Chapter 3
Synaptic Cooperation and Competition: Two Sides of the Same Coin?

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Abstract Activity-dependent plasticity of synaptic connections is a hallmark of the mammalian brain and represents a key mechanism for rewiring neural circuits during development, experience-dependent plasticity, and brain disorders. Understanding the rules that determine how different neuronal inputs interact with each other, allow us to gain insight on the cellular and molecular mechanisms involved in memory establishment and maintenance. One of the most intriguing aspects of memory formation is the observation that past and ongoing activity can influence how information is processed and maintained in the brain. At the cellular level, the synaptic tagging and capture (STC) theory states that the maintenance of activity-dependent synaptic changes is based on the interaction between synaptic-specific tags and the capture of plasticity-related proteins. The STC has provided a solid framework to account for the input specificity of synaptic plasticity but also provides a working model to understand the heterosynaptic interaction between different groups of synapses. In this chapter, I will discuss the evidence regarding the cooperative and competitive interactions between different groups of synapses. In particular, I will address the properties of synaptic cooperation and competition that contribute to the refinement of neuronal connections during development. Later, I will address the evidence that similar rules operate during the induction and maintenance of synaptic plasticity. Due to the intricate relationship between synaptic plasticity and memory formation, understanding the cellular rules of cooperative and competitive interactions between synapses, will allow us to further dissect the rules underlying associative learning.

Keywords Synaptic plasticity • Synaptic cooperation • Synaptic competition • Neuronal connectivity • Synaptic capture

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S. Sajikumar (ed.), *Synaptic Tagging and Capture*,
DOI 10.1007/978-1-4939-1761-7_3

3.1 Introduction

The most striking property of the nervous system is its ongoing ability to learn and adapt to the stimulus of the environment. However, this constant ability to adapt raises a fundamental problem: how to be able to change without losing identity. Indeed, the nervous system has evolved to be a highly plastic system but maintaining the identity of the individual and preserving the responses necessary for its survival. It is now well accepted that developmental and learning changes in the nervous system are implemented through modifications in synaptic strength and ultimately in neuronal connectivity (Malenka and Nicoll 1997, 1999). In this respect, Donald Hebb postulated "When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place, in one or both cells so that the efficacy of cell A in firing B is increased" (Hebb 1949). This learning rule, commonly referred as "neurons that fire together, wire together," implies that correlated activity between two connected neurons leads to a strengthening of their connectivity (Miller 1996). The observation that high-frequency electrical stimulation of hippocampal afferents results in a long-term potentiation (LTP) of synaptic strength was the first demonstration that this learning rule could be implemented in biological systems (Bliss et al. 2003; Bliss and Collingridge 1993). After this, it was also demonstrated that synaptic transmission can be decreased by the induction of long-term depression (LTD) (Becker et al. 2008; Malenka and Bear 2004; Malenka and Nicoll 1998). Since then, a substantial amount of work has been devoted to understand the rules underlying the induction and the maintenance of LTP and LTD (Kauer et al. 1990; Lisman et al. 1997).

It is also clear that learning is an ongoing process, in which past and present neuronal activity can influence how information is processed in the brain and ultimately how memories are formed and maintained (Redondo and Morris 2011). Similarly, at the cellular level, it is now well established that previous neuronal activity can modulate the induction and maintenance of LTP and LTD (Ehlers 2003; Fonseca et al. 2006a, b; Fonseca 2012; Sajikumar et al. 2005, 2007; Sajikumar and Frey 2004a, b). This continuous processing of information allows different groups of activated synapses to interact, modulating the ability to induce and maintain LTP and LTD (Alarcon et al. 2006; Fonseca et al. 2004; Govindarajan et al. 2011). In this chapter, I will provide a brief outlook of these dynamic interactions between activated synapses, particularly discussing the evidence that synapses can engage in synaptic cooperation or synaptic competition. Although the cellular mechanisms involved in LTP and LTD are in general similar, I will focus on the cooperative and competitive synaptic interactions involved in the induction and maintenance of LTP.

Classically, LTP is divided into three stages or phases, an induction phase, an early-LTP phase, not dependent on protein synthesis and a late-LTP phase, dependent on de novo protein synthesis (Bramham 2008; Bramham et al. 2010; Frey et al. 1988; Huang et al. 1996; Kelleher et al. 2004; Reymann and Frey 2007; Wikstrom et al. 2003). This distinction, based on pharmacological or genetic manipulations of the neuronal protein synthesis machinery, is clearly an artificial division, as protein

synthesis is activated at the time of LTP induction and activity-dependent mechanisms can modulate the length of these phases and their dependence on protein synthesis (Djakovic et al. 2009; Fonseca et al. 2006a, b). Nevertheless, I will maintain this classic distinction for the purpose of clarity.

At this point, it is also useful to define what one considers being synaptic cooperation and synaptic competition. Synaptic cooperation is any cellular mechanism that allows two distinct groups of synapses to synergically trigger the induction or the maintenance of LTP. Conversely, synaptic competition is any cellular mechanism in which distinct groups of synapses interact by a defined rule such that one of the participants emerge as a winner (Van Essen et al. 1990). This does not necessarily mean that the winner has to be potentiated nor does it consider the mechanism by which the winner is achieved. Indeed, there are two possible forms of competition. In an independent competition, there are no interactions between the different participants. In this case, each participant does not influence each other, but rather the winner is selected based on its own performance (Colman and Lichtman 1992). In an interdependent competition, the participants interact with each other that is the performance of each participant is influenced by other participants (van Ooyen 2001). In this form of competition participants can interact in a consumptive way, competing for a limited resource, or by interference, in which one input has a direct negative interaction with a second input (van Ooyen 2001). Since LTP can be divided, at least, in three phases, synapses can interact cooperatively and competitively during any of these phases, during the induction, the early-phase or the late-phase of LTP. This idea that synapses or neuronal inputs can cooperate or compete is not new. It was first described, more than 60 years ago, in the developing nervous system, when studying the formation of a cell receptive field (Hubel et al. 1977; Stent 1973). However, the fundamental question regarding the cooperative and competitive interactions between synapses remains to be unanswered: what are the rules underlying these interactions? Or in other words, which patterns of neuronal activity leads to synaptic cooperation or to synaptic competition? In this chapter, I will address this question by first making a brief overview of the rules of synaptic cooperation and competition in the developing nervous system and further discuss what is known in the adult learning brain.

