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Synapse-type-specific plasticity in local circuits

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Neuroscientists spent decades debating whether synaptic plasticity was presynaptically or postsynaptically expressed. It was eventually concluded that plasticity depends on many factors, including cell type. More recently, it has become increasingly clear that plasticity is regulated at an even finer grained level; it is specific to the synapse type, a concept we denote synapse-type-specific plasticity (STSP). Here, we review recent developments in the field of STSP, discussing both long-term and short-term variants and with particular emphasis on neocortical function. As there are dozens of neocortical cell types, there is a multiplicity of forms of STSP, the vast majority of which have never been explored. We argue that to understand the brain and synaptic diseases, we have to grapple with STSP.

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A definition of synapse-type-specific plasticity

Here, we define synapse-type-specific plasticity (STSP) as plasticity that varies with synapse type. STSP comes in different forms (Figure 1). Different synapses originating from the same presynaptic cell can have different forms of plasticity depending upon the on postsynaptic target, here termed divergent STSP. Conversely, plasticity may differ for the same postsynaptic cell depending on the type of input, which we denote convergent STSP. While more difficult to distinguish experimentally, STSP also encompasses plasticity that varies at the level of individual synaptic contacts between one presynaptic axon and individual postsynaptic neuron. In this review, we discuss examples of all three forms of STSP.

STSP should not be mixed up with synapse or input specificity in classical plasticity studies. A form of long-term plasticity that is input specific does not spread appreciably to neighboring synapses that were not stimulated during the induction of plasticity [1]. In other words, STSP may or may not be input specific. In the case of long-term plasticity, STSP is therefore not directly related to either homosynaptic or heterosynaptic plasticity [1].

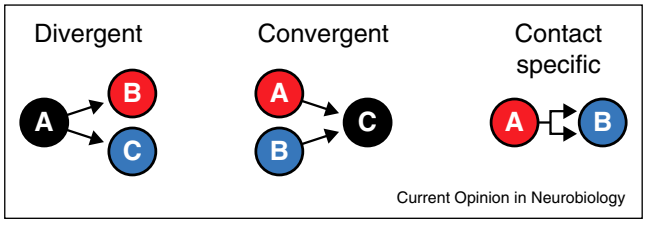
Synaptic plasticity may vary in several different ways. STSP may thus refer to distinct specificities in terms of phenomenology of plasticity, induction mechanism, and/or expression mechanism. Finally, STSP may also refer to either short or long-term plasticity, and we review both these scenarios here below, starting with the former.

Synapse-type-specific short-term plasticity

Short-term plasticity (STP) refers to a depression or facilitation of synaptic efficacy that last on the order of seconds [2]. The mechanisms underlying STP are typically presynaptic, including changes in the readily releasable vesicle pool size, changes in the number of release sites, and alterations in presynaptic calcium dynamics [3]. Early evidence that STP could be synapse-type-specific came from observations that the magnitude and variability of calcium influx in response to single action potentials was not uniform across a single axon collateral [4,5]. In addition, these differences in calcium influx across a single axon have been shown to contribute to distinct vesicular release probabilities at individual synapses [6,7]. Synapse-type-specific STP thought to result from such differences has been observed in both neocortex and hippocampus [8,9••,10]. These differences in STP are also likely correlated with differences in synaptic morphology. For example, the number of docked vesicles is known to be correlated with both presynaptic release probability and the readily releasable synaptic vesicle pool [11,12]. However, differences in docked vesicles do not account for different STP at different presynaptic terminals onto the same postsynaptic cell [13], suggesting these ultrastructural measurements may not always be sufficient to infer synapse-type-specific STP alone.

