptor-positive inhibitory interneurons can reopen the critical period for tonotopic plasticity in auditory cortex (Takesian et al., 2018). The serotonin reuptake inhibitor, fluoxetine, also enables improvement in vision in rats after monocular deprivation (Maya Vetencourt et al., 2008). Evidence in humans that re-opening critical periods may be possible comes from a recent study in which valproate, a common anti-epileptic medication that is thought to act as an epigenetic regulator, permitted perfect pitch learning in healthy adults (Gervain et al., 2013).

5.3. Neurodegenerative Disorders

5.3.1. Role for Neuromodulation of STDP in Neurodegenerative Disorders. Severe effects on neuromodulatory systems, in particular loss of cholinergic and dopaminergic cells, in neurodegenerative disorders including Alzheimer's and Parkinson's disease predict major deficits in the flexibility of learning rules for STDP. Moreover, neuronal hyperexcitability occurs in the early stages of Alzheimer's disease leading to a disruption of excitatory-inhibitory (E/I) balance in the cortex (Hall et al., 2015; Brown et al., 2018). Altered E/I balance could be caused, at least in part, by neuromodulatory effects on STDP and would also be expected to have further effects on STDP depending on behavioral state. Studies of STDP in animal models predict alterations in the induction requirements for STDP, as well as the polarity, due to loss of cholinergic tone. The net effect of reduced cholinergic modulation, however, may be difficult to deduce given the diverse actions on nicotinic and muscarinic receptors at different synapses and brain regions (2. Neuromodulation of STDP). Decreased activation of nAChR, for example, may permit t-LTP in prefrontal cortex through lowering the threshold for induction and/or removing the inhibition of t-LTP by inhibitory interneurons (Couey et al., 2007). Decreased activation of mAChR, in contrast, might be predicted to favor t-LTD in prefrontal cortex and hippocampus from some studies (Adams et al., 2004; Zaitsev and Anwyl, 2012; Sugisaki et al., 2016) but equally could be predicted to reduce t-LTD based on other studies (Seol et al., 2007; Brzosko et al., 2015). These effects, particularly in the human temporal cortex, may be layer-specific, as reduced cholinergic tone would be predicted to favor t-LTP over t-LTD at integration layers (i.e., L2/3) while reducing the facilitation of t-LTP in output layers (i.e., layer 6; Verhoog et al., 2016).

Evidence for a disruption in the neuromodulation of STDP comes from studies in mouse models of human gene mutations found in familial forms of Alzheimer's disease. Loss of t-LTP occurred at L2/3-to-L5 cortical synapses in 5xFAD mice (Buskila et al., 2013) and L2/3-to-L2/3 synapses in APP-swe/PS1dE9 mice (Shemer et al., 2006). The loss of t-LTP was age dependent (increasing from 3.5 to 7 months), and t-LTP could be abolished by the application of soluble Aβ oligomers. Both studies suggest the proximal cause is a decrease in synaptic AMPA receptor expression; however, the loss of acetylcholine and other neuromodulatory deficits in Alzheimer's disease likely also contributes. The reduction in cholinergic tone could also explain the reversal in the polarity of STDP observed at the L2/3-to-L5 synapses in the 5xFAD mice (Buskila et al., 2013).

Deficits in STDP were also observed in two mouse models of Parkinson's disease (Thiele et al., 2014). The 6-OHDA-lesioned mice replicate the slowing and difficulty with the initiation of movements, while the levodopa (L-DOPA)-induced dyskinesia mouse model recapitulates the unwanted increase of involuntary movements secondary to L-DOPA use. Consistent with animal studies of dopaminergic modulation of STDP (2. Neuromodulation of STDP), t-LTP could only be induced in the indirect pathway and t-LTD in the direct pathway at corticostriatal synapses in the 6-OHDA-lesioned mouse model of Parkinson's disease, whereas both t-LTP and t-LTD could be induced in either pathway in wild-type mice. In contrast, in the L-DOPA-induced dyskinesia mouse model, t-LTP could only be induced in the direct pathway and t-LTD in the indirect pathway (Thiele et al., 2014). Thus, altered dopaminergic modulation likely leads to loss of bidirectional plasticity at corticostriatial synapses in these two contrasting mouse models. Notably, the treatment of motor symptoms in Parkinson's disease with drugs targeting the dopamine system has revealed a high prevalence of non-motor symptoms in people with Parkinson's disease, including dementia

(Cheon et al., 2008). Thus, we would predict that alterations in other neuromodulatory systems (e.g., cholinergic) may also be affected with additional impacts on STDP outcomes, as in Alzheimer's disease.

