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The malleable brain: plasticity of neural circuits and behavior – A review from students to students

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fragile X mental retardation protein (FMRP); long-term potentiation (LTP); matrix metalloproteinase (MMP); monocular deprivation (MD); mitogen-activated protein kinase (MAPK); mushroom body (MB); neuromuscular junction (NMJ); PP2B/calcineurin (CaN); parvalbumin-expressing basket cells (PV cell), prefrontal cortex (PFC); primary motor cortex (M1); rapid eye movement (REM); Rab3-interacting molecule (RIM); RNA-binding protein (RBP); sharp wave ripple complex (SPW-R); slow-wave sleep (SWS); supplementary motor area (SMA); ventral striatum (VS); ventral tegmental area (VTA).

Abstract

One of the most intriguing features of the brain is its ability to be malleable, allowing it to adapt continually to changes in the environment. Specific neuronal activity patterns drive long-lasting increases or decreases in the strength of synaptic connections, referred to as long-term potentiation (LTP) and long-term depression (LTD) respectively. Such phenomena have been described in a variety of model organisms, which are used to study molecular, structural, and functional aspects of synaptic plasticity. This review originated from the first International Society for Neurochemistry (ISN) and Journal of Neurochemistry (JNC) Flagship School held in Alpbach, Austria (Sep 2016), and will use its curriculum and discussions as a framework to review some of the current knowledge in the field of synaptic plasticity. First, we describe the role of plasticity during development and the persistent changes of neural circuitry occurring when sensory input is altered during critical developmental stages. We then outline the signaling cascades resulting in the synthesis of new plasticity-related proteins, which ultimately enable sustained changes in synaptic strength. Going beyond the traditional understanding of synaptic plasticity conceptualized by LTP and LTD, we discuss system-wide modifications and recently unveiled homeostatic mechanisms, such as synaptic scaling. Finally, we describe the neural circuits and synaptic plasticity mechanisms driving

associative memory and motor learning. Evidence summarized in this review provides a current view of synaptic plasticity in its various forms, offers new insights into the underlying mechanisms and behavioral relevance, and provides directions for future research in the field of synaptic plasticity.

Introduction

The mammalian brain has the fascinating ability of processing and storing information in highly organized neuronal networks (Hofman 2014). Synaptic plasticity can be defined as the potential of neural activity patterns generated by experiences to induce alterations in synaptic connectivity (Citri & Malenka 2008, Bliss & Lomo 1973), thereby playing key roles in brain function. This concept was first proposed by Donald Hebb in 1949, who stated that concurrent activation of pre-synaptic and post-synaptic neurons increases the strength of their synaptic connections (reviewed in Cooper 2005).

The nervous system modulates connectivity of its networks depending on activity of neurons that receive inputs from their surroundings (Mayford *et al.* 2012) which is, for instance, widely discussed as a mechanism of memory formation (Fauth & Tetzlaff 2016). Such modulations could appear at the functional level, for example, through changes in transmitter release probability that result in altered strength of synaptic transmission at pre-existing synapses (Castellucci *et al.* 1970), and by changes in neuronal excitability (McKay *et al.* 2013). On the other hand, structural modifications are also possible through the emergence or disappearance of dendritic spines (Engert & Bonhoeffer 1999) or synapses (Martin & Kandel 1996).

Animal models have allowed a more complete understanding of multiple features of the nervous system at molecular, cellular, physiological, anatomical and behavioral levels. Simpler animal models are characterized by a number of technical advantages, such as a short lifespan, large numbers of offspring, mapped neural networks and a wide range of options for genetic modification (Jennings 2011).

In this context, *Drosophila melanogaster* (Frank *et al.* 2013), the transparent nematode *Caenorhabditis elegans* (Lau *et al.* 2013, Corsi 2006), as well as the snail *Aplysia californica* (Bailey & Chen 1983, Bailey & Chen 1988) have been widely used in neuroscience research during the past decades to study, for example, neurotransmitter release in synaptic transmission (Schwarz 2006), axon guidance (Dickson & Zou 2010), as well as potential neuroprotective strategies in disease (Sandin *et al.* 2016, Cutler *et al.* 2015). Fundamental mechanisms in fish locomotor control were uncovered by application of functional imaging approaches on larval zebrafish (Valente *et al.* 2012, Portugues & Engert 2009), which share basic brain organization with their vertebrate counterparts (Leung *et al.* 2013, Friedrich *et al.* 2010, Engert & Wilson 2012).

Nonetheless, the most commonly used models in neuroscience are rodents. Mice (*Mus musculus*) and rats *(Rattus norvegicus)* are particularly used in transgenic approaches*,* since they offer a great variety of opportunities for studying complex behaviors along with powerful genetic tools (Van Meer & Raber 2005, Ward *et al.* 2011, Kim *et al.* 2013, Rincon-Cortes & Sullivan 2016). Rodent hippocampal slice preparations are only one example of broadly used tools to study mammalian synaptic function and plasticity from genetic and epigenetic to protein and structural levels (Ch'ng *et al.* 2012, Hofer *et al.* 2009). Despite their advantages, mouse models alone cannot reflect the diversity of all organisms. Variations in motor

systems and behavior explain why larger animal models are often more suitable (Courtine et al. 2007). For example, early studies on the effects the visual cortex (Wiesel & Hubel 1963, Shatz & Luskin 1986, Shatz & Stryker 1978) and description of the mechanisms underlying plasticity on the proteomic level (Cnops et al. 2008) were carried out in kittens (Felis silvestris catus).

Although improvements in modeling have enabled considerable progress in understanding synaptic plasticity, many mechanistic, structural and regulatory factors remain elusive. To understand fully the computation of the brain in health and disease will therefore be a vital task in present and future neuroscience. By covering topics from developmental, molecular and systematic neuroscience, this review aims to provide an update on current knowledge in synaptic plasticity, as well as offer directions for future research in the field. The authors participated in the first Flagship School hosted by the International Society for Neurochemistry (ISN) and the Journal of Neurochemistry (JNC) on “The Malleable Brain” in September 2016 in Alpbach, Austria.

Synaptic plasticity during the critical period

During certain periods of development, brain circuits are highly receptive to specific experiences and undergo maximum plasticity rates. These sensitive temporal windows of heightened experience-dependent neural plasticity are known as critical periods (Hartley & Lee 2015), which can be defined as the timeframe in which development leads to permanent and irreversible changes in the neuronal networks of different brain regions (Ismail et al. 2016). Critical periods are initiated when the cortical circuitry begins to receive input from the sensory epithelium (Trachtenberg 2015) and are crucial for refining brain circuits based on

environmental inputs (Hensch 2005), leaving major impacts on behavior (Knudsen 2004). Timing, duration and strength of critical periods can be affected by neurological diseases that are associated with abnormal plasticity mechanisms, such as the autism spectrum disorders (ASD), Rett, Fragile X and Angelman syndromes (Ismail et al. 2016).

Knowledge of neuroplasticity within critical periods emerged primarily from research on sensory systems such as the visual system. The development and plasticity of the primary visual cortex have been studied using various animal models (Horton & Hocking 1997, Wiesel & Hubel 1963, Crowley & Katz 2000, Smith & Trachtenberg 2007, Faguet *et al.* 2009). Following eye opening, the primary visual cortex has a preference for inputs from one eye, known as ocular dominance, but this is reduced during the critical period (Hubel & Wiesel 1962, Espinosa & Stryker 2012). Monocular deprivation during early postnatal life causes connections to be eliminated in the closed eye and strengthens connections in the open eye in both humans and rodents (Antonini & Stryker 1993, Wiesel 1982). This leads to loss of visual acuity and a clinical condition called amblyopia (Wiesel 1982). Studies have also reported that children who develop discordant vision or a cataract in one eye during a critical period suffer from permanent defects in vision through that eye (Parsons-Smith 1953). As later-life monocular deprivation effects are not severe, it is apparent that visual experience during the critical period in early life is crucial for optimal development of the visual cortex (Nabel & Morishita 2013).

The initiation and closure of the visual critical period is driven by the maturation of the inhibitory circuitry in the cortex (Hensch *et al.* 1998, Katagiri *et al.* 2007). The shift to a predominantly inhibitory activity culminates in consolidation of

neuronal circuits through curtailing development of new synapses and pruning of existing ones. Although the role of inhibition in the initiation of the critical period is still elusive, it probably mediates plasticity by altering the composition of NMDARs (Kanold *et al.* 2009) and/or facilitating LTD (Choi *et al.* 2002). Moreover, its inhibition directly plays a role in ocular dominance shift. This was exemplified when intravenous injections of the GABAR antagonist bicuculline reinstated binocular responses in a significant proportion of neurons in the visual cortex of cats with vision loss (Duffy *et al.* 1976). Further studies have shown that transplantation of GABAergic precursor cells in mice after the closure of the critical period induces ocular dominance plasticity (Southwell *et al.* 2010, Tang *et al.* 2014).

The extracellular environment is also important for visual cortical plasticity, particularly perineuronal nets (PNN), which consist of chondroitin-sulfate proteoglycans (CSPGs). With age, GABAergic parvalbumin-expressing interneurons (PV cells) will eventually be encased by PNNs, thus marking the end of the critical period. Visual experience is essential for maturation of PV cells, and accurate critical period timing as dark rearing from birth results in a prolonged critical period due to stunted maturation of the PNNs (Pizzorusso *et al.* 2002). PNNs mediate the transfer and facilitate internalization of orthodenticle homeobox 2 (Otx2) homeoprotein in PV cells, in which specific Otx2-binding sites are present to maintain critical period closure (Beurdeley *et al.* 2012).

During the development of the primary auditory system, synapse elimination occurs in the brainstem in the first postnatal week of rodents, prior to hearing onset (Kim & Kandler 2003). Following the onset of hearing at P11-P12, the critical period is initiated in the auditory cortex (Blatchley *et al.* 1987, de Villers-Sidani *et al.* 2007) where synchronized and coherent environmental acoustic inputs are crucial for

maturation of the primary auditory system (Zhang *et al.* 2001, Chang & Merzenich 2003). Exposure to degraded noise conditions (i.e. incoherent continuous noise and absence of tones that stand out) causes a delay in the critical period leading to poor development of the auditory cortex (Zhang et al. 2001, Chang & Merzenich 2003, Hensch 2004). Thus, these studies indicate that, besides sensory deprivation, poor environmental noise can potentially halt or delay development of hearing in children (Zhang et al. 2001, Chang & Merzenich 2003).-Learning occurring in a rapid, period-sensitive manner independently of the behavioral consequences, and accompanied by synaptic elimination, comprises the concept of imprinting. Many species, including birds and mammals, exhibit imprinting, in which they display an innate tendency to follow the first suitable moving stimulus. The first extensive systematic study involving critical periods required for imprinting was carried out by Konrad Lorenz in the first half of the 20th century (Lorenz 1937). He demonstrated that incubator-hatched geese imprint on the first moving visual object during the critical period between the first 13 – 16 hours. Female offspring of monkeys (Harlow & Zimmermann 1959) or rats (Liu *et al.* 2000) that experience stress and anxiety during early postnatal days tend to display poor maternal care behavior later on in life. Parental care mediates the effects of environmental adversity on the development of the nervous system and, therefore, early postnatal experiences may subdue the genetic predispositions (Meaney 2001).

Similarly, SWS, which makes up most of adult sleep as compared to REM-like sleep during early life, augments critical period plasticity in the visual system (Jouvet-Mounier *et al.* 1970). It has also been suggested that sleep is configured and structured by experience (Miyamoto *et al.* 2003). Sound localization is another example of an intricate exercise that displays several aspects of critical period

development (Knudsen *et al.* 2000). Here, the auditory and visual experiences during early life cause adaptive changes in the auditory localization behavior and, correspondingly, in the functional and anatomical properties of the midbrain localization pathway. Extensive studies by Allison Doupe explained the need of young songbirds to hear adult sound (songs) during a sensitive period to learn their songs, which appears to be similar to speech acquisition in humans (Brainard & Doupe 2002, Brainard & Doupe 2013). We now have sufficient evidence to recognize critical periods as the windows that provide insights into the neural mechanisms of learning and synaptic plasticity.

Cellular and molecular mechanisms of synaptic plasticity

Synaptic plasticity requires functional and/or structural modifications at synapses upon persistent stimulation (Lepeta *et al.* 2016). Functional plasticity is essential to allow adaptation to different contexts and learning (Bailey *et al.* 2015, Kandel *et al.* 2014), which rely on precise, local and dynamic control of synapse function (Petzoldt *et al.* 2016). Presynaptic plasticity involves alteration of neurotransmitter release tonus or dynamics, while postsynaptic plasticity usually encompasses alterations in receptor number, availability or properties (Yang & Calakos 2013, Lepeta et al. 2016).

While several forms of structural and functional alterations in different neurotransmitter systems are speculated to exist, plasticity at glutamatergic synapses has been the most extensively characterized. Canonical mechanisms of functional plasticity at glutamatergic synapses involve changes in neurotransmitter receptor presence at the cleft with consequent modifications of post-synaptic ionic balance and kinase/phosphatase activation. For example, long-term plasticity

mechanisms that relate to memory (namely LTP and LTD) appear to derive from persistent stimulation of synapses at high or low frequency, respectively (Nabavi *et al.* 2014, Bliss & Lomo 1973). Persistent stimulation triggers ion influx through NMDARs that, in turn, determines the rate of exposure of AMPARs through post-translational modifications at the postsynaptic density. Fine-tuning of such complex cascades will therefore establish differential synaptic responses (Kandel et al. 2014, Luscher & Malenka 2012).

Despite some controversies (reviewed in (MacDougall & Fine 2014, Padamsey & Emptage 2014), presynaptic mechanisms, including increased neurotransmitter release, appear to contribute to LTP (Bliss & Collingridge 2013). Although mechanistic details are still not fully known, recent evidence has highlighted the role of extracellular proteases, including matrix metalloproteinases 7 and 9 (MMP-7 and MMP-9), ADAM10 and tissue plasminogen activator (tPA) (Peixoto *et al.* 2012, Szklarczyk *et al.* 2007, Jeanneret *et al.* 2016, Wiera *et al.* 2013, Borcel *et al.* 2016), and pre-synaptic cannabinoid receptor 1 as potential drivers of pre-synaptic contributions (Madronal *et al.* 2012). For instance, endocannabinoids could work as liaisons that bridge post- and pre-synaptic signals towards plasticity (Wang *et al.* 2016), in addition to well-known factors such as neurexins and ephrins (Sudhof 2008, Klein 2009).

In the short term, synaptic plasticity is protein synthesis-independent and relies on modification of the already existing proteins. For longer-lasting changes, local translation in response to stimulation that uses the local machinery is crucial, and can take place even in the dendritic compartment (Aakalu *et al.* 2001, Sutton & Schuman 2006). However, this can only last for several hours, suggesting that

transcriptional changes are required for maintaining long-lasting plasticity, such as LTP and LTD (Alberini & Kandel 2014, Frey *et al.* 1996).