STP differs with both presynaptic and postsynaptic cell type, suggesting that specific trans-synaptic signaling mechanisms define STP at a given synapse. These mechanisms are poorly understood, but recent findings suggest that extracellular leucine-rich repeat proteins such as Elfn1 trans-synaptically regulate synapse-type-specific STP [14••]. In hippocampus, Elfn1 is selectively expressed at somatostatin but not parvalbumin-positive interneurons, where it signals retrogradely to increase

Figure 1



Different forms of synapse-type-specific plasticity. Synapse-type-specific plasticity (STSP) comes in several different forms. It may be *divergent*, in which case synapses from the presynaptic cell type A to the postsynaptic cell type B do not undergo the same kind of plasticity as synapses onto type C. An example of this is illustrated in Figure 2 [9••]. STSP may also be *convergent*, so that connections from presynaptic cell type A onto postsynaptic cell type C do not have the same kind of plasticity as connections from presynaptic cell type B onto C do. This scenario is illustrated in Figure 3 [31••,67••]. Many connections in the brain, however, are made from multiple synaptic contacts [5], and a third possible STSP scenario exists in which plasticity is *contact specific*. This scenario is less well studied, but some studies indicate that different contacts of the same connection type are very similar with respect to plasticity [5,62•], whereas others imply that they may be different [52•,60].

facilitation at glutamatergic inputs. Adhesion molecules such as cadherins, neuroligins, or SynGAP also regulate synaptic dynamics [15•,16,17,18]. In addition, recent studies suggest that synapse-type-specific STP is influenced presynaptically by RIM, α2δ, calcineurin Aα, and CDK5, proteins that regulate release probability and STP by altering presynaptic calcium channel expression [19–21]. Similarly, synapse-type-specific expression of voltage-gated Na^+ and K^+ channels at individual axon boutons may influence action potential waveforms distinctly at individual synapses [22,23•]. A general mechanism for the specification of synapse-type-specific STP may therefore be cell-type specific expression of Elfn1 or related molecules, which govern the synapse-type-specific expression of adhesion molecules. These in turn may change the expression of voltage-gated ion channels or presynaptic neurotransmitter receptors, ultimately altering vesicular release [24].

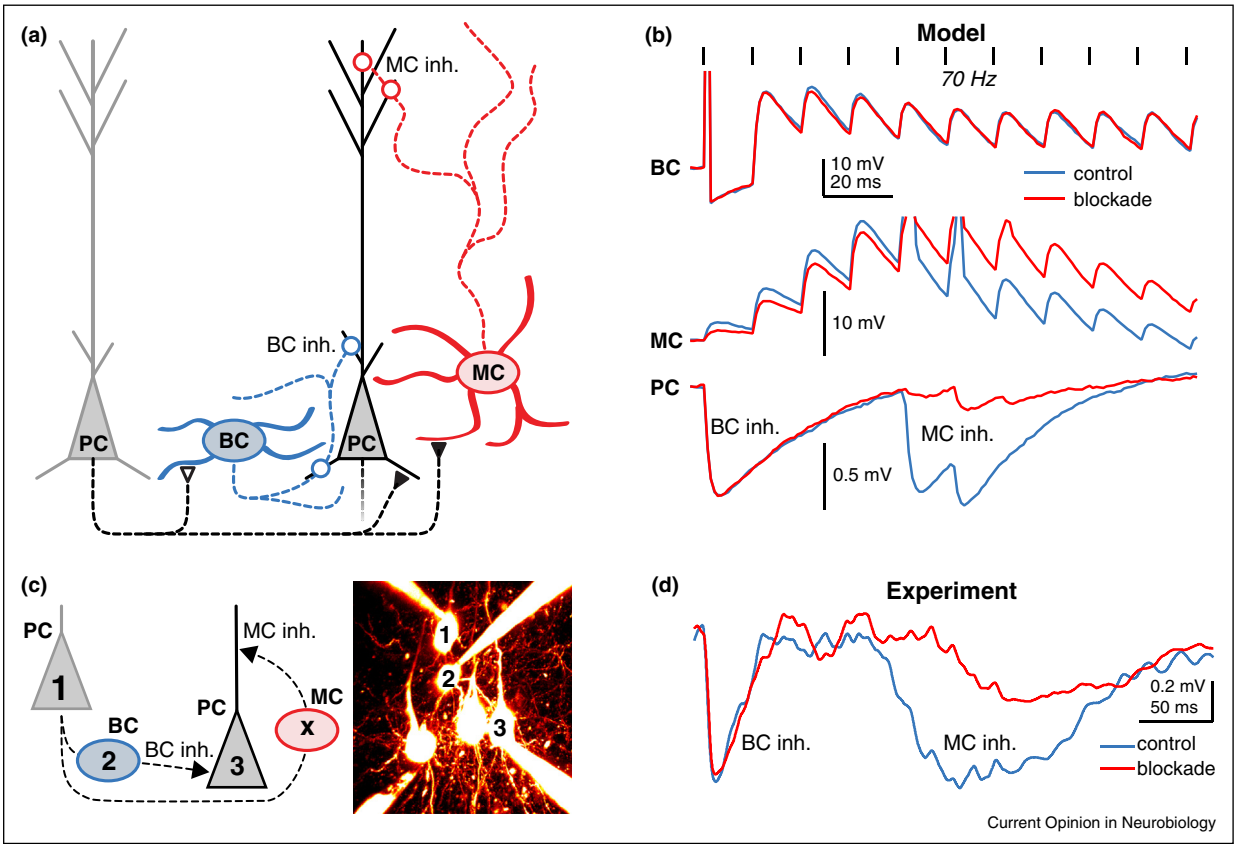
Genetic programs are not the sole determinants of STP, as it depends on age and activity. During development, for example, STP generally becomes less depressing [25–30]. This developmental change, however, is not homogenous across all synapse types. Connections between cortical layer 5 (L5) and L2/3 pyramidal neurons undergo a reduction in synaptic depression through development, but the reduction is larger at synapses between L5 neurons [25]. At L2/3 visual cortical neurons, L4 synapses undergo a reduction in short-term depression through development, but at intralaminar L2/3 synapses onto the same postsynaptic cell type do not undergo this change [27,31••,32••,33]. These layer-specific differences in STP may result from different developmental time points for layer formation [34], and therefore these differences may not always last into adulthood.

