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Functional roles of short-term synaptic plasticity with an emphasis on inhibition

Haroon Anwar, **Xinping Li**, **Dirk Bucher**, and **Farzan Nadim**

Federated Department of Biological Sciences, New Jersey Institute of Technology and Rutgers University, 323 Martin Luther King Blvd, Newark, NJ 07102, United States

Abstract

Almost all synapses show activity-dependent dynamic changes in efficacy. Numerous studies have explored the mechanisms underlying different forms of short-term synaptic plasticity (STP), but the functional role of STP for circuit output and animal behavior is less understood. This is particularly true for inhibitory synapses that can play widely varied roles in circuit activity. We review recent findings on the role of synaptic STP in sensory, pattern generating, thalamocortical, and hippocampal networks, with a focus on synaptic inhibition. These studies show a variety of functions including sensory adaptation and gating, dynamic gain control and rhythm generation. Because experimental manipulations of STP are difficult and nonspecific, a clear demonstration of STP function often requires a combination of experimental and computational techniques.

Introduction

Short-term synaptic plasticity (STP) or short-term synaptic dynamics refers to transient activity-dependent changes in synaptic strength [1–3]. Forms of STP include short-term depression and facilitation in the millisecond range, but also longer-lasting changes in response to highly repetitive activity, such as augmentation (lasting seconds) and post-tetanic potentiation (lasting minutes). These modifications are short-term in the sense that no persistent changes in the signaling machinery, such as membrane protein expression, are required. The cellular mechanisms of STP are relatively well understood and are predominantly presynaptic [1,3].

Many of the proximate functional roles of STP at the level of single synapses are relatively straightforward to understand [4]. For example, STP leads to stronger synaptic connections at some firing frequencies over others, and therefore conveys frequency-filtering properties (Fig. 1a). Other examples include adaption or sensitization (Fig. 1b), and gain control (Fig. 1c). Although theoretical studies have proposed numerous functions of STP at the circuit

Corresponding author: Nadim, Farzan (farzan@njit.edu).

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level [5], surprisingly few experimental studies address them. Therefore, the ultimate functional role of STP for circuit computations in the context of specific behaviors is poorly understood in most cases. Here we review some recent examples of a more integrated view of STP in a variety of systems, highlighting contributions to circuit dynamics and function. Of particular interest are findings that consider the functional implications of different dynamics for inhibitory and excitatory synapses, as such differential effects on synaptic strength can render the excitation/inhibition balance dependent on overall circuit activity levels.

Visual processing in the retina

Adaptation and sensitization (Fig. 1b) allows sensory networks to change their sensitivity and properly relay fluctuating sensory signals. These phenomena can be fast or slow, and occur both at the receptor level and at higher processing centers. The visual system shows great plasticity in order to increase its dynamic range. In a variety of animals, some retinal ganglion cells (RGCs) respond to increases in contrast, whereas others become sensitized following a strong stimulus [6]. In this way, RGCs can reliably respond to the changes in contrast in both directions. A recent study investigated the effect of STP in bipolar and amacrine synapses on contrast adaptation in zebrafish [7]. Some bipolar to RGC synapses depressed and a similar number facilitated. The corresponding RGCs showed adaptation or sensitization to contrast, respectively. Remarkably, the facilitation observed in bipolar cell synapses is caused by depression of inhibitory feedback from amacrine cells [7,8]. These findings demonstrate that the large dynamic range of visual contrast arises through circuit mechanisms, which directly depend on different forms of STP.

Auditory processing

The auditory system of birds is among the best-studied systems with regard to functional roles of STP [9,10]. For example, STP contributes differences in the processing of different sound frequencies. Neurons in the chicken nucleus magnocellularis (NM) are organized in a tonotopic manner, collecting inputs from auditory nerve fibers that are tuned according to different characteristic frequencies (CFs) of hair cells [11] (Fig. 2a). These inputs show prominent depression, and a recent study demonstrates that the level of depression is tonotopically organized, as inputs from higher CFs produce less depression and therefore more robust NM neuron responses [12]* (Fig. 2b). The functional consequences are not quite clear, but more depression in low CF inputs could bias NM neurons to respond preferably to many phase-locked inputs, whereas less depression in high CF inputs could elicit robust responses even in the absence of much integration.