3.2 Synaptic Cooperation and Competition in a Developing Nervous System

The first indication that synapses can engage in synaptic cooperation and competition to establish new connective partners, came from studies of the developing nervous system. Since Cajal's observations of the nervous system, it is clear that the development of the nervous system is based on pruning of synaptic connections. Moreover, it is now clear that long-lasting changes in neuronal connectivity in the developing and the mature brain share many common principles. For example, the Hebbian rule described above, in the context of synaptic plasticity, also applies to

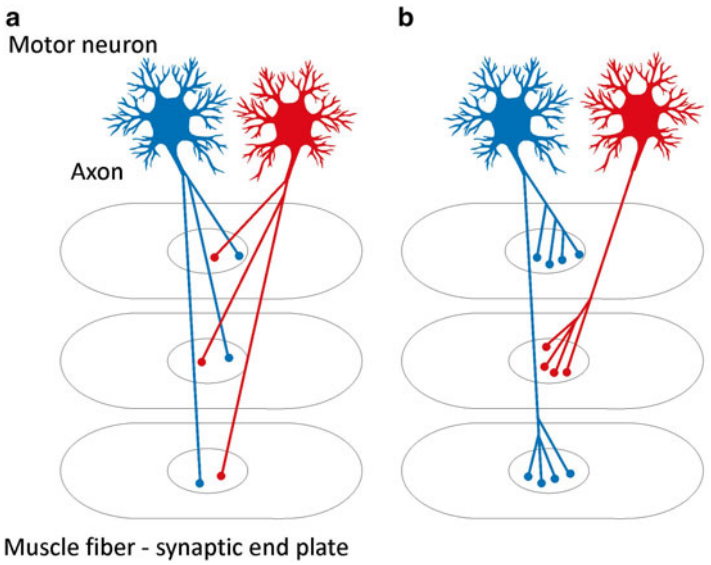

Fig. 3.1 Development of the neuromuscular junction. (**a**) Initially, each muscle fiber is innervated with axonal inputs originating from multiple motor neurons. (**b**) During development, synaptic cooperation and competition leads to neuronal refinement and single innervation of the neuromuscular junction

the developing nervous system, in which coincident spike activity leads to the strengthening of neuronal connections whereas non-coincident activity leads to the weakening of connections (Lo and Poo 1991; Stent 1973).

Although there are numerous examples described in the literature, the development of a mature neuromuscular junction is by far the most studied and clear example how synaptic cooperation and competition can shape the nervous system. In a mature system, in mammals, each muscle fiber is innervated by a single motor neuron. During development, however, this connective pattern is initially much less refined with each muscle fiber being innervated by several inputs originating from several motor neurons (Fig. 3.1). How does this system mature? For a muscle to function there are certain pre-requisites that need to be preserved: first, there must be a sufficient number of inputs terminating in a muscle fiber. This allows the neuromuscular junction to be sufficiently activated and overcome the contractility threshold so that the muscle can contract in an effective manner. Second, the correct target must be found so that groups of muscles are activated in a coordinated fashion. For example, during a simple moving such as walking, flexors and extensors muscles need to be contracting and relaxing in a coordinative manner so that their action does not oppose. During development, several mechanisms operate to achieve this level of coordination. Genetic mechanisms are clearly involved in the targeting of muscle cells by specific neuronal inputs and hence in their initial localization, but the connectivity pattern is highly unspecific, with each motor neuron innervating several targets simultaneously (Fig. 3.1a).

The initial unspecific innervation of muscle fiber is gradually being replaced by a single motor-neuron innervation (Fig. 3.1b). While the detailed cellular mechanisms involved in the refinement of the neuromuscular junction are still not entirely clear, there is substantial evidence that local synaptic interactions leads to the alteration of the functional connective pattern. This process of axonal refinement is gradual and asynchronous, linked to changes in synaptic efficacy, with inputs gradually retracting while others occupy their post-synaptic sites, once they become available (Colman et al. 1997; Walsh and Lichtman 2003). It is now clear that this activity-dependent remodelling of connections involves molecular cues that determine the best match between axonal input and muscle fiber, but synaptic cooperation and competition between axonal terminals of the same motor neuron and between different motor neurons (intra-neuronal and interneuronal) plays a fundamental role (Laskowski et al. 1998; Laskowski and Sanes 1987; Walsh and Lichtman 2003).

How can synaptic cooperation and competition ensure the refinement of the connective pattern between motor neurons and muscle fibers? In the mature neuromuscular junction, spike activity of motor neurons of the pool which innervates a given muscle is asynchronous (Buffelli et al. 2002, 2004). This ensures that muscle contraction is smooth. This asynchronous activity creates a local instability that may constitute the substrate for synaptic competition. Consistently, induction of synchronous activity by electrical stimulation or NMDA glutamate receptors inhibition blocks synaptic competition leading to a poly-innervated neuromuscular junction (Buffelli et al. 2004; Personius et al. 2008). Recent evidence suggests that individual axon branch removal occurs randomly, leaving a post-synaptic site unoccupied. This creates a triggering signal for neighboring axons to sprout. The re-occupation favors axons that better drive the post-synaptic target or in other words favors the motor neuron with the highest number of neighboring axons (Turney and Lichtman 2012). Eventually, this process leads to single innervation. Interestingly, there is also evidence that the same principle applies to synaptic rearrangements occurring in other areas of the nervous system. For example, climbing fibers on Purkinje cells elaborate new connections as other axons are eliminated. This process is highly complementary with losses being compensated with growth (Hashimoto et al. 2009). As in the neuromuscular junction, in the Purkinje cell—climbing fiber system, there is evidence that the limited resource is space. In both systems, the number of synaptic sites is mainly determined by the target cell, and under normal conditions input fibers can establish more connections than the ones available. This, of course, generates a competitive pressure for occupancy of the functional synapses.