Transcriptional regulation and synaptic plasticity

Nuclear transcription sets the cell at a ready state, following which the locally regulated translation at the synapse permits quick and space-restricted responses. From a canonical perspective, the set of persistent activity-driven molecular modifications at the synapse (e.g. ion influx, post-translational modifications) will drive the activation of a subset of transcription factors ultimately resulting in transcriptional reprogramming to maintain plasticity (Alberini & Kandel 2014). This may be further regulated by epigenetic status and by several classes of non-coding transcripts, including long non-coding RNAs (lncRNAs) and piwi-related RNAs (piRNAs) (Rajasethupathy *et al.* 2012, Maag *et al.* 2015). Nonetheless, two additional types of signals appear to shape the final response of a single synapse: the signal for translation of specific mRNAs already at the synapse and retrograde signals from the stimulated synapse to the nucleus, allowing for *de novo* transcription.

Several mechanisms that mediate retrograde signals from synapse to nucleus have been identified, including rapid electrochemical signaling, regenerative calcium waves orchestrated by the endoplasmic reticulum, and physical transport of signaling molecules (Ch'ng & Martin 2011). Synapse-localized importins that bind the nuclear localization signal-containing cargoes play a crucial role in mediating retrograde communication by translocating rapidly to the nucleus in response to a synaptic stimulus (Thompson *et al.* 2004, Jeffrey *et al.* 2009). This could offer a mechanism through which specific synapses could drive nuclear transcriptional changes. The list

of proteins that translocate from synapses to the nucleus upon stimulation has been ever growing and includes cAMP-Responsive Element Binding Protein-2 (CREB2, also known as ATF4), CAM Associated Protein (CAMAP), ErbB4, Jacob, nuclear factor kappa B (NF–κB), ErbB4, proline-rich protein 7 (PRR7), ring finger protein 10 (RFN10) and the APP intracellular domain (AICD) (Ch'ng & Martin 2011, Lai *et al.* 2008, Murata *et al.* 2005, Kravchick *et al.* 2016, Melgarejo da Rosa *et al.* 2016, Karpova *et al.* 2013, Dieterich *et al.* 2008, Lee *et al.* 2007, Dinamarca *et al.* 2016).

Recently, CREB-regulated transcription coactivator 1 (CRTC1) has emerged as an important coincidence detector that undergoes rapid nuclear import upon stimulation and subsequent CREB binding, coupling specific synaptic stimulation with activity-dependent transcription due to its nuclear import and localization (Ch'ng *et al.* 2015). CRTC1 appears to undergo a complex phosphorylation pattern that is controlled by both calcium influx/calcineurin activation and cAMP-dependent signaling. (Ch'ng et al. 2012).

Additional factors promoting synapse-nucleus communication remain to be identified in order to establish the full repertoire of mechanisms controlling activity-dependent transcription. For instance, determining the molecules that modulate the strength and target specificity of activity-induced transcription, as well as establishing how activity of a specific group of synapses could drive transcription to sustain their own plasticity, are current gaps in the field.

Local protein synthesis as an emerging mechanism of plasticity

Local regulation of protein synthesis is a key process allowing for focal physiological responses in many cell types. This is especially relevant for larger and polarized cells, conferring on them the ability to quickly respond to the local cues at a

single site in a nucleus-independent manner (Sutton & Schuman 2006). Given the diversity of synapses that can be present in the dendritic arborization of a single neuron, engagement of local mechanisms for regulating synapse strength and function coordinates multiple signals and facilitates proper responses (Rangaraju *et al.* 2017).

To date, multiple mRNAs required for neuronal function have been shown to undergo synaptic translation in response to local stimulation, including Arc, CaMKIIα and PSD95 (Aakalu et al. 2001, Bramham & Wells 2007). Furthermore, components of the translational machinery are present in dendritic spines (Steward & Levy 1982), together with Dicer and other components of the RISC complex as well as pre-miRNAs that are further cleaved to mature miRNA (Wang *et al.* 2012, Bicker *et al.* 2013). Importantly, some studies have determined that some miRNAs are synaptically enriched, and may play potential synapse-specific roles in translation (Lugli *et al.* 2008, Siegel *et al.* 2009, Sambandan *et al.* 2017). However, given that the translational machinery is not evenly distributed in dendrites, a single spine may not host the whole translational apparatus, and short stretches of the dendritic shafts presumably harbor larger subcellular structures, including stretches of endoplasmic reticulum, Golgi outposts, and ER-Golgi intermediate compartments (Cui-Wang *et al.* 2012, Hanus *et al.* 2014, Mikhaylova *et al.* 2016, Horton *et al.* 2005, Horton & Ehlers 2003).

The dendritic pool of synaptically translated mRNAs considerably differs from the cell soma, as recently shown by deep RNA sequencing of microdissected regions from hippocampal CA1 (Cajigas *et al.* 2012). Interestingly, sequencing of 3'UTRs allowing the identification of multiple polyadenylation sites in mRNAs revealed that longer 3'UTR isoforms are mainly localized to distal parts of the cell,

whereas the shorter ones mainly localize to the soma, suggesting a differential enrichment of mRNA variants of the same gene at synaptic sites (An *et al.* 2008, Epstein *et al.* 2014, Will *et al.* 2013, Vicario *et al.* 2015). A longer 3'UTR provides more flexibility for regulation, due to the presence of more miRNA and RNA-binding protein (RBP) recognition motifs.

Synapse-targeted mRNAs are usually transported in RBP-containing granules by microtubule-dependent transport (Doyle & Kiebler 2011). Although the precise cues that trigger local translation of specific mRNAs are yet to be determined, recent studies suggested that calcium-dependent retrograde netrin-1/DCC receptor signaling could be one such mechanism (Kim & Martin 2015). In addition, activity-dependent regulation of the fragile X mental retardation protein (FMRP) has been shown to promote a number of synaptic mRNAs by direct interaction (Darnell *et al.* 2001). FMRP is an RBP that physiologically represses mRNA translation. Upon synapse stimulation, however, FMRP becomes inhibited, allowing several mRNAs to incorporate into the translational machinery (Liu-Yesucevitz *et al.* 2011, Sidorov *et al.* 2013). In accordance, deregulation of FMRP levels has been implicated in multiple neurological disorders with a synaptic background, including bipolar disorder, schizophrenia and affective disorders (Bryant & Yazdani 2016). Lack of FMRP expression leads to Fragile X Syndrome, an ASD with severe cognitive impairments, further confirming the importance of precise regulation of local translation at the synapse (Bagni & Greenough 2005).

Controlling synaptic proteostasis to shape plasticity

The requirement of coordinated mRNA transport and local translation for synaptic plasticity adds support to the notion that maintaining protein homeostasis, or proteostasis, is critical for synapse stability and function (Hanus & Schuman 2013). In addition to local protein synthesis, protein degradation by the proteasome also emerges as a critical regulator of plasticity. In fact, neuronal activity recruits the proteasome to synaptic sites (Bingol & Schuman 2006) through CamKIIα anchoring (Bingol *et al.* 2010). Synaptic localization of the proteasome, in turn, promotes PSD protein degradation (Bingol & Schuman 2004), regulates neurotransmitter receptor trafficking (Ferreira *et al.* 2015) and plays important roles in shaping structural and functional plasticity (Djakovic *et al.* 2012, Hamilton *et al.* 2012, Santos *et al.* 2015, Li *et al.* 2016).

Schuman and colleagues have recently employed a variation of metabolic labeling termed “bio-orthogonal non-canonical amino acid tagging” (BONCAT) to determine proteome fluctuations during homeostatic plasticity and found the proteome size to be similar regardless of the increased cell activity in response to stimulation (Schanzenbacher *et al.* 2016). Their findings suggest that, while several proteins are upregulated during synaptic scaling, others are downregulated, maintaining the number of unique proteins being synthesized at a stable level (Schanzenbacher et al. 2016). These findings are in agreement with the revised “synaptic tagging” hypothesis, which states that expression of the so-called plasticity-related products, and not only early LTP formation, is required for long-lasting plasticity and, for example, memory formation (see Redondo & Morris 2011 for a review). Thus, maintaining synaptic proteostasis through tight control of protein

synthesis and degradation allows plastic stimuli to express, thereby remodeling synaptic function (Figure 1).

In addition to maintaining levels of synaptic proteins, it is noteworthy that post-translational modifications comprise an important step towards ultimate functional modulation of synaptic proteins. For instance, most neurotransmitter receptors, ion channels and scaffold proteins present at synaptic sites are post-translationally modified. Membrane insertion of synaptic AMPARs, for example, has been shown to depend on ubiquitination cycles (Goo *et al.* 2015, Mabb & Ehlers 2010).

Furthermore, tight control of protein maturation and stability is required for plasticity to develop. Several lines of evidence have indicated that local ER compartments regulate the availability of synaptic proteins, including glutamate receptors, in an activity-driven manner (Hanus et al. 2014, Cui-Wang et al. 2012, Pick *et al.* 2017, Xia *et al.* 2001, Mu *et al.* 2003). However, the precise mechanisms of subsequent Golgi sorting and additional post-translational modification have still been a matter of debate. Even though there is not a consensus on whether most dendrites harbor Golgi outposts (Gardiol *et al.* 1999, Horton & Ehlers 2003), data has suggested that some proteins might undergo Golgi-independent maturation, while others might be matured in tiny specialized ER compartments (Jeyifous *et al.* 2009) or in Golgi satellites, which diverge from traditional outposts (Mikhaylova et al. 2016). It is conceivable, therefore, that multiple modes of protein maturation could contribute to proteostasis and synaptic plasticity. Future studies are warranted to dissect the relative contribution of each of these mechanisms in the expression of plasticity.

Structural and homeostatic plasticity

Dendritic spines are primary sites for structural modifications during memory formation (Bailey et al. 2015). Spines are highly dynamic, as they grow, shrink, disappear, and change forms throughout lifetime (Chen *et al.* 2014, Parnass *et al.* 2000, Hering & Sheng 2001). There is an increase in spine turnover (growth and elimination) during adolescence, compared to adulthood (Holtmaat *et al.* 2005). Experiences such as exercise, learning, and environmental enrichment can influence spine turnover (Attardo *et al.* 2015, Chklovskii *et al.* 2004, Lamprecht & LeDoux 2004, Leuner & Gould 2010, Lovden *et al.* 2013).

For instance, monocular deprivation doubles the firing rate of spines in apical dendrites of pyramidal neurons in the mouse visual cortex, thereby resulting in an overall increase in spine density in layer 5 apical dendrites (Hofer et al. 2009). Thus, the shape and proportion of spines is constantly regulated by synaptic activity (Meyer *et al.* 2014) which, in turn, influences different aspects of spine function including abundance of receptors, diffusion of small molecules between spine and shaft, along with spine mobility and stability (Lai et al. 2008, Nimchinsky et al. 2002).

Reorganization of the spine cytoskeleton leads to modifications in spine morphology. The spine cytoskeleton is composed of actin filaments (F-actin) and microtubule components (Landis & Reese 1983, Cingolani & Goda 2008a). Although there is no apparent direct interaction between cytoskeletal elements (Geraldo & Gordon-Weeks 2009, Dent *et al.* 2011), proteins like drebrin (Dun & Chilton 2010), p140Cap (Jaworski *et al.* 2009) and Q motif-containing GTPase-activating protein 1 (Jausoro *et al.* 2012) are involved in mediating such interactions. There is an increase in actin stability and subsequent enlargement of spines upon induction of LTP, whereas LTD reduces F-actin stability, leading to decreased ~~in~~ spine volume.

Association between structural and functional plasticity

Over the past 20 years, structural modifications that occur at the synaptic level during LTP stimulation have been extensively investigated. It is now well-understood that LTP in hippocampal slices results in filopodia outgrowth and/or enlargement or bifurcation of pre-existing dendritic spines (Engert & Bonhoeffer 1999, Maletic-Savatic *et al.* 1999, Toni *et al.* 1999). Whether LTP-induced spine growth leads to formation of functional synapses remained unanswered for several years. By reconstructing dendritic spines with serial section electron microscopy (ssEM) from the barrel cortex of mice undergoing sensory experience by whisker trimming (removal of vibrissae), spine growth was found to precede synapse formation (Knott *et al.* 2006). In particular, nascent spines preferentially formed synapses with multi-synapse boutons four days after their formation. In a second study, Nägerl and colleagues performed time-lapse two-photon microscopy and ssEM analysis in organotypic hippocampal slices (Nägerl *et al.* 2004). This revealed that LTP induces formation of new spines, which make close contacts with presynaptic boutons and form functional synapses within 15-19 hours. A follow-up study in hippocampal slices showed a delay of just one hour between spontaneous spine growth and synapse formation (Zito *et al.* 2009). On the contrary, LTD-like low-frequency stimulation of dendritic spines in CA1 pyramidal neurons induces NMDAR-dependent spine retractions and causes loss of functional synapses (Nagerl *et al.* 2004, Okamoto *et al.* 2004, Zhou *et al.* 2004). Taken together, these observations show that there is bidirectional activity-dependent regulation of structural plasticity.

Homeostatic plasticity and synaptic scaling

Hebbian plasticity is a form of synaptic plasticity which creates positive feedback loops of activity-dependent changes in synaptic strength, that, in turn, cause perturbations in the stability of neuronal networks. Hebbian plasticity triggers long-lasting activity-dependent changes in synaptic strength resulting from both LTP and LTD (Figure 2). These durable forms of plasticity require correlated precise and strong firing of the pre- and post-synaptic neurons specific to active input, and therefore are thought to facilitate the empowerment of particular synaptic connections (Vitureira & Goda 2013).

To counterbalance unsustained activity arising from LTP or LTD processes, neurons have developed negative-feedback homeostatic mechanisms. The proper functioning of mammalian brain relies on joint interplay of homeostatic and Hebbian plasticity (Fernandes & Carvalho 2016). As such, homeostatic forms of synaptic plasticity not only reduce synaptic strength during elevated excitability conditions but also play a crucial role in preventing unnecessary synapse loss by increasing synaptic strength during chronic activity suppression conditions (Vitureira & Goda 2013) (Figure 2). It is interesting that these two opposing phenomena likely cooperate at the molecular level by regulating effectors at the synapses (Yger & Gilson 2015). Recently, disruptions in homeostatic plasticity have been associated with brain disorders such as ASD, schizophrenia, epilepsy, Alzheimer and Huntington diseases (Fernandes & Carvalho 2016).

Synaptic scaling of excitatory synapses is the most studied form of homeostatic plasticity in the central nervous system. It is involved in the stabilization of neuronal networks and synaptic strength in the brain. Synaptic scaling keeps the firing rates within a set-point range by increasing or decreasing the accumulation of

glutamate receptors (in particular the AMPARs) at synaptic sites (Turrigiano *et al.* 1998, Turrigiano 2008). Compensatory changes in the accumulation of glutamate receptors are achieved through sustained increase of activity using bicuculline or through prolonged activity deprivation using pharmacological agents such as tetrodotoxin (Turrigiano et al. 1998, Maffei & Turrigiano 2008, Hengen *et al.* 2013, Gainey *et al.* 2015). These changes maintain synaptic strength and overall network dynamics.