Depression also plays an important role in sound localization. Bilateral inputs from both ears are integrated through two pathways signaling the intra-aural time-difference (ITD) and the intra-aural level difference (ILD), respectively. Synapses from bilateral monaural NM neurons onto nucleus laminaris (NL) neurons transmit direct and precise bilateral timing information, which allows NL neurons to act as coincidence detectors of the ITD pathway [13] (Fig. 2a). Firing probability of NL neurons is highest when NM inputs from both sides arrive at NL neurons in phase, and lowest when out of phase [14]. Coincidence detection in NL neurons is independent of sound intensity because of strong depression in these synapses

[15], which is a direct experimental demonstration of the gain control mechanism [16] (Fig. 1C). Although temporal precision of inputs from the NM is essential for proper coincidence detection, NM neurons sensitize to ongoing stimuli by increasing firing rate and decreasing spike-timing precision. Using dynamic clamp simulated synaptic inputs, Higgs and colleagues show that these adaptations reduce the ITD sensitivity of NL neurons. However, reduction in ITD sensitivity is mitigated by synaptic depression [17], potentially because depression reduces postsynaptic firing resulting from less coincident presynaptic inputs at higher rates.

Unlike the ITD pathway synapses, which predominantly show depression, a number of synapses in the ILD pathway show depression or facilitation. Although multiple roles for STP have been suggested [18], there is little direct experimental evidence to support a particular function. Similarly, the calyx of the Held synapse in the mammalian auditory system, due to its accessibility and interesting dynamics [19], has been studied extensively for mechanisms of STP. However, no clear functional role for STP at this synapse has been found [20,21].

STP also contributes to the gating of multisensory integration in the auditory system, and the effect of STP in inhibitory synapses on the excitation/inhibition balance (Fig. 2) plays an important role. In the dorsal cochlear nucleus (DCN), the first site of multisensory integration involving auditory perception in rodents, multisensory signals are carried by parallel excitatory fibers and are integrated with auditory inputs by fusiform principal cells. Feedforward inhibition from cartwheel interneurons to fusiform principal cells in the DCN tempers the multisensory integration [22]. These inhibitory synapses show rapid short-term depression and, therefore, feedforward inhibition is greatly reduced by the spontaneous activity of the cartwheel cells [22]. Cartwheel cell activity is regulated by neuromodulators, including serotonin and norepinephrine (NE) [23]. Interestingly, NE changes the efficacy the cartwheel neuron to fusiform inhibition by reducing spontaneous activity of cartwheel neurons, but not affecting synaptic mechanisms directly, thereby relieving the synapse from tonic depression [22]. Consequently, NE may allow selective enhancement of auditory processing by fusiform cells, for example, during attentive states [22,24].

Olfactory processing

In the mammalian olfactory system, synapses exhibit a variety of STP types. Olfactory receptor neurons (ORNs) transmit odor information to mitral and tufted cells (M/T) in the olfactory bulb, which in turn make excitatory synapses to neurons in the piriform cortex. These excitatory synapses exhibit either facilitation, depression, or both [25], which results in dynamic filtering of olfactory bulb input. A recent study investigated the effect of different forms of STP on firing rate information transfer from mouse M/T cells to piriform cortical neurons at different breathing frequencies [26]**. M/T population synaptic current was simulated at different firing frequencies within each cycle of rhythmic modulation, either at the passive breathing frequency of 2Hz or at the sniffing frequency of 8 Hz (Fig. 3a). When this current was injected into piriform cortical neurons, their firing rate increased with presynaptic firing rate in all STP cases, but was overall highest for facilitation-dominated inputs, followed by mixed facilitating/depressing inputs and lowest for

depression-dominated inputs. Surprisingly, for all forms of STP, the change in breathing frequency modulation from 2 to 8 Hz enhanced the dynamic range of cortical responses (Fig. 3b). At 8 Hz modulation, peak firing rate in cortical neurons increased with presynaptic frequency, independent of STP type. In contrast, during 2 Hz modulation, cortical responses saturated, also independent of STP type. This difference arose because the peak of the presynaptic firing input within each cycle coincided with the lowest synaptic efficacy for 2 Hz modulated inputs, but with a high synaptic efficacy for 8 Hz inputs (Fig. 3c). This finding indicates that the interaction of synaptic depression and cycle frequency in oscillatory networks can shape the output response independently of the faster timescale effects of STP.