Developmental alterations in STP may involve both presynaptic and postsynaptic changes, demonstrating that synapse-type-specificity is not universally dictated by a single mechanism. For example, short-range but not long-range excitatory inputs onto parvalbumin-positive interneurons of visual cortex undergo a developmental reduction in short-term depression involving both a reduction in presynaptic release and increase in calcium-permeable AMPARs [32••]. In this case, increasing the number of calcium-permeable AMPARs increases short-term facilitation postsynaptically through a reduction in polyamine-dependent calcium-permeable AMPAR block during repetitive presynaptic cell firing [35,36]. Polyamine-dependent facilitation of AMPARs [35,36] and other postsynaptic phenomenology such as temporal summation [37] may be general mechanisms for postsynaptically mediated short-term STSP. In agreement with this view, CP-AMPARs are only expressed at specific subsets of synapses [36]. Overall, these findings suggest there is a developmental synapse-type-specific alteration in STP, rather than a uniform reduction in synaptic depression across all synapses.

Sensory experience also alters STP, however it is unclear whether experience *per se* is required because such alterations are also observed in cultured neurons [38]; perhaps neuronal activity is sufficient to drive changes in STP. Conversely, sensory deprivation alters STP at a variety of synapses. However, the effect of sensory deprivation on STP is often inconsistent even for the same synapse type, with specific types of sensory deprivation promoting facilitation but others increasing depression [31••,39–43]. A number of experimental factors, including the nature and age of deprivation [39,44], rate of presynaptic stimulation or firing [31••], and pharmacological receptor blockade [31••] likely contribute to such inconsistencies. These developmental alterations in STP are probably key to regulating neuronal excitation because excitatory short-term synaptic transmission depresses more when inhibition is still immature [27]. Subsequently, experience may alter STP to enable reliable information processing and to promote Hebbian plasticity.