Scaling AMPARs up or down through postsynaptic accumulation and/or changes in their subunit composition, requires a wide range of proteins. These include transcriptional and translational regulators, such as MeCP2 (Blackman *et al.* 2012, Qiu *et al.* 2012), FMRP (Soden & Chen 2010): the scaffolding proteins Stargazin (Louros *et al.* 2014), PICK1 (Anggono *et al.* 2011), GRIP1(Gainey et al. 2015) and Arc/Arg3.1 (Shepherd *et al.* 2006, Gao *et al.* 2010), cell-adhesion/trans-synaptic signaling molecules like β3-integrins (Cingolani & Goda 2008b, Cingolani *et al.* 2008), β-catenin (Okuda *et al.* 2007, Vitureira *et al.* 2011) and the released soluble factors BDNF (Rutherford *et al.* 1998) and TNFα (Stellwagen & Malenka 2006).

Synaptic scaling can globally adjust responses of all synapses in a given network (Turrigiano 2008). For instance, in a certain neuron all the synaptic populations activate simultaneously to increase/decrease AMPARs upon synaptic scaling (Turrigiano 2008). Thus, synaptic scaling helps to maintain synaptic homeostasis without interfering with the individual differences of stronger versus weaker synapses.

Presynaptic homeostatic plasticity

The homeostatic modulation of presynaptic plasticity was first described at the *Drosophila* neuromuscular junction (NMJ) (Davis *et al.* 1998, Davis & Goodman 1998). Subsequent studies have revealed that homeostatic modulation of the NMJ is evolutionarily conserved from flies to humans (Cull-Candy *et al.* 1980, Plomp *et al.* 1992).

Presynaptic homeostasis induces a fast, persistent and accurate modulation of presynaptic vesicle fusion in response to the levels of ongoing neuronal activity (Davis & Muller 2015). Presynaptic homeostasis principally requires increases in presynaptic Ca^{2+} influx through CaV2.1 channels (Muller & Davis 2012) and in the readily releasable vesicle pool (Weyhersmuller *et al.* 2011, Muller *et al.* 2012).

Several proteins are required for homeostatic signaling at the presynaptic NMJ site. Proteins such as dysbindin and snapin are involved in Ca^{2+} dependent synaptic vesicle endocytosis (Dickman & Davis 2009, Dickman *et al.* 2012) and influence the presynaptic strength of the NMJ. In addition, both ab3 and Rab3-interacting molecule (RIM) are essential regulators of presynaptic homeostasis. RIM interacts with the presynaptic protein ELKS/CAST, presynaptic voltage gated channels and munc13 (Sudhof 2012), and is required for the homeostatic plasticity-induced increase in the readily releasable pool of vesicles (Muller et al 2012). However, further studies are required to understand how presynaptic homeostasis plasticity can be integrated with activity-dependent plasticity.

Associative learning

Synaptic plasticity is now widely accepted to be a neural correlate of at least some types of learning and memory, enabling us to adapt to the environment and shape our behavior accordingly. In order to guide adaptive behavior, incoming

sensory information needs to be integrated into existing brain circuitry that drives behavioral output (Naumann *et al.* 2016). That is, the animal needs to encode the valence of a stimulus, form an association between the stimulus and previously executed behavior, use that information to make an accurate prediction about future outcomes, and alter its behavior accordingly.

Associative learning of involuntary behavior, known as classical conditioning, involves the experience of a neutral stimulus and a subsequently occurring appetitive or aversive stimulus eliciting an automatic response. Following learning, presentation of the previously neutral stimulus alone is sufficient to elicit the associated response (Fanselow & Wassum 2015).

In *Drosophila*, olfactory conditioning is linked to the convergence of signals from Kenyon cells (encoding olfactory cues) and dopaminergic neurons (encoding stimulus valence) onto the mushroom body (MB), which is a key learning center in flies (Aso *et al.* 2014, Davis 1993, de Belle & Heisenberg 1994). For example, optogenetic activation of dopamine cells during odor presentation induces LTD of MB synapses, and promotes olfactory aversive learning (Hige *et al.* 2015). Yamagata *et al.* extended these findings and identified a specific subset of protocerebral anterior medial dopamine cluster neurons, PAM-γ3 neurons, which relay reward signals to the MB. They also demonstrated that the inhibitory neuropeptide allostatin A is necessary and sufficient to suppress PAM-γ3 basal activity via Gα_o recruitment, and drive appetitive learning (Yamagata *et al.* 2016).

In the mammalian brain, neural substrates of classical learning have been studied extensively utilizing fear conditioning paradigms in rodents and is thought to involve synaptic plasticity in the amygdala (Romanski *et al.* 1993), auditory cortex (Letzkus *et al.* 2011) and prefrontal cortex (PFC) (Courtin *et al.* 2014). On the

molecular level, fear learning requires NMDAR activation (Fanselow & Kim 1994), while the MAPK/ERK signaling cascade is required for the expression and maintenance of fear memories (Atkins *et al.* 1998).

Due to its diversity and complexity, learning of voluntary behavior, also known as operant or instrumental conditioning is less well understood. In the mammalian brain, changes in the phasic firing rate of dopaminergic neurons in the ventral tegmental area (VTA) are thought to exert motivational control by encoding a value prediction error, i.e. the discrepancy between the actual and predicted outcome (Schultz *et al.* 1997, Eshel *et al.* 2016, Matsumoto *et al.* 2016). These neurons project to the ventral striatum (VS) (Ikemoto 2007), which receives additional inputs from other memory-associated regions such as the hippocampus (Lansink *et al.* 2016, Ito *et al.* 2006), amygdala (Everitt *et al.* 1991, Ito et al. 2006) and prefrontal cortex (Gourley *et al.* 2016). Thus, the VS is ideally situated to integrate signals from different circuits involved in goal-directed behavior and to initiate the appropriate behavioral output. Supporting this view, the plasticity-related immediate early gene Zif268 has been shown to be upregulated in the VS during instrumental learning (Maroteaux *et al.* 2014) whereas, blocking plasticity-related processes in the VS impaired spatial learning (Ferretti *et al.* 2010). Reward associative learning requires the activation of NMDARs (Zellner *et al.* 2009) and dopamine D1 receptors (D1Rs) (Kravitz *et al.* 2012, Higa *et al.* 2017), as well as its downstream targets cAMP and PKA (Lorenzetti *et al.* 2008, Beninger & Gerdjikov 2004), and the MAPK signaling cascade (Michel *et al.* 2011). In keeping with this, increased ERK 2 activity facilitates striatal LTP and long-term memory formation (Mazzucchelli *et al.* 2002, Ferguson *et al.* 2006).

Another line of evidence has linked specific patterns of synchronized cell firing, in particular theta rhythmic activity, to plasticity and memory mechanisms (Buzsaki & Draguhn 2004). Cell firing at theta frequency in the VS appears to be phase-locked to hippocampal theta waves, and reward-expectancy enhances theta and beta band activity (Berke *et al.* 2004, Lansink et al. 2016). Moreover, connectivity between hippocampal, cortical and striatal regions (driven by theta-alpha power) was correlated with memory retrieval in humans (Herweg *et al.* 2016), providing evidence that synchronization of cell firing across memory-related neural circuits may enable association between stimuli encoded in different aspects of the brain. Disrupting BDNF expression on the other hand alters theta power in the hippocampus and PFC, decreases theta phase synchrony between these areas, reduces late LTP and impairs fear extinction (Sakata *et al.* 2013, Hill *et al.* 2016).

For memories to guide future behavior, they need to be transformed into enduring representations (Dudai *et al.* 2015), which involve processes operating both at synapse (Frankland *et al.* 2004, Karunakaran *et al.* 2016) and system levels (Tse *et al.* 2007, Wei *et al.* 2016). Perhaps unsurprisingly, given their role in synaptic plasticity and learning, memory consolidation and reconsolidation require the activation of PKA (Kemenes *et al.* 2006), CREB mediated transcription (Limback-Stokin *et al.* 2004, Bourtchuladze *et al.* 1994), and NFκB (Freudenthal *et al.* 2005). There is also growing interest in specific activity patterns, such as the sharp wave-ripple complex (SPW-R), as a potential memory consolidation mechanism (Buzsaki 2015). Changes in SPW-Rs have been correlated with operant learning (Ponomarenko *et al.* 2008) and learning-induced plasticity (Grosmark & Buzsaki 2016), while blocking SPW-Rs impaired memory consolidation (Nakashiba *et al.* 2009), spatial learning (Ego-Stengel & Wilson 2010) and goal-directed behavior

(Jadhav *et al.* 2012). It is thought that SPW-Rs generate time-compressed replay loops of neural activity that occurred during an earlier state (Carr *et al.* 2011, Girardeau & Zugaro 2011). This allows for the repetition of new experiences and enables mechanisms supporting synaptic plasticity (Nadasdy *et al.* 1999, Buzsaki 2015, Jahnke *et al.* 2015, Sadowski *et al.* 2016). Several studies have highlighted the importance of interneurons in such system-wide modifications. In particular, plasticity of PV cells is crucial for maintaining gamma and SPW-R oscillations, synaptic plasticity and long-term memory consolidation (Karunakaran et al. 2016, Zarnadze *et al.* 2016, Polepalli *et al.* 2017).

While the specific neural systems involved in associative learning might differ depending on the specific model or tasks, it is now well established that synaptic plasticity phenomena drive the formation of a link between separate neural systems. The mechanisms underlying some forms of memory formation e.g. fear conditioning and spatial learning have been well described, but less is known about the specific signaling cascades driving more complex behavioral change. A large body of evidence has suggested a role of a rhythmic firing pattern in the formation and maintenance of memory. However, molecular and network mechanisms are often studied separately and more research is needed to integrate our understanding of molecular events at the synapse level with system-wide modifications.

Synapse plasticity and motor skill learning

Motor skill learning plays a fundamental role in many aspects of our lives, without which it would be impossible to master a piano piece or to learn how to hit a tennis ball. Motor skill learning comprises the acquisition of movement sequences and is characterized by executing movements faster and more accurately with

practice (Willingham 1998). When starting to learn a motor skill the movement is often disjointed, poorly controlled and executed with considerable variation and immense attention (Penhune & Steele 2012). Once learned, however, the skill is retained for a long period of time with minimal decay (Luft & Buitrago 2005).

It has been proposed that motor skill learning can be divided into separable acquisition stages with an early 'fast' phase, characterized by rapid and considerable learning improvements, and a later 'slow' stage, in which a nearly asymptotic level is reached and further improvements are gained only slowly (Dayan & Cohen 2011). Although different models exist regarding the brain areas and connections involved in processing motor skill learning, it is thought that interactions between cortico-thalamic-striatal and cortico-thalamic-cerebellar structures and the limbic system are essential to successfully build a motor memory trace (Hikosaka *et al.* 2002, Doyon & Benali 2005). These networks seem to be active during different time points of motor learning and, within each of them, specific associative-premotor and sensorimotor networks are activated (Lohse *et al.* 2014, Coynel *et al.* 2010, Lehericy *et al.* 2005). Furthermore, motor learning can modulate functional connectivity of the cortical motor network, and early skill learning has been shown to lead to enhanced inter- and intra-hemispheric coupling (Sun *et al.* 2007).

The primary motor cortex (M1) seems to play a crucial part in fast motor learning (Greenough *et al.* 1985, Kolb *et al.* 2008). Rodent studies have shown that motor learning can induce recruitment of neurons in the M1 and modulate synaptic efficacy through LTP and LTD (Costa *et al.* 2004, Rioult-Pedotti *et al.* 2000, Rioult-Pedotti *et al.* 1998, Monfils & Teskey 2004). These results are supported by human studies, which also suggest that LTP-like plasticity in the M1 is involved in motor learning. While LTP-like effects are reversed after a period of motor learning, LTD-

like effects were shown to be either enhanced or unchanged (Ziemann *et al.* 2004, Stefan *et al.* 2006, Rosenkranz *et al.* 2007).

Early motor learning increases dendritic spine number in M1 pyramidal cells (Fu *et al.* 2012, Xu *et al.* 2009, Harms *et al.* 2008). These learning-related spines cluster around or within a subset of dendritic branches (Yang & Lisberger 2014, Fu et al. 2012). Increased spine density is accompanied by expansion of the movement-related neuronal ensembles, as well as an induction of excitatory neuron activity (Peters *et al.* 2014). Furthermore, it is thought that stabilization of learning-induced nascent spines is essential for building durable memories (Xu et al. 2009, Yang *et al.* 2009). After the learning process, the overall spine density gradually returns to basal levels through selective elimination (Chen *et al.* 2015, Xu et al. 2009).

The cellular mechanisms underlying synaptic plasticity in the M1 still remain to be elucidated. *De novo* protein synthesis is essential for most of the plastic changes following motor learning (Alvarez *et al.* 2000, Bisby & Tetzlaff 1992) and inhibition of protein synthesis in the M1 impedes motor learning in rats (Luft *et al.* 2004). Furthermore, alterations in M1 gene expression were demonstrated in rats after learning a reach-and-grasp task (Cheung *et al.* 2013). Gene expression in the M1 after motor learning is thought to have distinct steps, with an initial suppression of genes influencing transcription, followed by genes that support mRNA translation and, finally, increased expression of genes that mediate plastic changes (Hertler *et al.* 2016).

Rodent studies suggest that BDNF is required for induction of neural plasticity related to motor learning (Kleim *et al.* 2003, Ploughman *et al.* 2009, Schabitz *et al.* 2004, Schabitz *et al.* 2007). Furthermore, it has been proposed that the Val66Met BDNF gene polymorphism reduces experience-dependent plasticity of human motor

cortex and influences motor skill learning (Kleim *et al.* 2006, Cheeran *et al.* 2008, Gajewski *et al.* 2011), although the functional implications of this polymorphism regarding motor learning are still unclear (Nakamura *et al.* 2011, Li Voti *et al.* 2011, McHughen & Cramer 2013).

Consolidation, occurring after both fast and slow motor learning, is defined by offline behavioral skill improvements and is characterized by a reduction in fragility of a motor memory trace (Robertson *et al.* 2004a). However, the neuronal processes that support motor memory consolidation remain to a large extent unknown. Studies suggest that the M1 and the striatum play major roles during memory consolidation (Jenkins *et al.* 1994, Ungerleider *et al.* 2002, Muellbacher *et al.* 2002, Fischer *et al.* 2005, Yin *et al.* 2009), and that functional connectivity in frontoparietal networks support consolidation after motor learning (Albert *et al.* 2009, Taubert *et al.* 2011, Ma *et al.* 2011, Sampaio-Baptista *et al.* 2015).