Electrosensory processing in weakly electric fish

In electrosensory processing in weakly electric fish, STP is an important component of coding strategies for directional and temporal selectivity. In both cases, a crucial part of this contribution is how converging synaptic inputs summate over time. Synapses signaling information from electroreceptors in the lateral line to midbrain neurons show depression. Directional selectivity arises in a similar way as first suggested for vision [27], in that the time course of depression is very different between inputs from different locations in a midbrain neuron's receptive field [28,29]. A stimulus moving over the receptive field in the preferred direction activates slowly depressing inputs first, and following inputs add to a barely depressed response to produce strong activation. In the opposite direction, more rapidly depressing inputs are activated first, and following inputs add only to a mostly depressed response.

Other midbrain neurons in electric fish respond selectively to particular intervals of activation, reflecting different intervals of electric organ discharge from conspecifics in electric communication. This interval tuning is achieved through a combination of summation and STP [30,31]. While high-pass and low-pass temporal filtering arises naturally from facilitation and depression, respectively [4] (Fig. 1a), all synapses onto these midbrain neurons are depressing. However, electrosensory information is relayed to the neurons through concomitant direct and feedforward excitation, and feedforward inhibition. Interval tuning results from differences in how the excitation/inhibition balance changes with time, depending on the amount of depression in excitatory versus inhibitory input (Fig 4a). High-pass tuning is achieved when excitatory inputs depress less than inhibitory ones, leading to more temporal summation of excitation. Low-pass tuning is achieved when inhibitory inputs depress less than excitatory ones, leading to more temporal summation of inhibition.

Thalamic relay of sensory information

Rapid adaptation of responses to repeated inputs occurs in the rat vibrissal sensory system, partly in the somatosensory cortex [32,33]. During this rapid adaptation, thalamocortical synapses undergo short-term depression and recover with a rate similar to that of sensory responses [32]. STP also plays a crucial role in the reciprocal interactions between the thalamus and cortex (Fig 4b). The cortex regulates the sensory input it receives by exerting dynamic control over the thalamus [34]. In the somatosensory system, during low-frequency

cortical activity, the activity of thalamocortical (TC) relay neurons briefly increases, and is then suppressed [35]*. This is due to monosynaptic excitation by layer 6 corticothalamic (CT) neurons, followed by disynaptic feedforward inhibition from thalamic reticular nucleus (TRN) neurons. During high-frequency cortical activity, such as gamma oscillations, the overall excitation of TC relay neurons increases significantly, enhancing the sensory signal flow to the cortex [35]*. This modulation occurs because of facilitation of excitation from CT neurons [35,36] and depression of inhibition from TRN neurons [35], which results in net increase of excitation in TC neurons (Fig. 4b).

Reciprocal synaptic interactions between the thalamus and the cortex also underlie oscillations during sleep and absence epilepsy, which rely on the ability of TC neurons to produce rebound bursts when inhibited by TRN neurons [34]. The CT to TRN synapses are strongly depressed through actions of presynaptic group III metabotropic glutamate auto-receptors (mGluRs). Inhibitory synapses from TRN neurons to TC neurons also are weakened, potentially also through mGluR actions. The net result is a depolarization of TC neurons; effectively blocking low-threshold activated depolarizing currents and reducing their post-inhibitory rebound properties [37]. Such a mechanism can dampen the oscillatory activity and protect against absence seizures, while maintaining proper sensory processing in the CT circuit.