Recent evidence suggests that synapse-type-specific expression of presynaptic NMDA receptors (preNMDARs) is an important determinant of developmental and sensory-experience driven alterations in STP. Within visual cortical L5, preNMDARs selectively influence STP at pyramidal cells synapsing onto neighboring pyramidal cells or onto somatostatin-positive Martinotti cells, but not onto parvalbumin-positive basket cells [9••] (Figure 2a). PreNMDARs typically modulate STP by acting as a high-pass filter for

Figure 2



PreNMDARs synapse-type-specifically reroute information flow in local neocortical circuits. **(a)** PreNMDARs are synapse-type-specifically expressed at connections (closed symbols) from pyramidal cells ('PC') to other pyramidal cells as well as to Martinotti cells ('MC'), but not at connections (open symbols) to basket cells ('BC'). Circles and triangles symbolize inhibitory and excitatory connections, respectively. **(b)** A small network model with synaptic dynamics tuned to experimental data predicted that during 70-Hz pyramidal-cell bursts (vertical lines), preNMDAR blockade would disrupt late Martinotti but not early basket-cell inhibition. Model prediction before and after preNMDAR blockade in blue and red, respectively. **(c)** 70-Hz spiking in pyramidal cell 1 evoked both Martinotti and basket-cell inhibition in pyramidal cell 3. Intermediate Martinotti cell ('X') was not patched. **(d)** Experiments verified model prediction: amplitude and latency of Martinotti but not basket-cell inhibition was affected by preNMDAR blockade. In other words, synapse-type-specific preNMDAR expression selectively boosts pyramid to Martinotti cell neurotransmission during high-frequency firing without affecting pyramidal cell connections to basket cells. Modified with permission from [9••].

presynaptic release [31••,45,46]. Through this action, preNMDARs at excitatory synapses onto L5 Martinotti cells increase frequency-dependent disynaptic inhibition (Figure 2b–d). Similarly, preNMDARs influence STP at synapses from L4 neurons onto L2/3 pyramidal neurons, but not at L2/3 intralaminar synapses [47]. Development and sensory experience regulate preNMDAR expression, suggesting that these receptors are well suited for regulating synapse-type-specific STP [31••,33,39,48]. Synapse-type-specific expression of preNMDARs may thus be a general principle governing the function of this receptor type. Since preNMDAR expression varies with postsynaptic cell identity, we propose that postsynaptic neurons retrogradely influence the expression of preNMDARs at specific synapse types. This may occur through postsynaptic proteins such as Elfn1, which is known to influence presynaptic ionotropic receptor expression [14••].

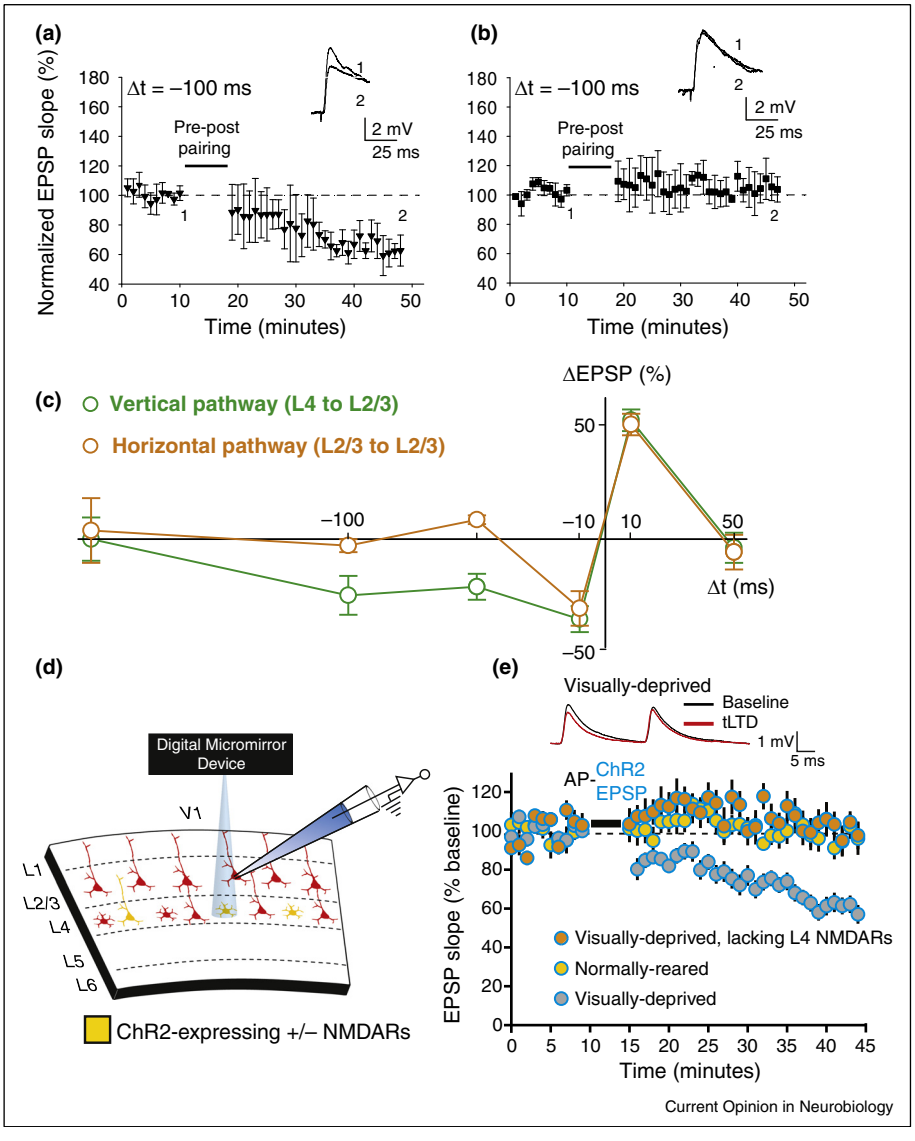
Synapse-type-specific long-term plasticity