It has further been suggested that sleep has an important function in memory consolidation after procedural learning (Fischer et al. 2005, Maquet *et al.* 2000, Walker *et al.* 2002, Morin *et al.* 2008, Ramanathan *et al.* 2015). Even short daytime naps can mediate these offline improvements (Nishida & Walker 2007, Korman *et al.* 2007, Walker *et al.* 2003). However, sleep does not seem to influence implicit learning (Robertson *et al.* 2004b, Song *et al.* 2007, Reis *et al.* 2015, Hotermans *et al.* 2008). It has been proposed that age-related changes may impact sleep-dependent memory processes (Spencer *et al.* 2007, Mander *et al.* 2014, Pace-Schott & Spencer 2011), and that changes in the grey matter of hippocampus and cerebellum are responsible for these deficits in sleep-related motor sequence memory consolidation (Fogel *et al.* 2016).

Acquisition, consolidation and retention of motor skills require neural plasticity in different brain areas. However, molecular mechanisms driving and supporting motor learning, as well as the underlying synapse plasticity still remain to be fully elucidated. Local inhibitory circuits may act as key regulators of synaptic changes during motor learning, memory consolidation and retrieval (Chen et al. 2015, Donato *et al.* 2013). Moreover, it has been proposed that the mesocortical dopaminergic pathway connecting the VTA with the M1 is essential for successful motor skill learning (Hosp *et al.* 2011). Dopamine D1Rs have been shown to be critically involved in LTP induction and D2 receptors (D2Rs) mediate spine addition in the M1 (Guo *et al.* 2015). Another study suggested that dopamine receptor activity influences motor skill acquisition and synaptic LTP via phospholipase C signaling (Rioult-Pedotti *et al.* 2015). Furthermore, the cAMP/PKA pathway has also been proposed to be critically involved in the acquisition of new motor skills (Qian *et al.* 2015). Nonetheless, more studies highlighting the molecular aspects of motor skill learning are needed.

Challenges and future directions

Neurodevelopmental research has made major contributions to our understanding of synaptic plasticity and learning. However, the mechanisms driving the development of synaptic plasticity, especially during critical periods, still remain to be clearly defined. Further studies are required to map the extent of learning-dependent changes that occur in developing brain, including variations in dendritic spine number (Chen *et al.* 2016) and connectivity (Karim *et al.* 2016), as well as molecular details underlying such modifications.

Establishing the molecular mechanisms underlying synapse plasticity is a key step towards understanding the malleable properties of the brain. For instance, synapse-to-nucleus translocation and the exact signals that drive information back to synapses still remain elusive. Application of novel metabolic labeling techniques to visualize newly synthesized proteins at the synapse (Dieterich *et al.* 2010, Aakalu et al. 2001, tom Dieck *et al.* 2015, Bowling *et al.* 2016) could fill gaps regarding the coordination of local translation and the cues that trigger space-restricted responses. Such approaches are further expected to unveil novel mechanisms connecting local translation to synaptic plasticity and to provide clues into how synapse proteostasis becomes deregulated in several neurological disorders, including Alzheimer's disease and ASD (Buffington *et al.* 2014, Lourenco *et al.* 2015).

While general principles are thought to govern synaptic responses, a wide variety of mechanisms appear to be stimulus-, region-, and neuron type-specific, ultimately resulting in different behavioral outputs. For instance, although LTP has been regarded as a universal event driving plasticity, new LTP mechanisms have been continually uncovered. A recent work demonstrated that diffusible factors released by glia can travel considerable distance and affect the likelihood of LTP onset at given synapses (Kronschlager *et al.* 2016). More of such yet unconventional mechanisms are expected to emerge in the future.

Emerging evidence has further highlighted the role of non-Hebbian forms of synapse plasticity in brain function. Such mechanisms, including homeostatic plasticity, have the potential to help to explain the diversity and complexity of cognitive and non-cognitive behaviors arising from synaptic modulation.

Recent efforts have allowed significant advances in the understanding of neural substrates of complex behavior. Nevertheless, significant challenges

comprise uncovering mechanisms that drive specific behavioral responses, as well as to track molecular responses in behaving animals. New techniques such as opto- or chemogenetics have fostered significant progress in our understanding of learning, memory and the synaptic changes during memory consolidation by allowing precise spatiotemporal control of synapses and network.

The field of synaptic plasticity is extremely broad, gathering molecular and cellular phenomena to system and higher order properties of the brain. Nonetheless, integrating genomic, molecular, cellular and system data still has been a caveat in the field, and should be a priority in current and future research. Identifying properties, mechanisms and regulations of synaptic plasticity may provide new avenues for treatment of neurological disorders.

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References

Aakalu, G., Smith, W. B., Nguyen, N., Jiang, C. and Schuman, E. M. (2001) Dynamic visualization of local protein synthesis in hippocampal neurons. *Neuron,* **30,** 489-502.

Alberini, C. M. and Kandel, E. R. (2014) The regulation of transcription in memory consolidation. *Cold Spring Harb Perspect Biol,* **7,** a021741.

Albert, N. B., Robertson, E. M. and Miall, R. C. (2009) The resting human brain and motor learning. *Curr Biol,* **19,** 1023-1027.

Alvarez, J., Giuditta, A. and Koenig, E. (2000) Protein synthesis in axons and terminals: significance for maintenance, plasticity and regulation of phenotype. With a critique of slow transport theory. *Prog Neurobiol,* **62,** 1-62.

An, J. J., Gharami, K., Liao, G. Y. et al. (2008) Distinct role of long 3' UTR BDNF mRNA in spine morphology and synaptic plasticity in hippocampal neurons. *Cell,* **134,** 175-187.

Anggono, V., Clem, R. L. and Huganir, R. L. (2011) PICK1 loss of function occludes homeostatic synaptic scaling. *J Neurosci,* **31,** 2188-2196.

Antonini, A. and Stryker, M. P. (1993) Rapid remodeling of axonal arbors in the visual cortex. *Science,* **260,** 1819-1821.

Aso, Y., Hattori, D., Yu, Y. et al. (2014) The neuronal architecture of the mushroom body provides a logic for associative learning. *eLife,* **3,** e04577.

Atkins, C. M., Selcher, J. C., Petraitis, J. J., Trzaskos, J. M. and Sweatt, J. D. (1998) The MAPK cascade is required for mammalian associative learning. *Nat Neurosci,* **1,** 602-609.

Attardo, A., Fitzgerald, J. E. and Schnitzer, M. J. (2015) Impermanence of dendritic spines in live adult CA1 hippocampus. *Nature,* **523,** 592-596.

Bagni, C. and Greenough, W. T. (2005) From mRNP trafficking to spine dysmorphogenesis: the roots of fragile X syndrome. *Nat Rev Neurosci,* **6,** 376-387.

Bailey, C. H. and Chen, M. (1983) Morphological basis of long-term habituation and sensitization in Aplysia. *Science,* **220,** 91-93.

Bailey, C. H. and Chen, M. (1988) Long-term memory in Aplysia modulates the total number of varicosities of single identified sensory neurons. *Proc Natl Acad Sci U S A,* **85,** 2373-2377.

Bailey, C. H., Kandel, E. R. and Harris, K. M. (2015) Structural Components of Synaptic Plasticity and Memory Consolidation. *Cold Spring Harb Perspect Biol,* **7,** a021758.

Beninger, R. J. and Gerdjikov, T. (2004) The role of signaling molecules in reward-related incentive learning. *Neurotox Res,* **6,** 91-104.

Berke, J. D., Okatan, M., Skurski, J. and Eichenbaum, H. B. (2004) Oscillatory entrainment of striatal neurons in freely moving rats. *Neuron,* **43,** 883-896.

Beurdeley, M., Spatazza, J., Lee, H. H., Sugiyama, S., Bernard, C., Di Nardo, A. A., Hensch, T. K. and Prochiantz, A. (2012) Otx2 binding to perineuronal nets persistently regulates plasticity in the mature visual cortex. *J Neurosci,* **32,** 9429-9437.

Bicker, S., Khudayberdiev, S., Weiss, K., Zocher, K., Baumeister, S. and Schratt, G. (2013) The DEAH-box helicase DHX36 mediates dendritic localization of the neuronal precursor-microRNA-134. *Genes Dev,* **27,** 991-996.

Bingol, B. and Schuman, E. M. (2004) A proteasome-sensitive connection between PSD-95 and GluR1 endocytosis. *Neuropharmacology,* **47,** 755-763.

Bingol, B. and Schuman, E. M. (2006) Activity-dependent dynamics and sequestration of proteasomes in dendritic spines. *Nature,* **441,** 1144-1148.

Bingol, B., Wang, C. F., Arnott, D., Cheng, D., Peng, J. and Sheng, M. (2010) Autophosphorylated CaMKIIalpha acts as a scaffold to recruit proteasomes to dendritic spines. *Cell,* **140,** 567-578.

Bisby, M. A. and Tetzlaff, W. (1992) Changes in cytoskeletal protein synthesis following axon injury and during axon regeneration. *Mol Neurobiol,* **6,** 107-123.

Blackman, M. P., Djukic, B., Nelson, S. B. and Turrigiano, G. G. (2012) A critical and cell-autonomous role for MeCP2 in synaptic scaling up. *J Neurosci,* **32,** 13529-13536.

Blatchley, B. J., Cooper, W. A. and Coleman, J. R. (1987) Development of auditory brainstem response to tone pip stimuli in the rat. *Brain Res,* **429,** 75-84.

Bliss, T. V. and Collingridge, G. L. (2013) Expression of NMDA receptor-dependent LTP in the hippocampus: bridging the divide. *Mol Brain,* **6,** 5.

Bliss, T. V. and Lomo, T. (1973) Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol,* **232,** 331-356.

Borcel, E., Palczynska, M., Krzisch, M., Dimitrov, M., Ulrich, G., Toni, N. and Fraering, P. C. (2016) Shedding of neurexin 3beta ectodomain by ADAM10 releases a soluble fragment that affects the development of newborn neurons. *Sci Rep,* **6,** 39310.

Bourtchuladze, R., Frenguelli, B., Blendy, J., Cioffi, D., Schutz, G. and Silva, A. J. (1994) Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. *Cell,* **79,** 59-68.

Bowling, H., Bhattacharya, A., Zhang, G. et al. (2016) BONLAC: A combinatorial proteomic technique to measure stimulus-induced translational profiles in brain slices. *Neuropharmacology,* **100,** 76-89.

Brainard, M. S. and Doupe, A. J. (2002) What songbirds teach us about learning. *Nature,* **417,** 351-358.

Brainard, M. S. and Doupe, A. J. (2013) Translating birdsong: songbirds as a model for basic and applied medical research. *Annu Rev Neurosci,* **36,** 489-517.

Bramham, C. R. and Wells, D. G. (2007) Dendritic mRNA: transport, translation and function. *Nat Rev Neurosci,* **8,** 776-789.

Bryant, C. D. and Yazdani, N. (2016) RNA-binding proteins, neural development and the addictions. *Genes Brain Behav,* **15,** 169-186.

Buffington, S. A., Huang, W. and Costa-Mattioli, M. (2014) Translational control in synaptic plasticity and cognitive dysfunction. *Annu Rev Neurosci,* **37,** 17-38.

Buzsaki, G. (2015) Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. *Hippocampus,* **25,** 1073-1188.

Buzsaki, G. and Draguhn, A. (2004) Neuronal oscillations in cortical networks. *Science,* **304,** 1926-1929.

Cajigas, I. J., Tushev, G., Will, T. J., tom Dieck, S., Fuerst, N. and Schuman, E. M. (2012) The local transcriptome in the synaptic neuropil revealed by deep sequencing and high-resolution imaging. *Neuron,* **74,** 453-466.

Carr, M. F., Jadhav, S. P. and Frank, L. M. (2011) Hippocampal replay in the awake state: a potential substrate for memory consolidation and retrieval. *Nat Neurosci,* **14,** 147-153.

Castellucci, V., Pinsker, H., Kupfermann, I. and Kandel, E. R. (1970) Neuronal mechanisms of habituation and dishabituation of the gill-withdrawal reflex in Aplysia. *Science,* **167,** 1745-1748.

Ch'ng, T. H., DeSalvo, M., Lin, P., Vashisht, A., Wohlschlegel, J. A. and Martin, K. C. (2015) Cell biological mechanisms of activity-dependent synapse to nucleus translocation of CRTC1 in neurons. *Front Mol Neurosci,* **8,** 48.

Ch'ng, T. H. and Martin, K. C. (2011) Synapse-to-nucleus signaling. *Curr Opin Neurobiol,* **21,** 345-352.

Ch'ng, T. H., Uzgil, B., Lin, P., Avliyakulov, N. K., O'Dell, T. J. and Martin, K. C. (2012) Activity-dependent transport of the transcriptional coactivator CRTC1 from synapse to nucleus. *Cell,* **150,** 207-221.

Chang, E. F. and Merzenich, M. M. (2003) Environmental noise retards auditory cortical development. *Science,* **300,** 498-502.

Cheeran, B., Talelli, P., Mori, F. et al. (2008) A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. *J Physiol,* **586,** 5717-5725.

Chen, C. C., Lu, J. and Zuo, Y. (2014) Spatiotemporal dynamics of dendritic spines in the living brain. *Front Neuroanat,* **8,** 28.

Chen, J. R., Lim, S. H., Chung, S. C., Lee, Y. F., Wang, Y. J., Tseng, G. F. and Wan, T. J. (2016) Reproductive experience modified dendritic spines on cortical pyramidal neurons to enhance sensory perception and spatial learning in rats. *Exp Anim*.

Chen, S. X., Kim, A. N., Peters, A. J. and Komiyama, T. (2015) Subtype-specific plasticity of inhibitory circuits in motor cortex during motor learning. *Nat Neurosci,* **18,** 1109-1115.

Cheung, V. C., Deboer, C., Hanson, E., Tunesi, M., D'Onofrio, M., Arisi, I., Brandi, R., Cattaneo, A. and Goosens, K. A. (2013) Gene expression changes in the motor cortex mediating motor skill learning. *PLoS One,* **8,** e61496.

Chklovskii, D. B., Mel, B. W. and Svoboda, K. (2004) Cortical rewiring and information storage. *Nature,* **431,** 782-788.

Choi, S. Y., Morales, B., Lee, H. K. and Kirkwood, A. (2002) Absence of long-term depression in the visual cortex of glutamic Acid decarboxylase-65 knock-out mice. *J Neurosci,* **22,** 5271-5276.

Cingolani, L. A. and Goda, Y. (2008a) Actin in action: the interplay between the actin cytoskeleton and synaptic efficacy. *Nat Rev Neurosci,* **9,** 344-356.

Cingolani, L. A. and Goda, Y. (2008b) Differential involvement of beta3 integrin in pre- and postsynaptic forms of adaptation to chronic activity deprivation. *Neuron Glia Biol,* **4,** 179-187.

Cingolani, L. A., Thalhammer, A., Yu, L. M., Catalano, M., Ramos, T., Colicos, M. A. and Goda, Y. (2008) Activity-dependent regulation of synaptic AMPA receptor composition and abundance by beta3 integrins. *Neuron,* **58,** 749-762.