Interestingly, there is also evidence that the synaptic instability described above can lead to synaptic cooperation. In a model of retinotopic refinement, in the Goldfish, if the number of retinotectal projections is low, a cooperative interaction between input projections is the dominant mechanism involved in the refinement of the connections (Olson and Meyer 1994). Because there is no competitive pressure in this situation, the authors suggest that the synaptic instability by itself would lead to the de-innervation of the target cells and only the inputs that are active in correlation with the target cell, following the Hebbian rule, would be reinforced, possibly

by a positive feedback signal (Olson and Meyer 1994). This positive feedback signal can actively promote an adjustable convergence of coactive fibers without the necessity of competition.

In an attempt to conciliate all these observations, Turney and Lichtman (2012) proposed a model in which the initial event leading to the refinement of the neuromuscular junction is the loss of motor-neuron synaptic contacts. This can occur following a Hebbian-based loss of connectivity in which non-correlated motor neurons are depressed, progressively becoming less and less efficient at stimulating their post-synaptic partners. There is evidence of a direct negative interaction by diffuse released proteins, such as proteases that are released by neuronal activation and precede synaptic elimination (Liu et al. 1994a, b). Once a post-synaptic site is vacant, neighboring neurons receive a potent signal to grow. One possible trigger for this growth is the release of diffusible neurotrophic factors from Schwann cells upon loss of contact with neuronal terminals (Henderson et al. 1994; Yan et al. 1995). Indeed, exogenous application of glial growth factors to postnatal muscles or overexpression of those factors in the developing system leads to polyneuronal innervation, which suggests that activity-dependent release of neurotrophic factors can function as the positive feedback signal stabilizing neuronal connections. Synaptic competition for non-occupied sites favors motor neurons that have the biggest number of axonal terminals, leading to single innervation (Turney and Lichtman 2012). This increase in the elaboration by a single motor neuron might also be the key for this stabilization since it increases the release of the positive feedback signals by the post-synaptic partner. During development, this system progresses from a dynamic competitive state to a long-lasting stable system. Although the detailed molecular orchestration involved in the neuromuscular junction development is still being revealed, the rules underlying the developing and the learning brain are quite similar and provided us with a strong conceptual framework to test the mechanisms of synaptic cooperation and competition in the context of learning and memory.

3.3 Synaptic Cooperation and Competition During LTP

As stated above, LTP can be divided in several stages or phases (Reymann and Frey 2007). This division opens the possibility for synapses to interact cooperatively and competitively in all these time periods. Interestingly, the induction of LTP is by itself a cooperative process (Froemke et al. 2010). LTP induction requires that multiple inputs have to be activated simultaneously so that the post-synaptic neuron is depolarized enough to induce a large calcium influx and downstream activation of signalling cascades (Sanhueza et al. 2011; Sanhueza and Lisman 2013). This form of synaptic cooperation allows "weaker" stimulus to summate electrically, leading to a sufficient membrane depolarization and induction of LTP (Mehta 2004). In this cooperative effect of synaptic plasticity, timing is everything: the level of temporal correlation is translated in the post-synaptic intracellular concentration of calcium. When activity is correlated, intracellular [Ca^{2+}] transiently increases leading to the induction of synaptic potentiation; non-correlated activity leads to a small but

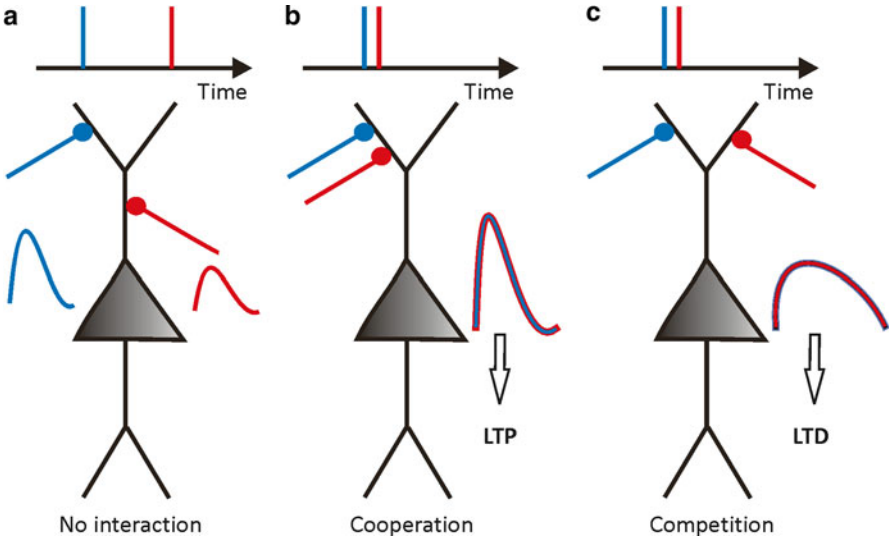

Fig. 3.2 Synaptic cooperation and competition at LTP induction. (**a**) Synaptic potential evoked by activation of two distinct inputs have no impact on each other, due to distinct timing of activation. (**b**, **c**) In the case where the two inputs are activated within a temporal significant window, they can either interact cooperatively or competitively depending on the localization within the dendritic arbor or the timing of activation relative to each other. In (**b**) the two inputs are localized close together leading to the summation of synaptic potentials and the induction of LTP. In (**c**) due to the localization of the two inputs the timing of arrival of the synaptic signals relative to the spike initiation zone leads to a broader and small signal leading to LTD induction

prolonged intracellular [Ca^{2+}] rise leading to a depression of synaptic strength. This synaptic plasticity rule, later on denominated as Spike-time dependent plasticity (STDP) (Bar et al. 2011; Froemke et al. 2010), relates the timing between synaptic-evoked potential and back-propagating action potentials or dendritic calcium spikes and can explain how two inputs can interact cooperatively or competitively depending on the timing of activation and relative position in the dendritic arbor (Fig. 3.2). Detailed analysis of this form of synaptic cooperation revealed several intriguing properties and constraints. Since it is based on the summation of local electrical signals, it is spatially limited for several reasons: first, most EPSPs in vivo have relative small amplitude so several EPSPs would need to cooperate to generate a signal over the threshold for LTP induction. Due to the cable properties of dendrites, the spatial spreading of those signals is very limited. This implies that cooperation is spatially limited. Second, active inhibition temporally and spatially significantly reduces the probability of two inputs to cooperate (Bar et al. 2011; Froemke et al. 2010). Together, these two properties create a temporal and anatomical constrain that restricts synaptic cooperation to temporally contiguous events. This also implies that the dendritic organization of synapses contains information about the temporal relationship of events. Such a mapping has several advantages, such as fast associative recall of entire sequences with a limited number of inputs (Mehta 2004).