Long-term plasticity refers to activity-dependent changes in synaptic efficacy that last for minutes up to days [49]. Long-term plasticity is typically mechanistically distinct from STP and includes processes such as Hebbian and homeostatic plasticity. Long-lasting increases or decreases in synaptic strength — long-term potentiation (LTP) or depression (LTD), respectively — are believed to be critical to circuit and memory formation [50]. Synapse-type-specific long-term plasticity may thus be important for adapting synapses to the overall function of the circuit in which they are embedded.

Homosynaptic forms of long-term plasticity are specific to activated synapses. The underlying mechanisms can be synapse-type-specific as well, resulting in differences in locus of expression or in activity requirements. Classically,

LTP and LTD are induced by the activation of postsynaptic NMDA, AMPA, and metabotropic glutamate receptors (mGluRs). The expression of these postsynaptic receptors as well as their presynaptic counterparts varies considerably with brain region, synapse type, and through development [51]. At large mature dendritic spines, LTD requires activation of both NMDARs and mGluRs as well as calcium release from internal stores [52•,53]. However, at small immature spines, LTD requires only NMDAR activation [52•,53]. Since large spines contain more AMPARs [54], these findings are consistent with synapse-type-specific metaplasticity, in which previous history of activity alters the subsequent threshold for plasticity [55]. Indeed, sensory experience and neuronal activity alter postsynaptic NMDAR subunit expression at many synapses within the brain [56]. In hippocampal

Figure 3



Experience-dependent regulation of synapse-type-specific long-term depression at layer 2/3 cortical synapses. In early cortical development, timing-dependent LTD (tLTD) at L4 to L2/3 synapses requires preNMDARs and can be induced with relatively long action potential-EPSP pairings (**a, c**). In contrast, tLTD at L2/3 to L2/3 horizontal connections requires postsynaptic NMDARs and has a shorter tLTD integration window (**b, c**). PreNMDAR-mediated tLTD at L4 to L2/3 is developmentally downregulated following the first 3-4 weeks of postnatal development, but this downregulation does not occur at visual cortical L2/3 to L2/3 synapses [31••,69]. Thus, in normally reared P85-95 mice, pairing action potentials with EPSPs generated by optogenetic stimulation of L4 neurons fails to induce tLTD at L4 to L2/3 synapses (**d**–**e**, yellow circles). However, visually depriving mice for 10-15 days during this developmental period restores preNMDAR-mediated tLTD at L4 to L2/3 synapses (**e**, gray circles). This effect of visual-deprivation is lost when preNMDARs are selectively deleted from L4 neurons (**e**, orange circles). Modified with permission from [31••,67••].