Citri, A. and Malenka, R. C. (2008) Synaptic plasticity: multiple forms, functions, and mechanisms. *Neuropsychopharmacology,* **33,** 18-41.

Cooper, S. J. (2005) Donald O. Hebb's synapse and learning rule: a history and commentary. *Neurosci Biobehav Rev,* **28,** 851-874.

Corsi, A. K. (2006) A biochemist's guide to Caenorhabditis elegans. *Anal Biochem,* **359,** 1-17.

Costa, R. M., Cohen, D. and Nicolelis, M. A. (2004) Differential corticostriatal plasticity during fast and slow motor skill learning in mice. *Curr Biol,* **14,** 1124-1134.

Courtin, J., Chaudun, F., Rozeske, R. R. et al. (2014) Prefrontal parvalbumin interneurons shape neuronal activity to drive fear expression. *Nature,* **505,** 92-96.

Coynel, D., Marrelec, G., Perlbarg, V., Pelegrini-Issac, M., Van de Moortele, P. F., Ugurbil, K., Doyon, J., Benali, H. and Lehericy, S. (2010) Dynamics of motor-related functional integration during motor sequence learning. *Neuroimage,* **49,** 759-766.

Crowley, J. C. and Katz, L. C. (2000) Early development of ocular dominance columns. *Science,* **290,** 1321-1324.

Cui-Wang, T., Hanus, C., Cui, T., Helton, T., Bourne, J., Watson, D., Harris, K. M. and Ehlers, M. D. (2012) Local zones of endoplasmic reticulum complexity confine cargo in neuronal dendrites. *Cell,* **148,** 309-321.

Cull-Candy, S. G., Miledi, R., Trautmann, A. and Uchitel, O. D. (1980) On the release of transmitter at normal, myasthenia gravis and myasthenic syndrome affected human end-plates. *J Physiol,* **299,** 621-638.

Cutler, T., Sarkar, A., Moran, M., Steffensmeier, A., Puli, O. R., Mancini, G., Tare, M., Gogia, N. and Singh, A. (2015) Drosophila Eye Model to Study Neuroprotective Role of CREB Binding Protein (CBP) in Alzheimer's Disease. *PLoS One,* **10,** e0137691.

Darnell, J. C., Jensen, K. B., Jin, P., Brown, V., Warren, S. T. and Darnell, R. B. (2001) Fragile X mental retardation protein targets G quartet mRNAs important for neuronal function. *Cell,* **107,** 489-499.

Davis, G. W., DiAntonio, A., Petersen, S. A. and Goodman, C. S. (1998) Postsynaptic PKA controls quantal size and reveals a retrograde signal that regulates presynaptic transmitter release in Drosophila. *Neuron,* **20,** 305-315.

Davis, G. W. and Goodman, C. S. (1998) Genetic analysis of synaptic development and plasticity: homeostatic regulation of synaptic efficacy. *Curr Opin Neurobiol,* **8,** 149-156.

Davis, G. W. and Muller, M. (2015) Homeostatic control of presynaptic neurotransmitter release. *Annu Rev Physiol,* **77,** 251-270.

Davis, R. L. (1993) Mushroom bodies and Drosophila learning. *Neuron,* **11,** 1-14.

Dayan, E. and Cohen, L. G. (2011) Neuroplasticity subserving motor skill learning. *Neuron,* **72,** 443-454.

de Belle, J. S. and Heisenberg, M. (1994) Associative odor learning in Drosophila abolished by chemical ablation of mushroom bodies. *Science,* **263,** 692-695.

de Villers-Sidani, E., Chang, E. F., Bao, S. and Merzenich, M. M. (2007) Critical period window for spectral tuning defined in the primary auditory cortex (A1) in the rat. *J Neurosci,* **27,** 180-189.

Dent, E. W., Merriam, E. B. and Hu, X. (2011) The dynamic cytoskeleton: backbone of dendritic spine plasticity. *Curr Opin Neurobiol,* **21,** 175-181.

Dickman, D. K. and Davis, G. W. (2009) The schizophrenia susceptibility gene dysbindin controls synaptic homeostasis. *Science,* **326,** 1127-1130.

Dickman, D. K., Tong, A. and Davis, G. W. (2012) Snapin is critical for presynaptic homeostatic plasticity. *J Neurosci,* **32,** 8716-8724.

Dickson, B. J. and Zou, Y. (2010) Navigating intermediate targets: the nervous system midline. *Cold Spring Harb Perspect Biol,* **2,** a002055.

Dieterich, D. C., Hodas, J. J., Gouzer, G., Shadrin, I. Y., Ngo, J. T., Triller, A., Tirrell, D. A. and Schuman, E. M. (2010) In situ visualization and dynamics of newly synthesized proteins in rat hippocampal neurons. *Nat Neurosci,* **13,** 897-905.

Dieterich, D. C., Karpova, A., Mikhaylova, M. et al. (2008) Caldendrin-Jacob: a protein liaison that couples NMDA receptor signalling to the nucleus. *PLoS Biol,* **6,** e34.

Dinamarca, M. C., Guzzetti, F., Karpova, A. et al. (2016) Ring finger protein 10 is a novel synaptonuclear messenger encoding activation of NMDA receptors in hippocampus. *Elife,* **5,** e12430.

Djakovic, S. N., Marquez-Lona, E. M., Jakawich, S. K., Wright, R., Chu, C., Sutton, M. A. and Patrick, G. N. (2012) Phosphorylation of Rpt6 regulates synaptic strength in hippocampal neurons. *J Neurosci,* **32,** 5126-5131.

Donato, F., Rompani, S. B. and Caroni, P. (2013) Parvalbumin-expressing basket-cell network plasticity induced by experience regulates adult learning. *Nature,* **504,** 272-276.

Doyle, M. and Kiebler, M. A. (2011) Mechanisms of dendritic mRNA transport and its role in synaptic tagging. *EMBO J,* **30,** 3540-3552.

Doyon, J. and Benali, H. (2005) Reorganization and plasticity in the adult brain during learning of motor skills. *Curr Opin Neurobiol,* **15,** 161-167.

Dudai, Y., Karni, A. and Born, J. (2015) The Consolidation and Transformation of Memory. *Neuron,* **88,** 20-32.

Duffy, F. H., Burchfiel, J. L. and Conway, J. L. (1976) Bicuculline reversal of deprivation amblyopia in the cat. *Nature,* **260,** 256-257.

Dun, X. P. and Chilton, J. K. (2010) Control of cell shape and plasticity during development and disease by the actin-binding protein Drebrin. *Histol Histopathol,* **25,** 533-540.

Ego-Stengel, V. and Wilson, M. A. (2010) Disruption of ripple-associated hippocampal activity during rest impairs spatial learning in the rat. *Hippocampus,* **20,** 1-10.

Engert, F. and Bonhoeffer, T. (1999) Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature,* **399,** 66-70.

Engert, F. and Wilson, S. W. (2012) Zebrafish neurobiology: from development to circuit function and behaviour. *Dev Neurobiol,* **72,** 215-217.

Epstein, I., Tushev, G., Will, T. J., Vlatkovic, I., Cajigas, I. J. and Schuman, E. M. (2014) Alternative polyadenylation and differential expression of Shank mRNAs in the synaptic neuropil. *Philos Trans R Soc Lond B Biol Sci,* **369,** 20130137.

Eshel, N., Tian, J., Bukwich, M. and Uchida, N. (2016) Dopamine neurons share common response function for reward prediction error. *Nature neuroscience,* **19,** 479-486.

Espinosa, J. S. and Stryker, M. P. (2012) Development and plasticity of the primary visual cortex. *Neuron,* **75,** 230-249.

Everitt, B. J., Morris, K. A., O'Brien, A. and Robbins, T. W. (1991) The basolateral amygdala-ventral striatal system and conditioned place preference: further evidence of limbic-striatal interactions underlying reward-related processes. *Neuroscience,* **42,** 1-18.

Faguet, J., Maranhao, B., Smith, S. L. and Trachtenberg, J. T. (2009) Ipsilateral eye cortical maps are uniquely sensitive to binocular plasticity. *J Neurophysiol,* **101,** 855-861.

Fanselow, M. S. and Kim, J. J. (1994) Acquisition of contextual Pavlovian fear conditioning is blocked by application of an NMDA receptor antagonist D,L-2-amino-5-phosphonovaleric acid to the basolateral amygdala. *Behav Neurosci,* **108,** 210-212.

Fanselow, M. S. and Wassum, K. M. (2015) The Origins and Organization of Vertebrate Pavlovian Conditioning. *Cold Spring Harb Perspect Biol,* **8,** a021717.

Fauth, M. and Tetzlaff, C. (2016) Opposing Effects of Neuronal Activity on Structural Plasticity. *Front Neuroanat,* **10,** 75.

Ferguson, S. M., Fasano, S., Yang, P., Brambilla, R. and Robinson, T. E. (2006) Knockout of ERK1 enhances cocaine-evoked immediate early gene expression and behavioral plasticity. *Neuropsychopharmacology,* **31,** 2660-2668.

Fernandes, D. and Carvalho, A. L. (2016) Mechanisms of homeostatic plasticity in the excitatory synapse. *J Neurochem*.

Ferreira, J. S., Schmidt, J., Rio, P., Aguas, R., Rooyakkers, A., Li, K. W., Smit, A. B., Craig, A. M. and Carvalho, A. L. (2015) GluN2B-Containing NMDA Receptors Regulate AMPA Receptor Traffic through Anchoring of the Synaptic Proteasome. *J Neurosci,* **35,** 8462-8479.

Ferretti, V., Roullet, P., Sargolini, F. et al. (2010) Ventral striatal plasticity and spatial memory. *Proceedings of the National Academy of Sciences of the United States of America,* **107,** 7945-7950.

Fischer, S., Nitschke, M. F., Melchert, U. H., Erdmann, C. and Born, J. (2005) Motor memory consolidation in sleep shapes more effective neuronal representations. *J Neurosci,* **25,** 11248-11255.

Fogel, S., Vien, C., Karni, A., Benali, H., Carrier, J. and Doyon, J. (2016) Sleep spindles: a physiological marker of age-related changes in gray matter in brain regions supporting motor skill memory consolidation. *Neurobiol Aging,* **49,** 154-164.

Frank, C. A., Wang, X., Collins, C. A., Rodal, A. A., Yuan, Q., Verstreken, P. and Dickman, D. K. (2013) New approaches for studying synaptic development, function, and plasticity using Drosophila as a model system. *J Neurosci,* **33,** 17560-17568.

Frankland, P. W., Josselyn, S. A., Anagnostaras, S. G., Kogan, J. H., Takahashi, E. and Silva, A. J. (2004) Consolidation of CS and US representations in associative fear conditioning. *Hippocampus,* **14,** 557-569.

Freudenthal, R., Boccia, M. M., Acosta, G. B., Blake, M. G., Merlo, E., Baratti, C. M. and Romano, A. (2005) NF-kappaB transcription factor is required for inhibitory avoidance long-term memory in mice. *Eur J Neurosci,* **21,** 2845-2852.

Frey, U., Frey, S., Schollmeier, F. and Krug, M. (1996) Influence of actinomycin D, a RNA synthesis inhibitor, on long-term potentiation in rat hippocampal neurons in vivo and in vitro. *J Physiol,* **490 (Pt 3),** 703-711.

Friedrich, R. W., Jacobson, G. A. and Zhu, P. (2010) Circuit neuroscience in zebrafish. *Curr Biol,* **20,** R371-381.

Fu, M., Yu, X., Lu, J. and Zuo, Y. (2012) Repetitive motor learning induces coordinated formation of clustered dendritic spines in vivo. *Nature,* **483,** 92-95.

Gainey, M. A., Tatavarty, V., Nahmani, M., Lin, H. and Turrigiano, G. G. (2015) Activity-dependent synaptic GRIP1 accumulation drives synaptic scaling up in response to action potential blockade. *Proc Natl Acad Sci U S A,* **112,** E3590-3599.

Gajewski, P. D., Hengstler, J. G., Golka, K., Falkenstein, M. and Beste, C. (2011) The Met-allele of the BDNF Val66Met polymorphism enhances task switching in elderly. *Neurobiol Aging,* **32,** 2327 e2327-2319.

Gao, M., Sossa, K., Song, L., Errington, L., Cummings, L., Hwang, H., Kuhl, D., Worley, P. and Lee, H. K. (2010) A specific requirement of Arc/Arg3.1 for visual experience-induced homeostatic synaptic plasticity in mouse primary visual cortex. *J Neurosci,* **30,** 7168-7178.

Gardiol, A., Racca, C. and Triller, A. (1999) Dendritic and postsynaptic protein synthetic machinery. *J Neurosci,* **19,** 168-179.

Geraldo, S. and Gordon-Weeks, P. R. (2009) Cytoskeletal dynamics in growth-cone steering. *J Cell Sci,* **122,** 3595-3604.

Girardeau, G. and Zugaro, M. (2011) Hippocampal ripples and memory consolidation. *Current opinion in neurobiology,* **21,** 452-459.

Goo, M. S., Scudder, S. L. and Patrick, G. N. (2015) Ubiquitin-dependent trafficking and turnover of ionotropic glutamate receptors. *Front Mol Neurosci,* **8,** 60.

Gourley, S. L., Zimmermann, K. S., Allen, A. G. and Taylor, J. R. (2016) The Medial Orbitofrontal Cortex Regulates Sensitivity to Outcome Value. *The Journal of neuroscience : the official journal of the Society for Neuroscience,* **36,** 4600-4613.

Greenough, W. T., Larson, J. R. and Withers, G. S. (1985) Effects of unilateral and bilateral training in a reaching task on dendritic branching of neurons in the rat motor-sensory forelimb cortex. *Behav Neural Biol,* **44,** 301-314.

Grosmark, A. D. and Buzsaki, G. (2016) Diversity in neural firing dynamics supports both rigid and learned hippocampal sequences. *Science,* **351,** 1440-1443.

Guo, L., Xiong, H., Kim, J. I., Wu, Y. W., Lalchandani, R. R., Cui, Y., Shu, Y., Xu, T. and Ding, J. B. (2015) Dynamic rewiring of neural circuits in the motor cortex in mouse models of Parkinson's disease. *Nat Neurosci,* **18,** 1299-1309.

Hamilton, A. M., Oh, W. C., Vega-Ramirez, H., Stein, I. S., Hell, J. W., Patrick, G. N. and Zito, K. (2012) Activity-dependent growth of new dendritic spines is regulated by the proteasome. *Neuron,* **74,** 1023-1030.

Hanus, C., Kochen, L., Tom Dieck, S., Racine, V., Sibarita, J. B., Schuman, E. M. and Ehlers, M. D. (2014) Synaptic control of secretory trafficking in dendrites. *Cell Rep,* **7,** 1771-1778.

Hanus, C. and Schuman, E. M. (2013) Proteostasis in complex dendrites. *Nat Rev Neurosci,* **14,** 638-648.

Harlow, H. F. and Zimmermann, R. R. (1959) Affectional responses in the infant monkey; orphaned baby monkeys develop a strong and persistent attachment to inanimate surrogate mothers. *Science,* **130,** 421-432.