On the other hand, it favors particular associations to be formed and reduces the plasticity of the system (Fig. 3.2b). It is interesting to note that, in this case, the limiting factor is space, similarly to what has been described in the developing neuromuscular junction.

Following the reasoning of the STDP, synaptic competition can also occur during LTP induction. Inputs that consistently are the best predictors of post-synaptic activation become the strongest inputs of the neuron. This can lead to the weakening of other inputs since the stronger input can more efficiently trigger spiking of the post-synaptic neuron, altering the correlation timing to other inputs (Fig. 3.2c). Also, in this form of synaptic competition, the dendritic localization of the inputs in relation to the spike initiation zone is critical (Bar et al. 2011; Song and Abbott 2001). Again, space seems to be the critical factor.

3.4 Synaptic Cooperation and Competition During LTP Maintenance

One of the critical features of memory formation is that not all learning events are maintained in the brain. Similarly, once synaptic plasticity is induced, it goes through a process of consolidation before it is stabilized as a functional and morphological change in neuronal connectivity. Synthesis of proteins, generally described as plasticity related proteins (PRPs), is necessary for the maintenance of synaptic plasticity (Barco et al. 2002; Bramham 2008). However, how to conciliate the input specificity of synaptic plasticity with the requirement of PRPs for plasticity maintenance? The working model that arose from the initial work of Frey and Morris, proposed that activated synapses are "tagged" so that newly synthesized PRPS could be specifically localized to these activated synapses allowing input-specific maintenance of plasticity (Frey and Morris 1997). This working model, later evolved into the synaptic tagging and capture model (STC), was the first demonstration that synapses could cooperate by sharing PRPs (Fig. 3.3). The authors showed that the induction of a long-lasting form of LTP in one set of synapses can stabilize a transient form of LTP induced in a second independent set of synapses (Frey and Morris 1997, 1998a). The stabilization of the transient form of LTP, induced by weak synaptic stimulation, is blocked if protein synthesis inhibitors are applied during the induction of the long-lasting form of LTP, suggesting that this form of synaptic cooperation is achieved by an interaction between the activity-dependent input-specific "synaptic tags," set by the weak synaptic activation, and the capture of (PRPs) induced by the strong synaptic activation. It is now clear that the setting of the "synaptic tag" and the long-lasting maintenance of LTP are independent processes and can occur separately in time (Fonseca 2012; Frey and Frey 2008; Frey and Morris 1998b; Redondo et al. 2010; Sajikumar et al. 2005, 2007).

Further analysis of this form of synaptic cooperation has revealed that the time in which the synaptic tag is able to capture the PRPs is limited, ranging from 1 to

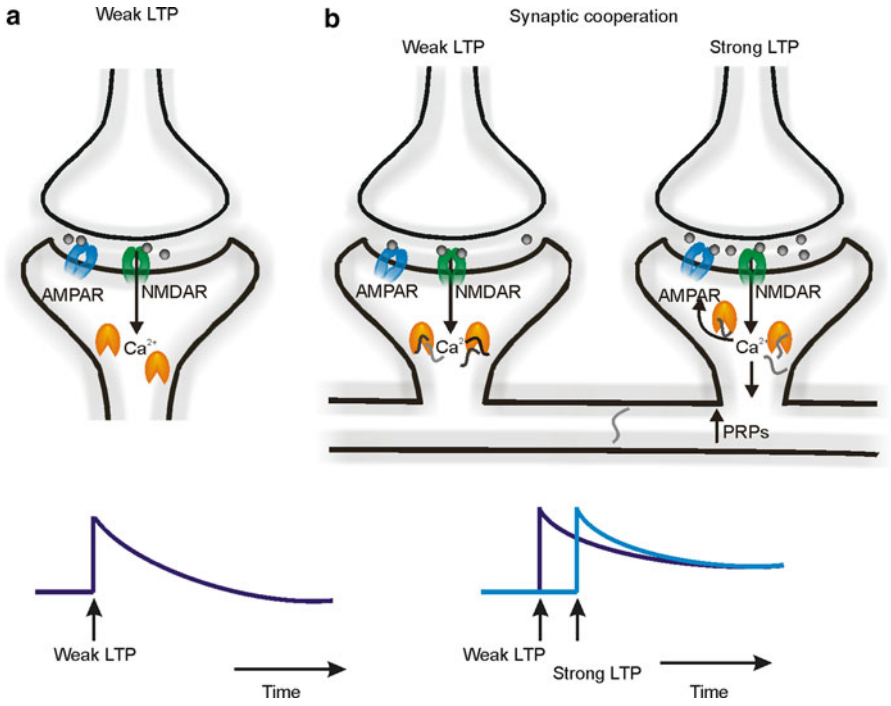

Fig. 3.3 Synaptic cooperation during LTP maintenance. (**a**) LTP induced by weak LTP induction leads to a transient form of LTP that generates tags (*yellow triangles*) at potentiated synapses but not the synthesis of PRPs and therefore decays with time. (**b**) If the weak synaptic stimulation is followed by a strong stimulation of a second set of synapses, the induction of long-lasting form of LTP leads to the synthesis of PRPs that are shared between the two activated inputs. This allows a cooperative maintenance of LTP in both activated groups of synapses

2 h (Fonseca 2012; Frey and Morris 1998b; Govindarajan et al. 2011). This transient activity of the synaptic tag limits the time interval in which synaptic cooperation can be induced, but it still allows different learning events to be associated in relatively larger time interval than the one described for LTP induction.