culture, alterations in synaptic activity at single synapses are sufficient to alter both postsynaptic NMDAR expression and later outcomes of plasticity, demonstrating that metaplasticity is an important determinant for synapse-type-specific long-term plasticity [57]. Synapse-type-specific differences in the expression of proteins signaling cascades downstream of neurotransmitter receptors such as CaMKII and MAPK may also be important for synapse-type-specific expression of plasticity, but how the expression of these molecules differs for a given neuron type based on synaptic source is largely unknown [58]. However, differences in postsynaptic signaling can influence multiple forms of long-term plasticity since synapse-type-specific expression of activity related proteins such as Arc have been shown to influence synapse-type-specific homeostatic plasticity [59]. The initial properties of long-term synaptic plasticity may thus be broadly defined in synapse-type-specific manners. Through alterations in neuronal activity, synapses may subsequently acquire specific signaling molecules that enable synapse-type-specific long-term plasticity.

Dendrite biophysics may also help determine long-term STSP. For example, distal excitatory synapses onto neocortical L5 pyramidal cells are less prone to long-term potentiation than the proximal ones are [60], because backpropagating action potentials — which determine potentiation in this cell type — fail to invade distal arbors [1]. But each synaptic connection is typically formed by multiple synaptic contacts, some quite distal and some proximal [61], which implies that plasticity might be synaptic contact specific, since distal contacts may undergo LTD when proximal contacts potentiate. Interestingly, in the hippocampal CA1 area, pairs of spines on the same dendrite that received input from the same axon are of similar size, whereas spines on different dendrites are not [62•,63]. Because spine volume is closely correlated with synaptic strength [12], this is concrete evidence that plasticity is specific even down to individual synaptic contacts [5].

PreNMDARs also mediate diverse forms of LTP and LTD at subsets of synapses, including timing-dependent LTD at cortical synapses and theta-burst stimulation induced cortical-striatal LTP [45,64–66]. PreNMDARs are therefore likely to bias plasticity and circuit modification. In early neocortical development, preNMDARs mediate timing-dependent LTD (tLTD) at L4 to L2/3

Table 1

Examples of STSP.

Brain region	Synapse types	Consequences	Mechanisms	Ref
Visual cortex	Excitatory connections from L4 neurons to L2/3 PCs	Experience-dependent regulation of LTD and STP	PreNMDARs	[31••]
Barrel cortex	Excitatory connections from L4 neurons to L2/3 PCs	Experience-dependent regulation of STP	PreNMDARs	[39]
Barrel cortex	Excitatory connections from L4 neurons to L2/3 PCs	Trigger LTD	PreNMDARs	[67••]
Barrel cortex	Excitatory connections from L4 neurons to L2/3 PCs	Upregulate short-term depression	PreNMDARs	[47]
Visual cortex	Excitatory connections between L5 PCs	Evoke LTD and upregulate short-term depression	PreNMDARs	[45]
Visual cortex	Excitatory connections from L5 PCs to MCs	Upregulate dendritic inhibition	PreNMDARs	[9••]
Visual Cortex	Short-range excitatory connections from PCs to L2/3 PV-positive basket cells	Increase short-term facilitation through polyamine-dependent AMPAR facilitation	CP-AMPARs	[32••]
Hippocampus	Excitatory connections from CA1 PCs to Sst-positive INs	Upregulate short-term facilitation	Presynaptic kainate receptors, postsynaptic Elfn1	[14••,78]
Hippocampus	Excitatory contacts to CA1 PCs	Homogenous STP for synaptic contacts with the same presynaptic and postsynaptic cells	Synaptic plasticity	[62•,63]
Hippocampus	Hippocampal CA3 and CA1 dissociated culture	Regulate presynaptic release probability through modulation of calcium channel number and/or function	VGCC auxiliary subunit $\alpha 2\delta$, calcineurin Aα, CDK5	[19,20]
Hippocampus	Large excitatory spines onto CA1 PCs	Regulates spine shrinkage, LTD	Type 1 mGluRs, calcium release from internal stores	[52•]
Cerebellum	Purkinje and basket cell terminals in dissociated culture	Regulation of STP by control of axon terminal excitability	Differential Na^+/K^+ channel ratio	[23•]
Cerebellum	Excitatory inputs to granule cells	Facilitation of pattern separation	Modality-specific STP	[73••]