Coding of spatial information in the hippocampus

In the hippocampus, facilitation of excitatory synapses and depression of inhibitory synapses act synergistically to amplify high-frequency inputs. Discharge of place cells in CA1 provides activity-encoded information about spatial positions (place fields) within the environment [38]. Place cells are typically silent, but produce a high frequency discharge when the animal passes through the place field, indicating temporally precise excitatory input to these cells. Facilitation of excitatory synapses induces nonlinear amplification of high-frequency inputs, which saturates rapidly [39,40]. Amplification is also aided by feedforward inhibitory synapses which show depression with similar temporal characteristics [39]. Thus, STP of excitatory and feedforward inhibitory synapses selects for high-frequency output observed in place cells [41]. In addition, CA1 pyramidal neurons receive feedback inhibition, which undergoes larger depression than feedforward inhibitory connections, and is thought to help avoid saturation at high gain [42]*.

The variety of inhibitory interneurons in the hippocampus show diverse forms of STP such as depression, facilitation, or both [43]. However, different interneuron types can play a more dynamic role when recruited by different pathways. CA1 receives input from CA3 and layer III of the entorhinal cortex (EC) [44]. Synapses to both parvalbumin and somatostatin positive interneurons show facilitation, followed by depression, when activated by CA3 input alone, but only have very weak responses to EC inputs. Consequently, they do not increase their firing rate when activated by both CA3 and EC, as compared to CA3 alone [45]**. In contrast, neuropeptide Y positive interneurons, which also show facilitation of CA3 inputs, increase their firing rate when CA3 and EC inputs are co-active. Together, the combination of STP and distinct summation of inputs to distinct classes of interneurons

allows for the inhibitory microcircuits to selectively gate the input from CA3 and EC to CA1 pyramidal neurons, which code spatial information [45]**.

Central Pattern Generation

STP has also been shown to play important roles in motor circuits, particularly rhythmic ones. Different phases of motor patterns are often generated based on reciprocal inhibitory connections. In the context of oscillatory networks, STP has been suggested to be a gain control mechanism [16,46]. Consistent with this hypothesis, theoretical studies show that short-term depression of inhibitory synapses promotes phase-maintenance between neurons, meaning that the latency between sequentially active neurons scales with the period of the oscillation [47,48]. When oscillation frequency increases, the strength of inhibitory synapses decreases. This in turn speeds up post-inhibitory rebound in postsynaptic neurons and therefore reduces delay. Thus delay decreases as frequency increases, shifting the network activity from constant latency to phase constancy. Such a mechanism was suggested to act in rhythmic motor patterns, such as the pyloric rhythm of the crustacean stomatogastric ganglion (STG), which maintains constant phase relationships between neurons across a large range of frequencies [49,50]. A recent study on the pyloric network demonstrates that the amplitudes of synapses change nonlinearly as a function of network frequency, with a smaller amplitudes at low or high frequencies [51]*. Mathematical analysis of such nonlinear frequency-strength relationship in a recurrent network demonstrates that it promotes stable oscillation frequency [52].

Another interesting example of STP function in rhythmic motor patterns comes from the periphery of the stomatogastric system. Here, differences across individual animals in the number of motor neurons innervating individual muscle fibers are compensated by facilitation [53]. Synapses onto muscle fibers that receive inputs from fewer motor neurons facilitate more, so that overall strength of concomitant synaptic inputs during motor bursts are independent of the number of motor neurons.

While STP has rarely been considered in models of spinal motor networks, a recent study in the lamprey spinal swim network suggests that different dynamics of excitatory and inhibitory synapses are important in determining speed and robustness of the locomotor pattern [54]*. Connections between excitatory interneurons show depression, and increased depression speeds up the motor pattern, potentially because depression promotes the termination of bursts. Inhibitory feedback synapses show facilitation, which indirectly limits the increase in network frequency, presumably by aiding in the recovery of excitatory synapses from depression.