A second interesting property of this form of synaptic cooperation is the observation that synapses do not cooperate in a cell wide manner but that this interaction is space restricted. Using extracellular recording that lack the fine-space analysis, there was already an indication that different dendritic branches in pyramidal cells do not cooperate (Alarcon et al. 2006; Fonseca et al. 2004). Recently, using 2-photon uncaging of glutamate to spatially restrict synaptic activation, it was shown that the ability to induce synaptic competition was inversely correlated with distance, and had a bias towards the same branch (Govindarajan et al. 2011). This space constrain is extremely intriguing, since during the development of the neuronal connective pattern there is already a bias for correlated neurons to establish connections in proximity (Turney and Lichtman 2012). It is, therefore, plausible that the rules of

synaptic cooperation and competition operating during the developing of the nervous system determine the cooperative and competitive interaction that one observes in the mature brain. It is also interesting to note that the synaptic cooperativity that occurs during LTP induction is also dependent on the localization of the interacting inputs (Mehta 2004). Inputs that terminate in the same dendritic branches have a higher probability to summate and to be able to induce LTP and the formation of synaptic tags. This supports the hypothesis that there is a bias during the development of the nervous system to establish clustered connections between correlated neurons, which are maintained in the mature brain. This hypothesis of clustered plasticity (Govindarajan et al. 2006), is quite attractive since it would allow in a highly efficient way to associate neutral or less relevant information into a single memory engram (Frey and Morris 1998a) and it would allow a faster and easier reactivation of the engram (Govindarajan et al. 2006).

Interestingly, this clustering of plasticity also increases the probability of activated inputs to engage in synaptic competition. If PRPs are limited, activation of multiple inputs can generate a competitive pressure since PRPs would be distributed among all activated synapses (Fig. 3.4a, b). In such case, the strength of the tags, the distance at which the activated synapses is from the translational initiation site as well as the time elapsed between the two events, would determine which activated synapses are stabilized (Fig. 3.4c). Although this competitive maintenance was initially demonstrated using protein synthesis inhibitors (Fonseca et al. 2004; Govindarajan et al. 2011), limitation of the initial available pool of PRPs, using a more naturalistic patterns of stimulation, can induce synaptic competition without blocking protein synthesis (Fonseca et al. 2004). Moreover, the degree of synaptic competition is directly proportional to the degree of synaptic potentiation induced at the winner input (Fonseca et al. 2004). This suggests that the activity of the synaptic tag is proportional to the degree of synaptic activation and that an increase in the tag activity leads to an increase in the capture of PRPs.

What is the relevance of these forms of synaptic cooperation and competition to memory formation and maintenance? Recently, a couple of studies have shown that novelty, presumably through activation of dopamine receptors, induces the synthesis of PRPs converting a short-lasting memory into a long-lasting memory (Moncada et al. 2011; Moncada and Viola 2007; Wang et al. 2010). However, these studies do not address the possibility that activation of different groups of synapses can interact either in a cooperative or competitive fashion to modulate memory formation.

3.5 Synaptic Cooperation in the Lateral Nucleus of the Amygdala: Link to Behavior?

As stated above, one question that remains unanswered is the relevance of synaptic cooperation and competition during learning. To tackle this question, I have recently studied the cooperative interaction between the cortical and thalamic afferents to projection neurons of the lateral amygdala, a circuitry necessary for the formation

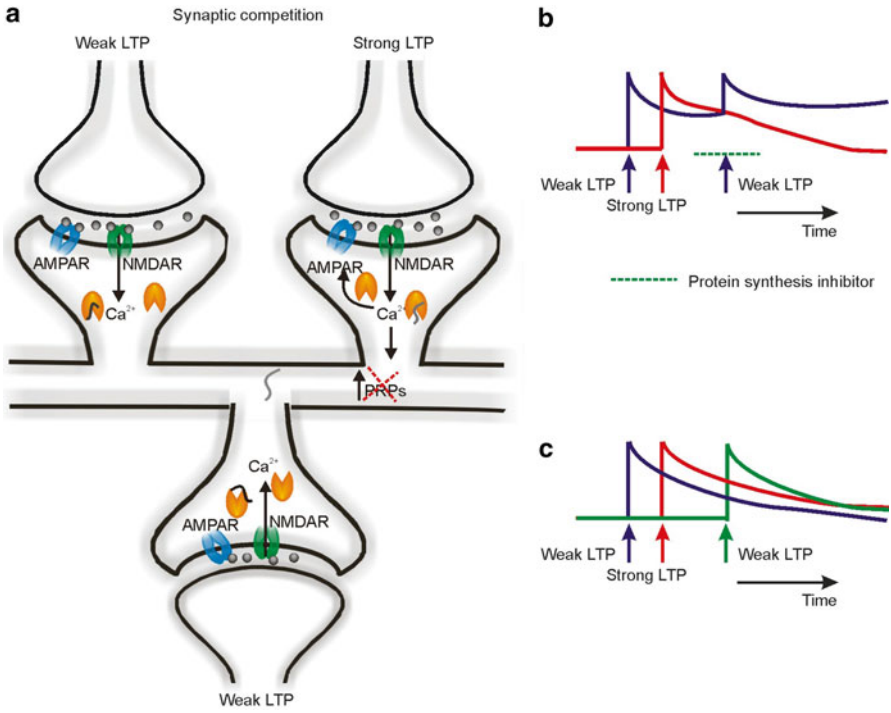

Fig. 3.4 Synaptic competition during LTP maintenance. (**a**) LTP induced by weak synaptic stimulation leads to a transient form of LTP that generates tags (*yellow triangles*) at potentiated synapses but not the synthesis of PRPs. The strong stimulation of a second set of synapses, up-regulates the synthesis of PRPs that are shared between the two activated inputs. (**b**) If protein synthesis is limited, by application of a protein synthesis inhibitor the reactivation of one of the previous activated synapses increases the number of tags creating a competitive pressure in the non-reactivated synapses. (**c**) If protein synthesis is not blocked but a third group of synapses is activated with a stimulus that generates synaptic tags but not the synthesis of PRPs, a similar scenario is created, with multiple groups of tagged synapses competing for a limited pool of proteins

of fear-conditioning memories (Fonseca 2013). I found that cortical and thalamic inputs to the lateral nucleus of amygdala can cooperate during LTP maintenance, similarly to what have been described in hippocampal synapses. Interestingly, the cooperation between cortical and thalamic inputs is bi-directional but asymmetrical (Fig. 3.5). I found that the ability to capture PRPs by the thalamic tag decays much faster than the ability of the cortical tag to capture PRPs. This argues for a restriction mechanism in thalamic cooperation. Consistent with this, inhibition of synaptic activation, inhibition of the metabotropic glutamate receptors (mGluR) or inhibition of the endocannabinoid receptor CB1, can extend the time window of thalamic cooperation. This is the first observation that synaptic cooperation can be asymmetrical, supporting the view that the synaptic tag is not a single molecule but a cellular process that allows the expression of LTP in an input-specific manner.