Harms, K. J., Rioult-Pedotti, M. S., Carter, D. R. and Dunaevsky, A. (2008) Transient spine expansion and learning-induced plasticity in layer 1 primary motor cortex. *J Neurosci,* **28,** 5686-5690.

Hartley, C. A. and Lee, F. S. (2015) Sensitive periods in affective development: nonlinear maturation of fear learning. *Neuropsychopharmacology,* **40,** 50-60.

Hengen, K. B., Lambo, M. E., Van Hooser, S. D., Katz, D. B. and Turrigiano, G. G. (2013) Firing rate homeostasis in visual cortex of freely behaving rodents. *Neuron,* **80,** 335-342.

Hensch, T. K. (2004) Critical period regulation. *Annu Rev Neurosci,* **27,** 549-579.

Hensch, T. K. (2005) Critical period plasticity in local cortical circuits. *Nat Rev Neurosci,* **6,** 877-888.

Hensch, T. K., Fagiolini, M., Mataga, N., Stryker, M. P., Baekkeskov, S. and Kash, S. F. (1998) Local GABA circuit control of experience-dependent plasticity in developing visual cortex. *Science,* **282,** 1504-1508.

Hering, H. and Sheng, M. (2001) Dendritic spines: structure, dynamics and regulation. *Nat Rev Neurosci,* **2,** 880-888.

Hertler, B., Buitrago, M. M., Luft, A. R. and Hosp, J. A. (2016) Temporal course of gene expression during motor memory formation in primary motor cortex of rats. *Neurobiol Learn Mem,* **136,** 105-115.

Herweg, N. A., Apitz, T., Leicht, G., Mulert, C., Fuentemilla, L. and Bunzeck, N. (2016) Theta-Alpha Oscillations Bind the Hippocampus, Prefrontal Cortex, and Striatum during Recollection:

Evidence from Simultaneous EEG-fMRI. *The Journal of neuroscience : the official journal of the Society for Neuroscience,* **36,** 3579-3587.

Higa, K. K., Young, J. W., Ji, B., Nichols, D. E., Geyer, M. A. and Zhou, X. (2017) Striatal dopamine D1 receptor suppression impairs reward-associative learning. *Behav Brain Res,* **323,** 100-110.

Hige, T., Aso, Y., Modi, M. N., Rubin, G. M. and Turner, G. C. (2015) Heterosynaptic Plasticity Underlies Aversive Olfactory Learning in Drosophila. *Neuron,* **88,** 985-998.

Hikosaka, O., Nakamura, K., Sakai, K. and Nakahara, H. (2002) Central mechanisms of motor skill learning. *Curr Opin Neurobiol,* **12,** 217-222.

Hill, J. L., Hardy, N. F., Jimenez, D. V., Maynard, K. R., Kardian, A. S., Pollock, C. J., Schloesser, R. J. and Martinowich, K. (2016) Loss of promoter IV-driven BDNF expression impacts oscillatory activity during sleep, sensory information processing and fear regulation. *Transl Psychiatry,* **6,** e873.

Hofer, S. B., Mrsic-Flogel, T. D., Bonhoeffer, T. and Hubener, M. (2009) Experience leaves a lasting structural trace in cortical circuits. *Nature,* **457,** 313-317.

Hofman, M. A. (2014) Evolution of the human brain: when bigger is better. *Front Neuroanat,* **8,** 15.

Holtmaat, A. J., Trachtenberg, J. T., Wilbrecht, L., Shepherd, G. M., Zhang, X., Knott, G. W. and Svoboda, K. (2005) Transient and persistent dendritic spines in the neocortex in vivo. *Neuron,* **45,** 279-291.

Horton, A. C. and Ehlers, M. D. (2003) Dual modes of endoplasmic reticulum-to-Golgi transport in dendrites revealed by live-cell imaging. *J Neurosci,* **23,** 6188-6199.

Horton, A. C., Racz, B., Monson, E. E., Lin, A. L., Weinberg, R. J. and Ehlers, M. D. (2005) Polarized secretory trafficking directs cargo for asymmetric dendrite growth and morphogenesis. *Neuron,* **48,** 757-771.

Horton, J. C. and Hocking, D. R. (1997) Timing of the critical period for plasticity of ocular dominance columns in macaque striate cortex. *J Neurosci,* **17,** 3684-3709.

Hosp, J. A., Pekanovic, A., Rioult-Pedotti, M. S. and Luft, A. R. (2011) Dopaminergic projections from midbrain to primary motor cortex mediate motor skill learning. *J Neurosci,* **31,** 2481-2487.

Hotermans, C., Peigneux, P., de Noordhout, A. M., Moonen, G. and Maquet, P. (2008) Repetitive transcranial magnetic stimulation over the primary motor cortex disrupts early boost but not delayed gains in performance in motor sequence learning. *Eur J Neurosci,* **28,** 1216-1221.

Hubel, D. H. and Wiesel, T. N. (1962) Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J Physiol,* **160,** 106-154.

Ikemoto, S. (2007) Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain research reviews,* **56,** 27-78.

Ismail, F. Y., Fatemi, A. and Johnston, M. V. (2016) Cerebral plasticity: Windows of opportunity in the developing brain. *Eur J Paediatr Neurol*.

Ito, R., Robbins, T. W., McNaughton, B. L. and Everitt, B. J. (2006) Selective excitotoxic lesions of the hippocampus and basolateral amygdala have dissociable effects on appetitive cue and place conditioning based on path integration in a novel Y-maze procedure. *The European journal of neuroscience,* **23,** 3071-3080.

Jadhav, S. P., Kemere, C., German, P. W. and Frank, L. M. (2012) Awake hippocampal sharp-wave ripples support spatial memory. *Science,* **336,** 1454-1458.

Jahnke, S., Timme, M. and Memmesheimer, R. M. (2015) A Unified Dynamic Model for Learning, Replay, and Sharp-Wave/Ripples. *J Neurosci,* **35,** 16236-16258.

Jausoro, I., Mestres, I., Remedi, M., Sanchez, M. and Caceres, A. (2012) IQGAP1: A microtubule-microfilament scaffolding protein with multiple roles in nerve cell development and synaptic plasticity. *Histol Histopathol,* **27,** 1385-1394.

Jaworski, J., Kapitein, L. C., Gouveia, S. M. et al. (2009) Dynamic microtubules regulate dendritic spine morphology and synaptic plasticity. *Neuron,* **61,** 85-100.

Jeanneret, V., Wu, F., Merino, P., Torre, E., Diaz, A., Cheng, L. and Yepes, M. (2016) Tissue-type Plasminogen Activator (tPA) Modulates the Postsynaptic Response of Cerebral Cortical Neurons to the Presynaptic Release of Glutamate. *Front Mol Neurosci,* **9,** 121.

Jeffrey, R. A., Ch'ng, T. H., O'Dell, T. J. and Martin, K. C. (2009) Activity-dependent anchoring of importin alpha at the synapse involves regulated binding to the cytoplasmic tail of the NR1-1a subunit of the NMDA receptor. *J Neurosci,* **29,** 15613-15620.

Jenkins, I. H., Brooks, D. J., Nixon, P. D., Frackowiak, R. S. and Passingham, R. E. (1994) Motor sequence learning: a study with positron emission tomography. *J Neurosci,* **14,** 3775-3790.

Jennings, B. H. (2011) Drosophila – a versatile model in biology & medicine. *Materials Today,* **14,** 190-195.

Jeyifous, O., Waites, C. L., Specht, C. G. et al. (2009) SAP97 and CASK mediate sorting of NMDA receptors through a previously unknown secretory pathway. *Nat Neurosci,* **12,** 1011-1019.

Jouvet-Mounier, D., Astic, L. and Lacote, D. (1970) Ontogenesis of the states of sleep in rat, cat, and guinea pig during the first postnatal month. *Dev Psychobiol,* **2,** 216-239.

Kandel, E. R., Dudai, Y. and Mayford, M. R. (2014) The molecular and systems biology of memory. *Cell,* **157,** 163-186.

Kanold, P. O., Kim, Y. A., GrandPre, T. and Shatz, C. J. (2009) Co-regulation of ocular dominance plasticity and NMDA receptor subunit expression in glutamic acid decarboxylase-65 knock-out mice. *J Physiol,* **587,** 2857-2867.

Karim, H. T., Huppert, T. J., Erickson, K. I., Wollam, M. E., Sparto, P. J., Sejdic, E. and VanSwearingen, J. M. (2016) Motor sequence learning-induced neural efficiency in functional brain connectivity. *Behav Brain Res,* **319,** 87-95.

Karpova, A., Mikhaylova, M., Bera, S. et al. (2013) Encoding and transducing the synaptic or extrasynaptic origin of NMDA receptor signals to the nucleus. *Cell,* **152,** 1119-1133.

Karunakaran, S., Chowdhury, A., Donato, F., Quairiaux, C., Michel, C. M. and Caroni, P. (2016) PV plasticity sustained through D1/5 dopamine signaling required for long-term memory consolidation. *Nat Neurosci,* **19,** 454-464.

Katagiri, H., Fagiolini, M. and Hensch, T. K. (2007) Optimization of somatic inhibition at critical period onset in mouse visual cortex. *Neuron,* **53,** 805-812.

Kemenes, G., Kemenes, I., Michel, M., Papp, A. and Muller, U. (2006) Phase-dependent molecular requirements for memory reconsolidation: differential roles for protein synthesis and protein kinase A activity. *J Neurosci,* **26,** 6298-6302.

Kim, G. and Kandler, K. (2003) Elimination and strengthening of glycinergic/GABAergic connections during tonotopic map formation. *Nat Neurosci,* **6,** 282-290.

Kim, H., Kim, E., Park, M., Lee, E. and Namkoong, K. (2013) Organotypic hippocampal slice culture from the adult mouse brain: a versatile tool for translational neuropsychopharmacology. *Prog Neuropsychopharmacol Biol Psychiatry,* **41,** 36-43.

Kim, S. and Martin, K. C. (2015) Neuron-wide RNA transport combines with netrin-mediated local translation to spatially regulate the synaptic proteome. *Elife,* **4**.

Kleim, J. A., Chan, S., Pringle, E., Schallert, K., Procaccio, V., Jimenez, R. and Cramer, S. C. (2006) BDNF val66met polymorphism is associated with modified experience-dependent plasticity in human motor cortex. *Nat Neurosci,* **9,** 735-737.

Kleim, J. A., Jones, T. A. and Schallert, T. (2003) Motor enrichment and the induction of plasticity before or after brain injury. *Neurochem Res,* **28,** 1757-1769.

Klein, R. (2009) Bidirectional modulation of synaptic functions by Eph/ephrin signaling. *Nat Neurosci,* **12,** 15-20.

Knott, G. W., Holtmaat, A., Wilbrecht, L., Welker, E. and Svoboda, K. (2006) Spine growth precedes synapse formation in the adult neocortex in vivo. *Nat Neurosci,* **9,** 1117-1124.

Knudsen, E. I. (2004) Sensitive periods in the development of the brain and behavior. *J Cogn Neurosci,* **16,** 1412-1425.

Knudsen, E. I., Zheng, W. and DeBello, W. M. (2000) Traces of learning in the auditory localization pathway. *Proc Natl Acad Sci U S A,* **97,** 11815-11820.

Kolb, B., Cioe, J. and Comeau, W. (2008) Contrasting effects of motor and visual spatial learning tasks on dendritic arborization and spine density in rats. *Neurobiol Learn Mem,* **90,** 295-300.

Korman, M., Doyon, J., Doljansky, J., Carrier, J., Dagan, Y. and Karni, A. (2007) Daytime sleep condenses the time course of motor memory consolidation. *Nat Neurosci,* **10,** 1206-1213.

Kravchick, D. O., Karpova, A., Hrdinka, M., Lopez-Rojas, J., Iacobas, S., Carbonell, A. U., Iacobas, D. A., Kreutz, M. R. and Jordan, B. A. (2016) Synaptonuclear messenger PRR7 inhibits c-Jun ubiquitination and regulates NMDA-mediated excitotoxicity. *EMBO J,* **35,** 1923-1934.

Kravitz, A. V., Tye, L. D. and Kreitzer, A. C. (2012) Distinct roles for direct and indirect pathway striatal neurons in reinforcement. *Nat Neurosci,* **15,** 816-818.

Kronschlager, M. T., Drdla-Schutting, R., Gassner, M., Honsek, S. D., Teuchmann, H. L. and Sandkuhler, J. (2016) Gliogenic LTP spreads widely in nociceptive pathways. *Science,* **354,** 1144-1148.

Lai, K. O., Zhao, Y., Ch'ng, T. H. and Martin, K. C. (2008) Importin-mediated retrograde transport of CREB2 from distal processes to the nucleus in neurons. *Proc Natl Acad Sci U S A,* **105,** 17175-17180.

Lamprecht, R. and LeDoux, J. (2004) Structural plasticity and memory. *Nat Rev Neurosci,* **5,** 45-54.

Landis, D. M. and Reese, T. S. (1983) Cytoplasmic organization in cerebellar dendritic spines. *J Cell Biol,* **97,** 1169-1178.

Lansink, C. S., Meijer, G. T., Lankelma, J. V., Vinck, M. A., Jackson, J. C. and Pennartz, C. M. (2016) Reward Expectancy Strengthens CA1 Theta and Beta Band Synchronization and Hippocampal-Ventral Striatal Coupling. *The Journal of neuroscience : the official journal of the Society for Neuroscience,* **36,** 10598-10610.

Lau, H. L., Timbers, T. A., Mahmoud, R. and Rankin, C. H. (2013) Genetic dissection of memory for associative and non-associative learning in Caenorhabditis elegans. *Genes Brain Behav,* **12,** 210-223.

Lee, S. H., Lim, C. S., Park, H. et al. (2007) Nuclear translocation of CAM-associated protein activates transcription for long-term facilitation in Aplysia. *Cell,* **129,** 801-812.

Lehericy, S., Benali, H., Van de Moortele, P. F., Pelegrini-Issac, M., Waechter, T., Ugurbil, K. and Doyon, J. (2005) Distinct basal ganglia territories are engaged in early and advanced motor sequence learning. *Proc Natl Acad Sci U S A,* **102,** 12566-12571.

Lepeta, K., Lourenco, M. V., Schweitzer, B. C. et al. (2016) Synaptopathies: synaptic dysfunction in neurological disorders - A review from students to students. *J Neurochem,* **138,** 785-805.

Letzkus, J. J., Wolff, S. B., Meyer, E. M., Tovote, P., Courtin, J., Herry, C. and Luthi, A. (2011) A disinhibitory microcircuit for associative fear learning in the auditory cortex. *Nature,* **480,** 331-335.

Leuner, B. and Gould, E. (2010) Structural plasticity and hippocampal function. *Annu Rev Psychol,* **61,** 111-140, C111-113.

Leung, L. C., Wang, G. X. and Mourrain, P. (2013) Imaging zebrafish neural circuitry from whole brain to synapse. *Front Neural Circuits,* **7,** 76.