The studies in this table illustrate in several different brain regions how STSP can be produced mechanistically and what the functional consequences can be. This list is not intended to be exhaustive.

synapses [48,66], but tLTD at horizontal L2/3 to L2/3 synapses requires postsynaptic NMDARs [67••,68]. These mechanistic differences may underlie the considerably longer tLTD window at L4 to L2/3 synapses [67••] (Figure 3a–c). Due to developmental downregulation of preNMDARs, tLTD at L4-to-L2/3, but not at L2/3-to-L2/3 synapses, is more readily induced in early development and becomes increasingly dependent on postsynaptic NMDAR activation in later development [48,69]. In the visual cortex, dark rearing prolongs preNMDAR-mediated tLTD at L4 to L2/3 synapses, suggesting preNMDARs enable specific synapses to uniquely respond to changes in the sensory environment [31••] (Figure 3d–e). Taken together, these studies show that preNMDARs are well positioned for synapse-type-specific control of both long and short-term plasticity.

Conclusions and future directions

In this review, we have discussed recent research on STSP learning rules and synaptic dynamics, as well as their potential functional roles (summarized in Table 1). We argue that STSP may have evolved of necessity to enable more complex computations in local circuits. The existence of STSP is furthermore expected, since the nodes of biological neuronal networks are made up of dozens of different cell types [70–72]. Presumably, these different cell types need to be governed by distinct synaptic plasticity learning rules, because activity patterns and excitabilities vary tremendously with cell type. Indeed, it was recently shown that pattern separation in the cerebellum is enhanced by input-specific STP onto granule cells, since the distinct activity patterns of modality-specific afferents means coding benefits from differential short-term STSP [73••]. Furthermore, activity levels must be kept within reasonable bounds, and it is likely that one or several interneuron types specifically adjust their inhibitory influence according to key developmental events such as eye opening, or in pathological states such as physical trauma, inflammation, or epilepsy. Indeed, STSP dysfunction has been observed in a variety of disease states ranging from schizophrenia [74], Alzheimer's disease [75], to autism spectrum disorders [76,77], demonstrating that an understanding of the properties of STSP may be fundamental to treating neurological diseases.

While there are many mechanisms for regulating STSP, we have focused on the preNMDAR as one important example of a determinant of STSP in local circuits that controls both short-term [9••] and long-term plasticity [67••] and that is linked to the closing of the visual cortex critical period [31••]. This preNMDAR focus is not to imply that this receptor type necessarily holds a special status in the brain; it is merely a case study and a starting point for further research on STSP. Indeed, we suggest that control of STSP by particular receptor types is a general principle in the brain. For example, presynaptic kainate receptors also determine STSP, by promoting facilitation at excitatory inputs onto somatostatin-positive hippocampal interneurons [14••,15•,78].

When it comes to complexity, neuronal network computer models are invariably a far cry from their biological counterparts. In models, synaptic weights typically have no short-term dynamics, neurons do not accommodate, that is if they spike at all, and nodes are often perfectly homogenous. This is natural, as most computer models are not intended to simulate detail, nor do they need to. But for aficionados of detail, this is of course entirely wrong. Large-scale detailed computer models of neuronal circuits have recently received much attention as well as criticism [79,80]. Although a natural next step in computer modeling might seem to require incorporating considerably more detail, our review highlights just how much detail there is. For every cell type — and there is a lot of them [70–72] — there is a corresponding multiplicity of STSP learning rules and short-term dynamics. Yet, to understand the brain and synaptic diseases such as autism, anxiety, or epilepsy [81], it appears that we have no choice but to grapple with STSP. The task that lies ahead is nothing short of formidable, as we have just barely scratched the surface.

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