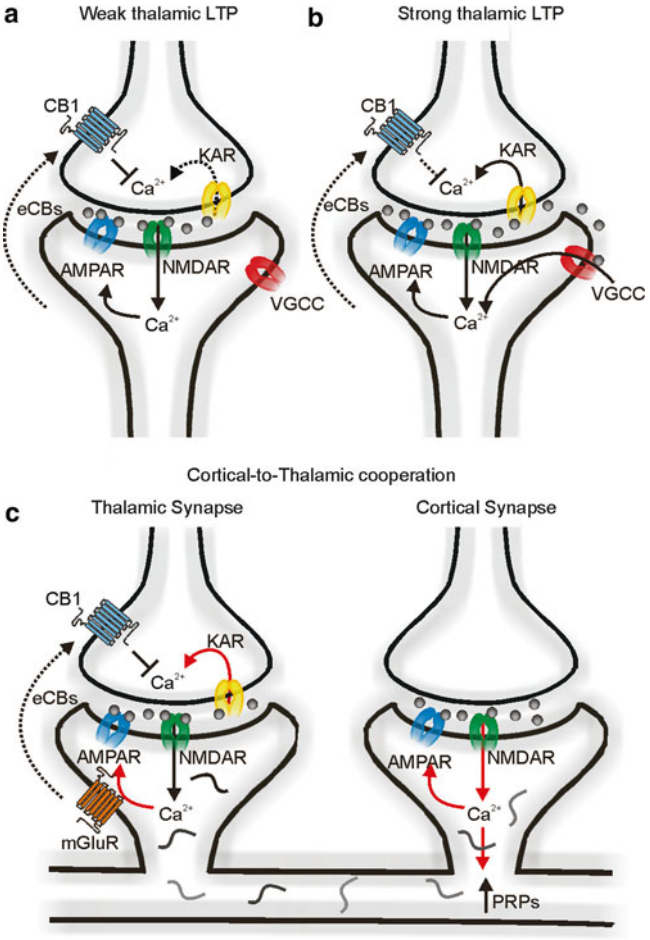

Fig. 3.5 Synaptic cooperation between thalamic and cortical inputs to the lateral nucleus of the amygdala. (**a**) LTP induced by weak stimulation of the thalamic input leads to a transient form of LTP that decays with time. (**b**) Strong stimulation of the thalamic input leads to the induction of a long-lasting form of LTP that is dependent on the activation of kainate glutamate receptors (KAR). (**c**) If the weak thalamic stimulation is followed by a strong stimulation of the cortical inputs the thalamic tag can capture the PRPs synthesized upon strong cortical stimulation. This occurs only if the time interval between thalamic and cortical stimulation is within a short time interval, to avoid the inhibitory effect of CB1 receptor activation

What might be the significance of this asymmetrical thalamic and cortical synaptic cooperation? It is possible that the association between cortical and thalamic projection is necessary for a discriminative form of fear-learning. While the activation of either the cortical or thalamic inputs is sufficient for fear-conditioning learning (Campeau and Davis 1995; Kwon and Choi 2009), in auditory discriminative fear-learning, co-activation of both inputs might be necessary for discrimination

(Antunes and Moita 2010). It is therefore conceivable, that synaptic cooperation between cortical and thalamic inputs underlies the establishment of a discriminative fear memory.

What could be the functional consequence of the time asymmetry? One possibility is that restricting the time window of thalamic cooperation, protects from generalizing fear responses. Increasing the expression of CREB in the direct thalamic-LA input enhances fear-learning and leads to generalization in discriminative fear-learning task (Han et al. 2008). It is, therefore, conceivable that restricting the time window for cortical-to-thalamic cooperation decreases the induction of incorrect associations and hence generalization. Although this is highly speculative, this is a powerful system to test whether synaptic competition and cooperation has a fundamental role in learning.

3.6 Conclusion Remarks

Synaptic cooperation and competition are powerful cellular mechanisms that in one hand contribute to maintain the overall activity of the neuron constant, but also determine the pattern of connectivity between neurons and ultimately the information that is stored in the brain. There are however, several open questions that remain. Due to the properties of signal processing in neurons it is clear that the anatomical organization of inputs determines the probability of synaptic cooperative and competitive interactions to occur. Since the pattern of connectivity is already determined following the same principles of neuronal cooperation and competition then in the mature brain the possible cooperative and competitive synaptic interactions are quite limited. This argues in favor of the clustered plasticity theory, suggesting that events with similar properties may be mapped in similar groups of neurons and on close by locations in the dendritic arbor. As stated above, this is a highly efficient manner to optimize associations but also to keep a constant update of the relative strengths of the various components of the engram. Further analysis of the relevance of synaptic cooperative and competitive synaptic interactions in associative learning will allow us to construct better models of memory formation and maintenance.