Li, Q., Korte, M. and Sajikumar, S. (2016) Ubiquitin-Proteasome System Inhibition Promotes Long-Term Depression and Synaptic Tagging/Capture. *Cereb Cortex,* **26,** 2541-2548.

Li Voti, P., Conte, A., Suppa, A., Iezzi, E., Bologna, M., Aniello, M. S., Defazio, G., Rothwell, J. C. and Berardelli, A. (2011) Correlation between cortical plasticity, motor learning and BDNF genotype in healthy subjects. *Exp Brain Res,* **212,** 91-99.

Limback-Stokin, K., Korzus, E., Nagaoka-Yasuda, R. and Mayford, M. (2004) Nuclear calcium/calmodulin regulates memory consolidation. *J Neurosci,* **24,** 10858-10867.

Liu-Yesucevitz, L., Bassell, G. J., Gitler, A. D., Hart, A. C., Klann, E., Richter, J. D., Warren, S. T. and Wolozin, B. (2011) Local RNA translation at the synapse and in disease. *J Neurosci,* **31,** 16086-16093.

Liu, D., Diorio, J., Day, J. C., Francis, D. D. and Meaney, M. J. (2000) Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nat Neurosci,* **3,** 799-806.

Lohse, K. R., Wadden, K., Boyd, L. A. and Hodges, N. J. (2014) Motor skill acquisition across short and long time scales: a meta-analysis of neuroimaging data. *Neuropsychologia,* **59,** 130-141.

Lorenz, K. Z. (1937) *The Companion in the Bird's World,* Vol. 3: The Auk. American Ornithological Society.

Lorenzetti, F. D., Baxter, D. A. and Byrne, J. H. (2008) Molecular mechanisms underlying a cellular analog of operant reward learning. *Neuron,* **59,** 815-828.

Lourenco, M. V., Ferreira, S. T. and De Felice, F. G. (2015) Neuronal stress signaling and eIF2alpha phosphorylation as molecular links between Alzheimer's disease and diabetes. *Prog Neurobiol,* **129,** 37-57.

Louros, S. R., Hooks, B. M., Litvina, L., Carvalho, A. L. and Chen, C. (2014) A role for stargazin in experience-dependent plasticity. *Cell Rep,* **7,** 1614-1625.

Lovden, M., Wenger, E., Martensson, J., Lindenberger, U. and Backman, L. (2013) Structural brain plasticity in adult learning and development. *Neurosci Biobehav Rev,* **37,** 2296-2310.

Luft, A. R. and Buitrago, M. M. (2005) Stages of motor skill learning. *Mol Neurobiol,* **32,** 205-216.

Luft, A. R., Buitrago, M. M., Ringer, T., Dichgans, J. and Schulz, J. B. (2004) Motor skill learning depends on protein synthesis in motor cortex after training. *J Neurosci,* **24,** 6515-6520.

Lugli, G., Torvik, V. I., Larson, J. and Smalheiser, N. R. (2008) Expression of microRNAs and their precursors in synaptic fractions of adult mouse forebrain. *J Neurochem,* **106,** 650-661.

Luscher, C. and Malenka, R. C. (2012) NMDA receptor-dependent long-term potentiation and long-term depression (LTP/LTD). *Cold Spring Harb Perspect Biol,* **4**.

Ma, L., Narayana, S., Robin, D. A., Fox, P. T. and Xiong, J. (2011) Changes occur in resting state network of motor system during 4 weeks of motor skill learning. *Neuroimage,* **58,** 226-233.

Maag, J. L., Panja, D., Sporild, I., Patil, S., Kaczorowski, D. C., Bramham, C. R., Dinger, M. E. and Wibrand, K. (2015) Dynamic expression of long noncoding RNAs and repeat elements in synaptic plasticity. *Front Neurosci,* **9,** 351.

Mabb, A. M. and Ehlers, M. D. (2010) Ubiquitination in postsynaptic function and plasticity. *Annu Rev Cell Dev Biol,* **26,** 179-210.

MacDougall, M. J. and Fine, A. (2014) The expression of long-term potentiation: reconciling the preists and the postivists. *Philos Trans R Soc Lond B Biol Sci,* **369,** 20130135.

Madronal, N., Gruart, A., Valverde, O., Espadas, I., Moratalla, R. and Delgado-Garcia, J. M. (2012) Involvement of cannabinoid CB1 receptor in associative learning and in hippocampal CA3-CA1 synaptic plasticity. *Cereb Cortex,* **22,** 550-566.

Maffei, A. and Turrigiano, G. G. (2008) Multiple modes of network homeostasis in visual cortical layer 2/3. *J Neurosci,* **28,** 4377-4384.

Maletic-Savatic, M., Malinow, R. and Svoboda, K. (1999) Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. *Science,* **283,** 1923-1927.

Mander, B. A., Rao, V., Lu, B., Saletin, J. M., Ancoli-Israel, S., Jagust, W. J. and Walker, M. P. (2014) Impaired prefrontal sleep spindle regulation of hippocampal-dependent learning in older adults. *Cereb Cortex,* **24,** 3301-3309.

Maquet, P., Laureys, S., Peigneux, P. et al. (2000) Experience-dependent changes in cerebral activation during human REM sleep. *Nat Neurosci,* **3,** 831-836.

Maroteaux, M., Valjent, E., Longueville, S., Topilko, P., Girault, J. A. and Herve, D. (2014) Role of the plasticity-associated transcription factor zif268 in the early phase of instrumental learning. *PloS one,* **9,** e81868.

Martin, K. C. and Kandel, E. R. (1996) Cell adhesion molecules, CREB, and the formation of new synaptic connections. *Neuron,* **17,** 567-570.

Matsumoto, H., Tian, J., Uchida, N. and Watabe-Uchida, M. (2016) Midbrain dopamine neurons signal aversion in a reward-context-dependent manner. *eLife,* **5**.

Mayford, M., Siegelbaum, S. A. and Kandel, E. R. (2012) Synapses and memory storage. *Cold Spring Harb Perspect Biol,* **4**.

Mazzucchelli, C., Vantaggiato, C., Ciamei, A. et al. (2002) Knockout of ERK1 MAP kinase enhances synaptic plasticity in the striatum and facilitates striatal-mediated learning and memory. *Neuron,* **34,** 807-820.

McHughen, S. A. and Cramer, S. C. (2013) The BDNF val(66)met polymorphism is not related to motor function or short-term cortical plasticity in elderly subjects. *Brain Res,* **1495,** 1-10.

McKay, B. M., Oh, M. M. and Disterhoft, J. F. (2013) Learning increases intrinsic excitability of hippocampal interneurons. *J Neurosci,* **33,** 5499-5506.

Meaney, M. J. (2001) Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annu Rev Neurosci,* **24,** 1161-1192.

Melgarejo da Rosa, M., Yuanxiang, P., Brambilla, R., Kreutz, M. R. and Karpova, A. (2016) Synaptic GluN2B/CaMKII-alpha Signaling Induces Synapto-Nuclear Transport of ERK and Jacob. *Front Mol Neurosci,* **9,** 66.

Meyer, D., Bonhoeffer, T. and Scheuss, V. (2014) Balance and stability of synaptic structures during synaptic plasticity. *Neuron,* **82,** 430-443.

Michel, M., Green, C. L., Eskin, A. and Lyons, L. C. (2011) PKG-mediated MAPK signaling is necessary for long-term operant memory in Aplysia. *Learn Mem,* **18,** 108-117.

Mikhaylova, M., Bera, S., Kobler, O., Frischknecht, R. and Kreutz, M. R. (2016) A Dendritic Golgi Satellite between ERGIC and Retromer. *Cell Rep,* **14,** 189-199.

Miyamoto, H., Katagiri, H. and Hensch, T. (2003) Experience-dependent slow-wave sleep development. *Nat Neurosci,* **6,** 553-554.

Monfils, M. H. and Teskey, G. C. (2004) Skilled-learning-induced potentiation in rat sensorimotor cortex: a transient form of behavioural long-term potentiation. *Neuroscience,* **125,** 329-336.

Morin, A., Doyon, J., Dostie, V. et al. (2008) Motor sequence learning increases sleep spindles and fast frequencies in post-training sleep. *Sleep,* **31,** 1149-1156.

Mu, Y., Otsuka, T., Horton, A. C., Scott, D. B. and Ehlers, M. D. (2003) Activity-dependent mRNA splicing controls ER export and synaptic delivery of NMDA receptors. *Neuron,* **40,** 581-594.

Muellbacher, W., Ziemann, U., Wissel, J., Dang, N., Kofler, M., Facchini, S., Boroojerdi, B., Poewe, W. and Hallett, M. (2002) Early consolidation in human primary motor cortex. *Nature,* **415,** 640-644.

Muller, M. and Davis, G. W. (2012) Transsynaptic control of presynaptic Ca(2)(+) influx achieves homeostatic potentiation of neurotransmitter release. *Curr Biol,* **22,** 1102-1108.

Muller, M., Liu, K. S., Sigrist, S. J. and Davis, G. W. (2012) RIM controls homeostatic plasticity through modulation of the readily-releasable vesicle pool. *J Neurosci,* **32,** 16574-16585.

Murata, Y., Doi, T., Taniguchi, H. and Fujiyoshi, Y. (2005) Proteomic analysis revealed a novel synaptic proline-rich membrane protein (PRR7) associated with PSD-95 and NMDA receptor. *Biochem Biophys Res Commun,* **327,** 183-191.

Nabavi, S., Fox, R., Proulx, C. D., Lin, J. Y., Tsien, R. Y. and Malinow, R. (2014) Engineering a memory with LTD and LTP. *Nature,* **511,** 348-352.

Nabel, E. M. and Morishita, H. (2013) Regulating critical period plasticity: insight from the visual system to fear circuitry for therapeutic interventions. *Front Psychiatry,* **4,** 146.

Nadasdy, Z., Hirase, H., Czurko, A., Csicsvari, J. and Buzsaki, G. (1999) Replay and time compression of recurring spike sequences in the hippocampus. *The Journal of neuroscience : the official journal of the Society for Neuroscience,* **19,** 9497-9507.

Nagerl, U. V., Eberhorn, N., Cambridge, S. B. and Bonhoeffer, T. (2004) Bidirectional activity-dependent morphological plasticity in hippocampal neurons. *Neuron,* **44,** 759-767.

Nakamura, K., Enomoto, H., Hanajima, R. et al. (2011) Quadri-pulse stimulation (QPS) induced LTP/LTD was not affected by Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene. *Neurosci Lett,* **487,** 264-267.

Nakashiba, T., Buhl, D. L., McHugh, T. J. and Tonegawa, S. (2009) Hippocampal CA3 output is crucial for ripple-associated reactivation and consolidation of memory. *Neuron,* **62,** 781-787.

Naumann, E. A., Fitzgerald, J. E., Dunn, T. W., Rihel, J., Sompolinsky, H. and Engert, F. (2016) From Whole-Brain Data to Functional Circuit Models: The Zebrafish Optomotor Response. *Cell,* **167,** 947-960 e920.

Nimchinsky, E. A., Sabatini, B. L. and Svoboda, K. (2002) Structure and function of dendritic spines. *Annu Rev Physiol,* **64,** 313-353.

Nishida, M. and Walker, M. P. (2007) Daytime naps, motor memory consolidation and regionally specific sleep spindles. *PLoS One,* **2,** e341.

Okamoto, K., Nagai, T., Miyawaki, A. and Hayashi, Y. (2004) Rapid and persistent modulation of actin dynamics regulates postsynaptic reorganization underlying bidirectional plasticity. *Nat Neurosci,* **7,** 1104-1112.

Okuda, T., Yu, L. M., Cingolani, L. A., Kemler, R. and Goda, Y. (2007) beta-Catenin regulates excitatory postsynaptic strength at hippocampal synapses. *Proc Natl Acad Sci U S A,* **104,** 13479-13484.

Pace-Schott, E. F. and Spencer, R. M. (2011) Age-related changes in the cognitive function of sleep. *Prog Brain Res,* **191,** 75-89.

Padamsey, Z. and Emptage, N. (2014) Two sides to long-term potentiation: a view towards reconciliation. *Philos Trans R Soc Lond B Biol Sci,* **369,** 20130154.

Parnass, Z., Tashiro, A. and Yuste, R. (2000) Analysis of spine morphological plasticity in developing hippocampal pyramidal neurons. *Hippocampus,* **10,** 561-568.

Parsons-Smith, G. (1953) Activity of the cerebral cortex in amblyopia. *Br J Ophthalmol,* **37,** 359-364.

Peixoto, R. T., Kunz, P. A., Kwon, H., Mabb, A. M., Sabatini, B. L., Philpot, B. D. and Ehlers, M. D. (2012) Transsynaptic signaling by activity-dependent cleavage of neuroligin-1. *Neuron,* **76,** 396-409.

Penhune, V. B. and Steele, C. J. (2012) Parallel contributions of cerebellar, striatal and M1 mechanisms to motor sequence learning. *Behav Brain Res,* **226,** 579-591.

Peters, A. J., Chen, S. X. and Komiyama, T. (2014) Emergence of reproducible spatiotemporal activity during motor learning. *Nature,* **510,** 263-267.

Petzoldt, A. G., Lutzkendorf, J. and Sigrist, S. J. (2016) Mechanisms controlling assembly and plasticity of presynaptic active zone scaffolds. *Curr Opin Neurobiol,* **39,** 69-76.

Pick, J. E., Khatri, L., Sathler, M. F. and Ziff, E. B. (2017) mGluR long-term depression regulates GluA2 association with COPII vesicles and exit from the endoplasmic reticulum. *EMBO J,* **36,** 232-244.

Pizzorusso, T., Medini, P., Berardi, N., Chierzi, S., Fawcett, J. W. and Maffei, L. (2002) Reactivation of ocular dominance plasticity in the adult visual cortex. *Science,* **298,** 1248-1251.

Plomp, J. J., van Kempen, G. T. and Molenaar, P. C. (1992) Adaptation of quantal content to decreased postsynaptic sensitivity at single endplates in alpha-bungarotoxin-treated rats. *J Physiol,* **458,** 487-499.

Ploughman, M., Windle, V., MacLellan, C. L., White, N., Dore, J. J. and Corbett, D. (2009) Brain-derived neurotrophic factor contributes to recovery of skilled reaching after focal ischemia in rats. *Stroke,* **40,** 1490-1495.

Polepalli, J. S., Wu, H., Goswami, D., Halpern, C. H., Sudhof, T. C. and Malenka, R. C. (2017) Modulation of excitation on parvalbumin interneurons by neuroligin-3 regulates the hippocampal network. *Nat Neurosci,* **20,** 219-229.

Ponomarenko, A. A., Li, J. S., Korotkova, T. M., Huston, J. P. and Haas, H. L. (2008) Frequency of network synchronization in the hippocampus marks learning. *The European journal of neuroscience,* **27,** 3035-3042.