STP has recently been considered as a crucial mechanism for the generation of the mammalian respiratory rhythm. Rhythmic inspiratory activity in the brainstem pre-Bötzinger complex (preBötC) was traditionally considered to be driven by a group of pacemaker neurons [55], which make reciprocal inhibitory connections with post-inspiratory and expiratory neurons in other brainstem nuclei, thus producing the different phases of the respiratory pattern [56,57]. An alternative group-pacemaker hypothesis was suggested in order to explain experimental results that appear to rule out direct roles for pacemaker neurons or synaptic inhibition [56], but instead suggest that rhythmic inspiratory activity is

driven by mutual excitation among preBötC neurons. However, no clear mechanism for burst termination, and therefore rhythmicity, was found. Recent computational work suggests that rhythm generation can be driven by mixed short-term synaptic dynamics of excitatory connections [58]**. In the model, the initiation of inspiratory bursts depends on synaptic facilitation, whereas early-stage depression terminates the bursts and late-stage depression produces the refractoriness of the neurons between bursts. Slice recordings of preBötC neurons reveal synaptic facilitation and depression within the timescale predicted by the model. The role of synaptic depression in producing the refractory period is also supported by experiments on specific preBötC neurons [59]*, which have been shown to be necessary for inspiratory rhythm generation [60].

Conclusions

At the single synapse level, STP can convey frequency-filtering, adaptation/sensitization, and gain control. However, these properties are only proximate functional consequences of STP and do not necessarily provide insight into the ultimate functional role of STP for circuit activity and behavior. If the type, frequency- and time-dependence, and magnitude of STP differs at different synapses within a circuit, quantitative assessment of consequences for circuit activity becomes challenging and often requires both experimental and modeling approaches. The proximate functions of different forms of STP are also not conceptually different between excitatory and inhibitory synapses. However, the sign of synaptic currents obviously matters for circuit processing. A number of recent examples we discussed show that differences in short-term dynamics of excitatory and inhibitory synapses render the overall balance of excitation and inhibition dependent on activity. One emerging principle shared across a number of systems appears to be that changes in the balance of parallel excitation and feedforward inhibition can be used for gating information flow in an activity-dependent manner.

Acknowledgments

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Highlights

- Short-term depression and facilitation can act as dynamic control mechanisms through which a sensory system produces adaptation or sensitization.
- Different dynamics of short-term depression in feed-forward inhibitory synapses can produce distinct balances of excitation and inhibition.
- The balance of excitation and feedforward inhibition through synaptic short-term plasticity produces a gating mechanism for sensory information, depending on cortical activity levels or on neuromodulation.

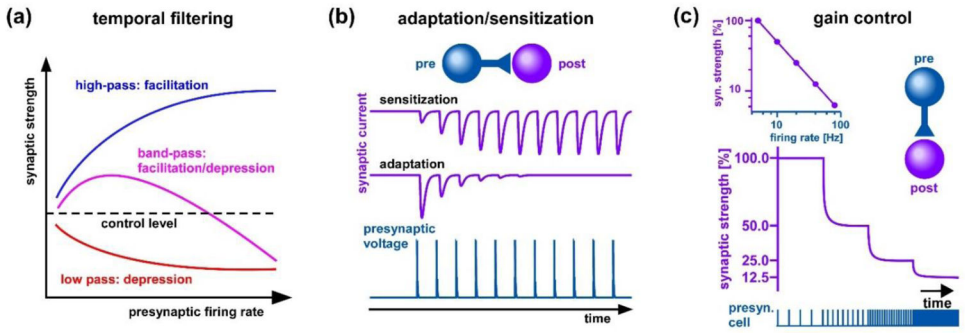

Figure 1.

Schematics of functional roles of STP at the level of single synapses. **(a)** STP conveys frequency-filtering properties to synapses. During repetitive activity, facilitating synapses are high-pass filters because they are strongest at high frequencies, depressing synapses are low-pass filters because they are strongest at low frequencies, and synapses exhibiting both facilitation and depression are band-pass filters. **(b)** Sensitization and adaptation to incoming stimuli can be due to facilitation and depression, respectively. Synaptic facilitation increases the likelihood of postsynaptic firing over time, while depression decreases it. **(c)** Depression can constitute a gain control mechanism. In this case, a fixed percentage change in presynaptic frequency causes a fixed percentage change in synaptic strength, independent of the absolute frequencies.