References

Alarcon JM, Barco A, Kandel ER (2006) Capture of the late phase of long-term potentiation within and across the apical and basilar dendritic compartments of CA1 pyramidal neurons: synaptic tagging is compartment restricted. J Neurosci 26:256–264

Antunes R, Moita MA (2010) Discriminative auditory fear learning requires both tuned and non-tuned auditory pathways to the amygdala. J Neurosci 30:9782–9787

Bar IL, Gidon A, Segev I (2011) Interregional synaptic competition in neurons with multiple STDP-inducing signals. J Neurophysiol 105:989–998

Barco A, Alarcon JM, Kandel ER (2002) Expression of constitutively active CREB protein facilitates the late phase of long-term potentiation by enhancing synaptic capture. Cell 108:689–703

Becker N, Wierenga CJ, Fonseca R, Bonhoeffer T, Nagerl UV (2008) LTD induction causes morphological changes of presynaptic boutons and reduces their contacts with spines. Neuron 60:590–597

Bliss TV, Collingridge GL (1993) A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361:31–39

Bliss TV, Collingridge GL, Morris RG (2003) Introduction. Long-term potentiation and structure of the issue. Philos Trans R Soc Lond B Biol Sci 358:607–611

Bramham CR (2008) Local protein synthesis, actin dynamics, and LTP consolidation. Curr Opin Neurobiol 18:524–531

Bramham CR, Alme MN, Bittins M, Kuipers SD, Nair RR, Pai B, Panja D, Schubert M, Soule J, Tiron A, Wibrand K (2010) The Arc of synaptic memory. Exp Brain Res 200:125–140

Buffelli M, Busetto G, Cangiano L, Cangiano A (2002) Perinatal switch from synchronous to asynchronous activity of motoneurons: link with synapse elimination. Proc Natl Acad Sci U S A 99:13200–13205

Buffelli M, Busetto G, Bidoia C, Favero M, Cangiano A (2004) Activity-dependent synaptic competition at mammalian neuromuscular junctions. News Physiol Sci 19:85–91

Campeau S, Davis M (1995) Involvement of subcortical and cortical afferents to the lateral nucleus of the amygdala in fear conditioning measured with fear-potentiated startle in rats trained concurrently with auditory and visual conditioned stimuli. J Neurosci 15:2312–2327

Colman H, Lichtman JW (1992) 'Cartellian' competition at the neuromuscular junction. Trends Neurosci 15:197–199

Colman H, Nabekura J, Lichtman JW (1997) Alterations in synaptic strength preceding axon withdrawal. Science 275:356–361

Djakovic SN, Schwarz LA, Barylko B, DeMartino GN, Patrick GN (2009) Regulation of the proteasome by neuronal activity and calcium/calmodulin-dependent protein kinase II. J Biol Chem 284:26655–26665

Ehlers MD (2003) Activity level controls postsynaptic composition and signaling via the ubiquitin–proteasome system. Nat Neurosci 6:231–242

Fonseca R (2012) Activity-dependent actin dynamics are required for the maintenance of long-term plasticity and for synaptic capture. Eur J Neurosci 35:195–206

Fonseca R (2013) Asymmetrical synaptic cooperation between cortical and thalamic inputs to the amygdale. Neuropsychopharmacology 38:2675–2687

Fonseca R, Nagerl UV, Morris RG, Bonhoeffer T (2004) Competing for memory: hippocampal LTP under regimes of reduced protein synthesis. Neuron 44:1011–1020

Fonseca R, Nagerl UV, Bonhoeffer T (2006a) Neuronal activity determines the protein synthesis dependence of long-term potentiation. Nat Neurosci 9:478–480

Fonseca R, Vabulas RM, Hartl FU, Bonhoeffer T, Nagerl UV (2006b) A balance of protein synthesis and proteasome-dependent degradation determines the maintenance of LTP. Neuron 52:239–245

Frey S, Frey JU (2008) 'Synaptic tagging' and 'cross-tagging' and related associative reinforcement processes of functional plasticity as the cellular basis for memory formation. Prog Brain Res 169:117–143

Frey U, Morris RG (1997) Synaptic tagging and long-term potentiation. Nature 385:533–536

Frey U, Morris RG (1998a) Synaptic tagging: implications for late maintenance of hippocampal long-term potentiation. Trends Neurosci 21:181–188

Frey U, Morris RG (1998b) Weak before strong: dissociating synaptic tagging and plasticity-factor accounts of late-LTP. Neuropharmacology 37:545–552

Frey U, Krug M, Reymann KG, Matthies H (1988) Anisomycin, an inhibitor of protein synthesis, blocks late phases of LTP phenomena in the hippocampal CA1 region in vitro. Brain Res 452:57–65

Froemke RC, Letzkus JJ, Kampa BM, Hang GB, Stuart GJ (2010) Dendritic synapse location and neocortical spike-timing-dependent plasticity. Front Synaptic Neurosci 2:29

Govindarajan A, Kelleher RJ, Tonegawa S (2006) A clustered plasticity model of long-term memory engrams. Nat Rev Neurosci 7:575–583