5.3.2. Neuromodulation of STDP as a Potential Therapeutic Target for Neurodegenerative Disorders. Testing the neuromodulatory effects on STDP in animal models of Alzheimer's and Parkinson's disease may yield further mechanistic insight into the cognitive decline and provide additional drug targets. In both Parkinson's and Alzheimer's disease, the loss of neurons affects many areas important for neuromodulation and would thus be expected to alter STDP rules in response to past history, behavioral state, and behavioral outcomes. While current therapies primarily target dopaminergic and cholinergic function, serotonergic modulation is an attractive target for future therapeutics. A new drug inhibiting serotonin receptor 6 (5-HT_6R) improves cognitive function in Alzheimer's disease (Johnson et al., 2008), and a 5-HT_6R antagonist blocks the attenuation of theta-burst-stimulation-induced LTP in CA1 of the hippocampus (West et al., 2009).

5.3.3. Can Old Synapses Be Made Plastic Again? One problem in developing therapeutics for neurodegenerative disorders is whether deficits in synaptic plasticity can be reversed. Employing a similar strategy as that used in neurodevelopmental disorders, targeting perineuronal nets (PNNs), which maintain parvalbumin-positive inhibitory neurons in a mature state, in an Alzheimer's disease mouse model restored synaptic defects and improved memory on behavioral testing (Yang et al., 2015). Moreover, deletion of histone deacetylase 3 (*Hdac3*) in 18-month-old mice improved performance on hippocampal-dependent object learning memory tasks—which is typically impaired in aging mice—and restored the ability to induce LTP with theta-burst stimulation (Kwapis et al., 2018). Thus, further research is warranted to determine whether alterations in the neuromodulation of STDP in neurodegenerative disorders can also be reversed.

5.4. Modulation of STDP as a Therapeutic Target for Recovery from Stroke and Brain Injury?

There is growing interest in enhancing the functional remapping in the brain after stroke or traumatic brain injury. Neuronal plasticity facilitates the cortical reorganization necessary to regain function in a weak or paralyzed limb; however, plasticity mechanisms post-stroke can also worsen function through increased inhibition of the affected hemisphere by the unaffected hemisphere (Bashir et al., 2010). Transcranial magnetic stimulation (TMS) has been used clinically to release the inhibition from the intact hemisphere (Bashir et al., 2010) and is also under investigation to improve motor symptoms in Parkinson's disease (Zhu et al., 2015). Attempts have been made to replicate *in vitro* synaptic plasticity induction protocols with TMS including "theta-burst" protocols (e.g., by applying bursts of 3 pulses at 50 Hz every 200 ms, which increased the amplitude of TMS-induced potentials in motor cortex for 20–30 min post-stimulation) and a combination of peripheral nerve stimulation with TMS of the motor cortex (Rodrigues et al., 2008; Zamir et al., 2012; Wessel et al., 2015; Casula et al., 2016; Foysal et al., 2016). While it is tempting for authors to compare the latter to spike-timing-dependent plasticity, TMS lacks the spatial resolution to study synaptic plasticity. Moreover, modulation of cortical inhibition on a regional scale seems an equally likely contributor to the observed changes in TMS response for both protocols.

6. Conclusion

Neuromodulation of STDP to incorporate prior experience, current behavioral state, and feedback from learning outcomes allows the adaptation of synaptic plasticity to the different computational needs across brain regions and bridging the multiple timescales on which learning takes place. Neuromodulation also enables flexible adaptation to changes in the external environment and internal brain state. Basic science investigations into the parameters and mechanisms underlying STDP has also been translated to mouse models of neurologic and psychiatric disorders. The most pressing issues to address in future research are, first, whether the same plasticity rules operate *in vivo* as those found in *ex vivo* and *in vitro* preparations; second, how STDP is controlled by local spiking activity and neuromodulatory inputs; and, third, the function of this plasticity in behavioral learning and memory and their involvement in different brain disorders. Further exploration of how the neuromodulation of STDP is altered in different behavioral and disease states is likely to reveal new mechanisms underlying the cognitive function and dysfunction in these disorders and may offer novel treatment strategies for improving cognition throughout the lifespan.

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AUTHOR CONTRIBUTIONS

All authors contributed to writing the paper.

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