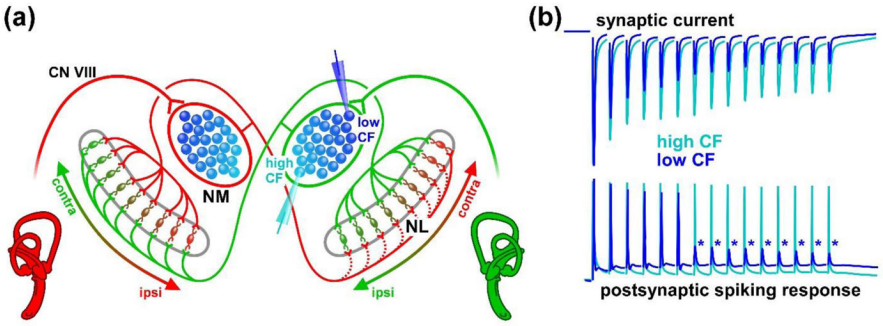

Figure 2.

Short-term synaptic depression is topographically distributed in the avian cochlear nucleus magnocellularis (NM). **(a)** Schematic diagram of auditory nerve (CN VIII) input to NM and intra-aural time difference (ITD) detection by the nucleus laminaris (NL) neurons. Auditory inputs from CN VIII tonotopically map to NM neurons, with higher characteristic frequency (CF) neurons distributed medially. NL neurons measure ITD by binaural coincidence detection, with inputs from ipsilateral sounds detected more medially. **(b)** Normalized synaptic inputs to two NM neurons recorded at the extremes of the tonotopic axis shows that the level of depression is higher for low CF input neurons (top), resulting in potential spike failures (*) in response to tonic inputs. Panel (b) modified from [12].

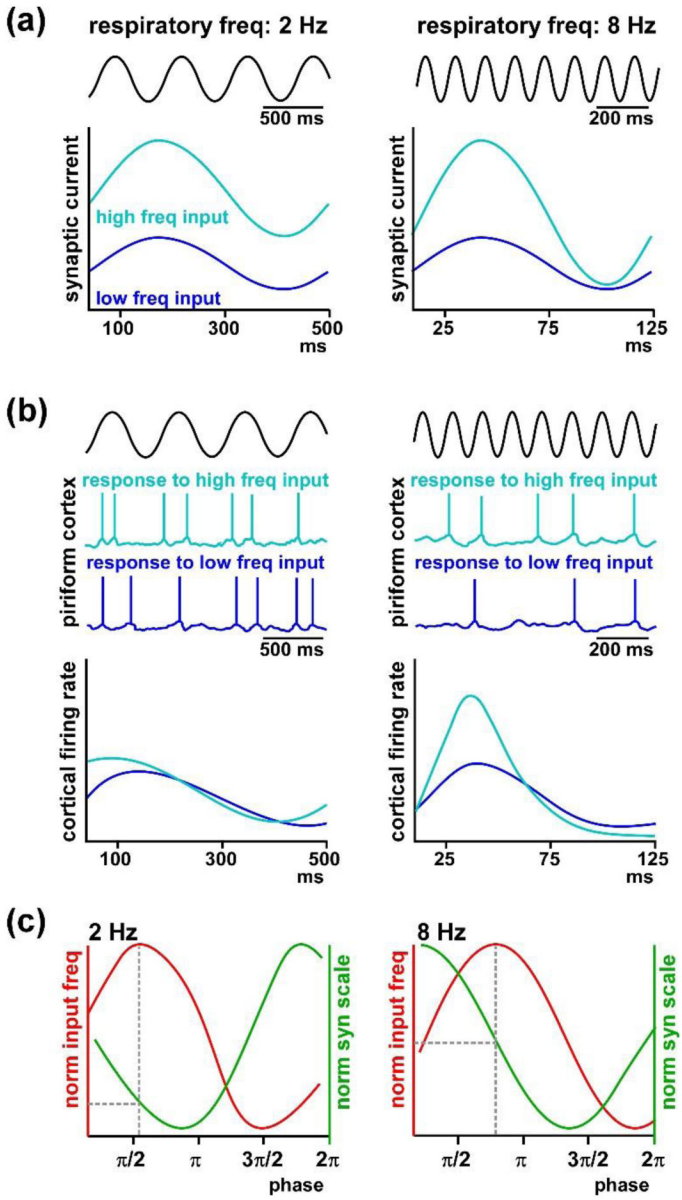

Figure 3.