Govindarajan A, Israely I, Huang SY, Tonegawa S (2011) The dendritic branch is the preferred integrative unit for protein synthesis-dependent LTP. Neuron 69:132–146
Han JH, Yiu AP, Cole CJ, Hsiang HL, Neve RL, Josselyn SA (2008) Increasing CREB in the auditory thalamus enhances memory and generalization of auditory conditioned fear. Learn Mem 15:443–453
Hashimoto K, Ichikawa R, Kitamura K, Watanabe M, Kano M (2009) Translocation of a "winner" climbing fiber to the Purkinje cell dendrite and subsequent elimination of "losers" from the soma in developing cerebellum. Neuron 63:106–118
Hebb DO (1949) Organization of behaviour. Wiley, New York
Henderson CE, Phillips HS, Pollock RA, Davies AM, Lemeulle C, Armanini M, Simmons L, Moffet B, Vandlen RA, Simpson LC [corrected to Simmons L] et al (1994) GDNF: a potent survival factor for motoneurons present in peripheral nerve and muscle. Science 266:1062–1064
Huang YY, Nguyen PV, Abel T, Kandel ER (1996) Long-lasting forms of synaptic potentiation in the mammalian hippocampus. Learn Mem 3:74–85
Hubel DH, Wiesel TN, LeVay S (1977) Plasticity of ocular dominance columns in monkey striate cortex. Philos Trans R Soc Lond B Biol Sci 278:377–409
Kauer JA, Malenka RC, Perkel DJ, Nicoll RA (1990) Postsynaptic mechanisms involved in long-term potentiation. Adv Exp Med Biol 268:291–299
Kelleher RJ III, Govindarajan A, Tonegawa S (2004) Translational regulatory mechanisms in persistent forms of synaptic plasticity. Neuron 44:59–73
Kwon JT, Choi JS (2009) Cornering the fear engram: long-term synaptic changes in the lateral nucleus of the amygdala after fear conditioning. J Neurosci 29:9700–9703
Laskowski MB, Sanes JR (1987) Topographic mapping of motor pools onto skeletal muscles. J Neurosci 7:252–260
Laskowski MB, Colman H, Nelson C, Lichtman JW (1998) Synaptic competition during the reformation of a neuromuscular map. J Neurosci 18:7328–7335
Lisman J, Malenka RC, Nicoll RA, Malinow R (1997) Learning mechanisms: the case for CaMKII. Science 276:2001–2002
Liu Y, Fields RD, Festoff BW, Nelson PG (1994a) Proteolytic action of thrombin is required for electrical activity-dependent synapse reduction. Proc Natl Acad Sci U S A 91:10300–10304
Liu Y, Fields RD, Fitzgerald S, Festoff BW, Nelson PG (1994b) Proteolytic activity, synapse elimination, and the Hebb synapse. J Neurobiol 25:325–335
Lo YJ, Poo MM (1991) Activity-dependent synaptic competition in vitro: heterosynaptic suppression of developing synapses. Science 254:1019–1022
Malenka RC, Bear MF (2004) LTP and LTD: an embarrassment of riches. Neuron 44:5–21
Malenka RC, Nicoll RA (1997) Learning and memory. Never fear, LTP is hear. Nature 390:552–553
Malenka RC, Nicoll RA (1998) Long-term depression with a flash. Nat Neurosci 1:89–90
Malenka RC, Nicoll RA (1999) Long-term potentiation—a decade of progress? Science 285:1870–1874
Mehta MR (2004) Cooperative LTP can map memory sequences on dendritic branches. Trends Neurosci 27:69–72
Miller KD (1996) Synaptic economics: competition and cooperation in synaptic plasticity. Neuron 17:371–374
Moncada D, Viola H (2007) Induction of long-term memory by exposure to novelty requires protein synthesis: evidence for a behavioral tagging. J Neurosci 27:7476–7481
Moncada D, Ballarini F, Martinez MC, Frey JU, Viola H (2011) Identification of transmitter systems and learning tag molecules involved in behavioral tagging during memory formation. Proc Natl Acad Sci U S A 108:12931–12936
Olson MD, Meyer RL (1994) Activity-dependent retinotopic refinement in a low-density retinotectal projection in the goldfish: evidence favoring synaptic cooperation over competition. J Neurosci 14:208–218

Personius KE, Karnes JL, Parker SD (2008) NMDA receptor blockade maintains correlated motor neuron firing and delays synapse competition at developing neuromuscular junctions. J Neurosci 28:8983–8992

Redondo RL, Morris RG (2011) Making memories last: the synaptic tagging and capture hypothesis. Nat Rev Neurosci 12:17–30

Redondo RL, Okuno H, Spooner PA, Frenguelli BG, Bito H, Morris RG (2010) Synaptic tagging and capture: differential role of distinct calcium/calmodulin kinases in protein synthesis-dependent long-term potentiation. J Neurosci 30:4981–4989

Reymann KG, Frey JU (2007) The late maintenance of hippocampal LTP: requirements, phases, 'synaptic tagging', 'late-associativity' and implications. Neuropharmacology 52:24–40

Sajikumar S, Frey JU (2004a) Late-associativity, synaptic tagging, and the role of dopamine during LTP and LTD. Neurobiol Learn Mem 82:12–25

Sajikumar S, Frey JU (2004b) Resetting of 'synaptic tags' is time- and activity-dependent in rat hippocampal CA1 in vitro. Neuroscience 129:503–507

Sajikumar S, Navakkode S, Sacktor TC, Frey JU (2005) Synaptic tagging and cross-tagging: the role of protein kinase Mzeta in maintaining long-term potentiation but not long-term depression. J Neurosci 25:5750–5756

Sajikumar S, Navakkode S, Frey JU (2007) Identification of compartment- and process-specific molecules required for "synaptic tagging" during long-term potentiation and long-term depression in hippocampal CA1. J Neurosci 27:5068–5080

Sanhueza M, Lisman J (2013) The CaMKII/NMDAR complex as a molecular memory. Mol Brain 6:10

Sanhueza M, Fernandez-Villalobos G, Stein IS, Kasumova G, Zhang P, Bayer KU, Otmakhov N, Hell JW, Lisman J (2011) Role of the CaMKII/NMDA receptor complex in the maintenance of synaptic strength. J Neurosci 31:9170–9178

Song S, Abbott LF (2001) Cortical development and remapping through spike timing-dependent plasticity. Neuron 32:339–350

Stent GS (1973) A physiological mechanism for Hebb's postulate of learning. Proc Natl Acad Sci U S A 70:997–1001

Turney SG, Lichtman JW (2012) Reversing the outcome of synapse elimination at developing neuromuscular junctions in vivo: evidence for synaptic competition and its mechanism. PLoS Biol 10:e1001352

Van Essen DC, Gordon H, Soha JM, Fraser SE (1990) Synaptic dynamics at the neuromuscular junction: mechanisms and models. J Neurobiol 21:223–249

van Ooyen A (2001) Competition in the development of nerve connections: a review of models. Network 12:R1–R47

Walsh MK, Lichtman JW (2003) In vivo time-lapse imaging of synaptic takeover associated with naturally occurring synapse elimination. Neuron 37:67–73

Wang SH, Redondo RL, Morris RG (2010) Relevance of synaptic tagging and capture to the persistence of long-term potentiation and everyday spatial memory. Proc Natl Acad Sci U S A 107:19537–19542

Wikstrom MA, Matthews P, Roberts D, Collingridge GL, Bortolotto ZA (2003) Parallel kinase cascades are involved in the induction of LTP at hippocampal CA1 synapses. Neuropharmacology 45:828–836

Yan Q, Matheson C, Lopez OT (1995) In vivo neurotrophic effects of GDNF on neonatal and adult facial motor neurons. Nature 373:341–344