STP enables olfactory cortical neurons to discriminate different input frequencies from the olfactory bulb when these inputs are modulated at the sniff respiratory frequency. **(a)** Population peak synaptic inputs (simulated here) from the olfactory bulb to cortical neurons is modulated by the respiratory frequency (passive freq. at 2 Hz, sniffing freq. at 8 Hz). Compared to low frequency inputs (12–16 Hz), high frequency inputs (24 Hz), when modulated at 2 Hz increase the peak synaptic response in amplitude but not in slope. However, due to STP, when modulated at 8 Hz, high frequency inputs increase both the amplitude and slope of the synaptic response. **(b)** Cortical neurons increase their firing rate in response to high frequency inputs modulated at 8 Hz, but not 2 Hz. **(c)** Normalized peak population synaptic inputs and input frequencies shown as a function of the phase of the respiratory cycle at 2 and 8 Hz. At 2 Hz modulation, due to STP, synaptic scale is nearly

minimal (~0.1, dashed lines) when firing rates peak. At 8 Hz modulation, in contrast, synaptic scale is ~0.5 when firing rates peak. In the 2 Hz case, temporal overlap between presynaptic spiking and the recruitment of depression counteracts increases in firing rate. Modified from [26].

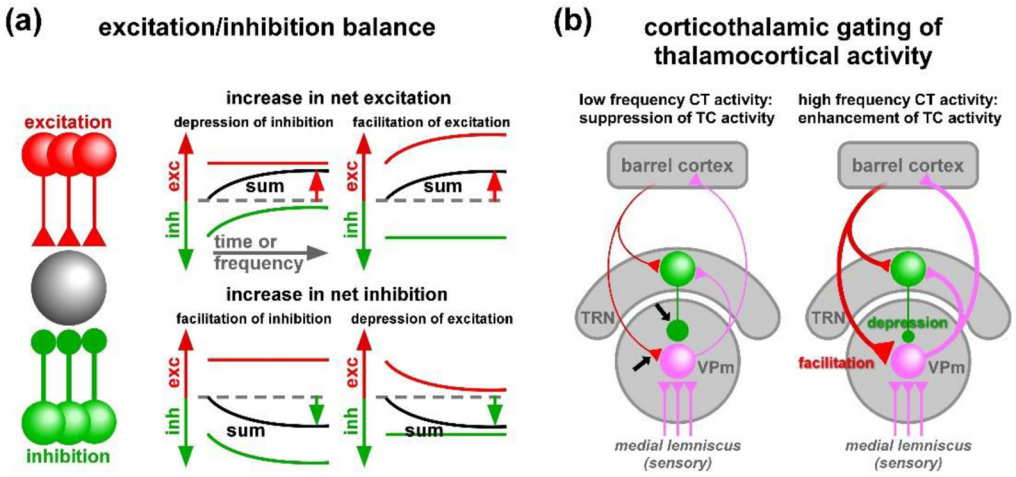

Figure 4.

Schematics of functional roles of STP of inhibitory synapses at the circuit level. **(a)** The balance of excitation and inhibition determines excitability and activity levels in many neurons and circuits. STP can tune this balance, as a function of either time or frequency. Net excitation increases when the inhibitory synapses depress, or the excitatory synapses facilitate. Net inhibition increases when inhibitory synapses facilitate, or excitatory synapses depress. **(b)** In mouse, sensory information from whiskers is relayed by the vibrissal region of the thalamus (ventral posterior medial nucleus, VPm) to the vibrissal region of the somatosensory cortex (barrel cortex). The thalamus receives massive amounts of descending synaptic input from corticothalamic (CT) projections, presumably a mechanism of cortical control of ascending sensory information flow, depending on behavioral context. The effect of descending input on thamalocortical (TC) activity is ambiguous because CT projections make both direct excitatory connections and feedforward inhibitory ones through GABAergic neurons in the thalamic reticular nucleus (TRN). Excitatory connections show facilitation, whereas inhibitory ones show depression. At low levels of TC activity, feedforward inhibition is dominant and TC activity is suppressed. At higher levels of CT activity, TC activity rapidly becomes enhanced as inhibitory synapses depress, and excitatory ones facilitate [35].