Portugues, R. and Engert, F. (2009) The neural basis of visual behaviors in the larval zebrafish. *Curr Opin Neurobiol,* **19,** 644-647.

Qian, Y., Forssberg, H. and Diaz Heijtz, R. (2015) Motor Skill Learning Is Associated with Phase-Dependent Modifications in the Striatal cAMP/PKA/DARPP-32 Signaling Pathway in Rodents. *PLoS One,* **10,** e0140974.

Qiu, Z., Sylwestrak, E. L., Lieberman, D. N., Zhang, Y., Liu, X. Y. and Ghosh, A. (2012) The Rett syndrome protein MeCP2 regulates synaptic scaling. *J Neurosci,* **32,** 989-994.

Rajasethupathy, P., Antonov, I., Sheridan, R., Frey, S., Sander, C., Tuschl, T. and Kandel, E. R. (2012) A role for neuronal piRNAs in the epigenetic control of memory-related synaptic plasticity. *Cell,* **149,** 693-707.

Ramanathan, D. S., Gulati, T. and Ganguly, K. (2015) Sleep-Dependent Reactivation of Ensembles in Motor Cortex Promotes Skill Consolidation. *PLoS Biol,* **13,** e1002263.

Rangaraju, V., Tom Dieck, S. and Schuman, E. M. (2017) Local translation in neuronal compartments: how local is local? *EMBO Rep*.

Redondo, R. L. and Morris, R. G. (2011) Making memories last: the synaptic tagging and capture hypothesis. *Nat Rev Neurosci,* **12,** 17-30.

Reis, J., Fischer, J. T., Prichard, G., Weiller, C., Cohen, L. G. and Fritsch, B. (2015) Time- but not sleep-dependent consolidation of tDCS-enhanced visuomotor skills. *Cereb Cortex,* **25,** 109-117.

Rincon-Cortes, M. and Sullivan, R. M. (2016) Emergence of social behavior deficit, blunted corticolimbic activity and adult depression-like behavior in a rodent model of maternal maltreatment. *Transl Psychiatry,* **6,** e930.

Rioult-Pedotti, M. S., Friedman, D. and Donoghue, J. P. (2000) Learning-induced LTP in neocortex. *Science,* **290,** 533-536.

Rioult-Pedotti, M. S., Friedman, D., Hess, G. and Donoghue, J. P. (1998) Strengthening of horizontal cortical connections following skill learning. *Nat Neurosci,* **1,** 230-234.

Rioult-Pedotti, M. S., Pekanovic, A., Atiemo, C. O., Marshall, J. and Luft, A. R. (2015) Dopamine Promotes Motor Cortex Plasticity and Motor Skill Learning via PLC Activation. *PLoS One,* **10,** e0124986.

Robertson, E. M., Pascual-Leone, A. and Miall, R. C. (2004a) Current concepts in procedural consolidation. *Nat Rev Neurosci,* **5,** 576-582.

Robertson, E. M., Pascual-Leone, A. and Press, D. Z. (2004b) Awareness modifies the skill-learning benefits of sleep. *Curr Biol,* **14,** 208-212.

Romanski, L. M., Clugnet, M. C., Bordi, F. and LeDoux, J. E. (1993) Somatosensory and auditory convergence in the lateral nucleus of the amygdala. *Behavioral neuroscience,* **107,** 444-450.

Rosenkranz, K., Kacar, A. and Rothwell, J. C. (2007) Differential modulation of motor cortical plasticity and excitability in early and late phases of human motor learning. *J Neurosci,* **27,** 12058-12066.

Rutherford, L. C., Nelson, S. B. and Turrigiano, G. G. (1998) BDNF has opposite effects on the quantal amplitude of pyramidal neuron and interneuron excitatory synapses. *Neuron,* **21,** 521-530.

Sadowski, J. H., Jones, M. W. and Mellor, J. R. (2016) Sharp-Wave Ripples Orchestrate the Induction of Synaptic Plasticity during Reactivation of Place Cell Firing Patterns in the Hippocampus. *Cell Rep,* **14,** 1916-1929.

Sakata, K., Martinowich, K., Woo, N. H., Schloesser, R. J., Jimenez, D. V., Ji, Y., Shen, L. and Lu, B. (2013) Role of activity-dependent BDNF expression in hippocampal-prefrontal cortical regulation of behavioral perseverance. *Proc Natl Acad Sci U S A,* **110,** 15103-15108.

Sambandan, S., Akbalik, G., Kochen, L. et al. (2017) Activity-dependent spatially localized miRNA maturation in neuronal dendrites. *Science,* **355,** 634-637.

Sampaio-Baptista, C., Filippini, N., Stagg, C. J., Near, J., Scholz, J. and Johansen-Berg, H. (2015) Changes in functional connectivity and GABA levels with long-term motor learning. *Neuroimage,* **106,** 15-20.

Sandin, L., Bergkvist, L., Nath, S. et al. (2016) Beneficial effects of increased lysozyme levels in Alzheimer's disease modelled in Drosophila melanogaster. *FEBS J,* **283,** 3508-3522.

Santos, A. R., Mele, M., Vaz, S. H. et al. (2015) Differential role of the proteasome in the early and late phases of BDNF-induced facilitation of LTP. *J Neurosci,* **35,** 3319-3329.

Schabitz, W. R., Berger, C., Kollmar, R., Seitz, M., Tanay, E., Kiessling, M., Schwab, S. and Sommer, C. (2004) Effect of brain-derived neurotrophic factor treatment and forced arm use on functional motor recovery after small cortical ischemia. *Stroke,* **35,** 992-997.

Schabitz, W. R., Steigleder, T., Cooper-Kuhn, C. M., Schwab, S., Sommer, C., Schneider, A. and Kuhn, H. G. (2007) Intravenous brain-derived neurotrophic factor enhances poststroke sensorimotor recovery and stimulates neurogenesis. *Stroke,* **38,** 2165-2172.

Schanzenbacher, C. T., Sambandan, S., Langer, J. D. and Schuman, E. M. (2016) Nascent Proteome Remodeling following Homeostatic Scaling at Hippocampal Synapses. *Neuron,* **92,** 358-371.

Schultz, W., Dayan, P. and Montague, P. R. (1997) A neural substrate of prediction and reward. *Science,* **275,** 1593-1599.

Schwarz, T. L. (2006) Transmitter release at the neuromuscular junction. *Int Rev Neurobiol,* **75,** 105-144.

Shepherd, J. D., Rumbaugh, G., Wu, J., Chowdhury, S., Plath, N., Kuhl, D., Huganir, R. L. and Worley, P. F. (2006) Arc/Arg3.1 mediates homeostatic synaptic scaling of AMPA receptors. *Neuron,* **52,** 475-484.

Sidorov, M. S., Auerbach, B. D. and Bear, M. F. (2013) Fragile X mental retardation protein and synaptic plasticity. *Mol Brain,* **6,** 15.

Siegel, G., Obernosterer, G., Fiore, R. et al. (2009) A functional screen implicates microRNA-138-dependent regulation of the depalmitoylation enzyme APT1 in dendritic spine morphogenesis. *Nat Cell Biol,* **11,** 705-716.

Smith, S. L. and Trachtenberg, J. T. (2007) Experience-dependent binocular competition in the visual cortex begins at eye opening. *Nat Neurosci,* **10,** 370-375.

Soden, M. E. and Chen, L. (2010) Fragile X protein FMRP is required for homeostatic plasticity and regulation of synaptic strength by retinoic acid. *J Neurosci,* **30,** 16910-16921.

Song, S., Howard, J. H., Jr. and Howard, D. V. (2007) Sleep does not benefit probabilistic motor sequence learning. *J Neurosci,* **27,** 12475-12483.

Southwell, D. G., Froemke, R. C., Alvarez-Buylla, A., Stryker, M. P. and Gandhi, S. P. (2010) Cortical plasticity induced by inhibitory neuron transplantation. *Science,* **327,** 1145-1148.

Spencer, R. M., Gouw, A. M. and Ivry, R. B. (2007) Age-related decline of sleep-dependent consolidation. *Learn Mem,* **14,** 480-484.

Stefan, K., Wycislo, M., Gentner, R., Schramm, A., Naumann, M., Reiners, K. and Classen, J. (2006) Temporary occlusion of associative motor cortical plasticity by prior dynamic motor training. *Cereb Cortex,* **16,** 376-385.

Stellwagen, D. and Malenka, R. C. (2006) Synaptic scaling mediated by glial TNF-alpha. *Nature,* **440,** 1054-1059.

Steward, O. and Levy, W. B. (1982) Preferential localization of polyribosomes under the base of dendritic spines in granule cells of the dentate gyrus. *J Neurosci,* **2,** 284-291.

Sudhof, T. C. (2008) Neuroligins and neurexins link synaptic function to cognitive disease. *Nature,* **455,** 903-911.

Sudhof, T. C. (2012) The presynaptic active zone. *Neuron,* **75,** 11-25.

Sun, F. T., Miller, L. M., Rao, A. A. and D'Esposito, M. (2007) Functional connectivity of cortical networks involved in bimanual motor sequence learning. *Cereb Cortex,* **17,** 1227-1234.

Sutton, M. A. and Schuman, E. M. (2006) Dendritic protein synthesis, synaptic plasticity, and memory. *Cell,* **127,** 49-58.

Szklarczyk, A., Conant, K., Owens, D. F., Ravin, R., McKay, R. D. and Gerfen, C. (2007) Matrix metalloproteinase-7 modulates synaptic vesicle recycling and induces atrophy of neuronal synapses. *Neuroscience,* **149,** 87-98.

Tang, Y., Stryker, M. P., Alvarez-Buylla, A. and Espinosa, J. S. (2014) Cortical plasticity induced by transplantation of embryonic somatostatin or parvalbumin interneurons. *Proc Natl Acad Sci U S A,* **111,** 18339-18344.

Taubert, M., Lohmann, G., Margulies, D. S., Villringer, A. and Ragert, P. (2011) Long-term effects of motor training on resting-state networks and underlying brain structure. *Neuroimage,* **57,** 1492-1498.

Thompson, K. R., Otis, K. O., Chen, D. Y., Zhao, Y., O'Dell, T. J. and Martin, K. C. (2004) Synapse to nucleus signaling during long-term synaptic plasticity; a role for the classical active nuclear import pathway. *Neuron,* **44,** 997-1009.

tom Dieck, S., Kochen, L., Hanus, C. et al. (2015) Direct visualization of newly synthesized target proteins in situ. *Nat Methods,* **12,** 411-414.

Toni, N., Buchs, P. A., Nikonenko, I., Bron, C. R. and Muller, D. (1999) LTP promotes formation of multiple spine synapses between a single axon terminal and a dendrite. *Nature,* **402,** 421-425.

Trachtenberg, J. T. (2015) Competition, inhibition, and critical periods of cortical plasticity. *Curr Opin Neurobiol,* **35,** 44-48.

Tse, D., Langston, R. F., Kakeyama, M., Bethus, I., Spooner, P. A., Wood, E. R., Witter, M. P. and Morris, R. G. (2007) Schemas and memory consolidation. *Science,* **316,** 76-82.

Turrigiano, G. G. (2008) The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell,* **135,** 422-435.

Turrigiano, G. G., Leslie, K. R., Desai, N. S., Rutherford, L. C. and Nelson, S. B. (1998) Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature,* **391,** 892-896.

Ungerleider, L. G., Doyon, J. and Karni, A. (2002) Imaging brain plasticity during motor skill learning. *Neurobiol Learn Mem,* **78,** 553-564.

Valente, A., Huang, K. H., Portugues, R. and Engert, F. (2012) Ontogeny of classical and operant learning behaviors in zebrafish. *Learn Mem,* **19,** 170-177.

Van Meer, P. and Raber, J. (2005) Mouse behavioural analysis in systems biology. *Biochem J,* **389,** 593-610.

Vicario, A., Colliva, A., Ratti, A. et al. (2015) Dendritic targeting of short and long 3' UTR BDNF mRNA is regulated by BDNF or NT-3 and distinct sets of RNA-binding proteins. *Front Mol Neurosci,* **8,** 62.

Vitureira, N. and Goda, Y. (2013) Cell biology in neuroscience: the interplay between Hebbian and homeostatic synaptic plasticity. *J Cell Biol,* **203,** 175-186.

Vitureira, N., Letellier, M., White, I. J. and Goda, Y. (2011) Differential control of presynaptic efficacy by postsynaptic N-cadherin and beta-catenin. *Nat Neurosci,* **15,** 81-89.

Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A. and Stickgold, R. (2002) Practice with sleep makes perfect: sleep-dependent motor skill learning. *Neuron,* **35,** 205-211.

Walker, M. P., Brakefield, T., Seidman, J., Morgan, A., Hobson, J. A. and Stickgold, R. (2003) Sleep and the time course of motor skill learning. *Learn Mem,* **10,** 275-284.

Wang, W., Kwon, E. J. and Tsai, L. H. (2012) MicroRNAs in learning, memory, and neurological diseases. *Learn Mem,* **19,** 359-368.

Wang, W., Trieu, B. H., Palmer, L. C. et al. (2016) A Primary Cortical Input to Hippocampus Expresses a Pathway-Specific and Endocannabinoid-Dependent Form of Long-Term Potentiation. *eNeuro,* **3**.

Ward, R. D., Simpson, E. H., Kandel, E. R. and Balsam, P. D. (2011) Modeling motivational deficits in mouse models of schizophrenia: behavior analysis as a guide for neuroscience. *Behav Processes,* **87,** 149-156.

Wei, Y., Krishnan, G. P. and Bazhenov, M. (2016) Synaptic Mechanisms of Memory Consolidation during Sleep Slow Oscillations. *The Journal of neuroscience : the official journal of the Society for Neuroscience,* **36,** 4231-4247.

Weyhersmuller, A., Hallermann, S., Wagner, N. and Eilers, J. (2011) Rapid active zone remodeling during synaptic plasticity. *J Neurosci,* **31,** 6041-6052.

Wiera, G., Wozniak, G., Bajor, M., Kaczmarek, L. and Mozrzymas, J. W. (2013) Maintenance of long-term potentiation in hippocampal mossy fiber-CA3 pathway requires fine-tuned MMP-9 proteolytic activity. *Hippocampus,* **23,** 529-543.

Wiesel, T. N. (1982) Postnatal development of the visual cortex and the influence of environment. *Nature,* **299,** 583-591.

Wiesel, T. N. and Hubel, D. H. (1963) Single-Cell Responses in Striate Cortex of Kittens Deprived of Vision in One Eye. *J Neurophysiol,* **26,** 1003-1017.

Will, T. J., Tushev, G., Kochen, L., Nassim-Assir, B., Cajigas, I. J., Tom Dieck, S. and Schuman, E. M. (2013) Deep sequencing and high-resolution imaging reveal compartment-specific localization of Bdnf mRNA in hippocampal neurons. *Sci Signal,* **6,** rs16.

Willingham, D. B. (1998) A neuropsychological theory of motor skill learning. *Psychol Rev,* **105,** 558-584.

Xia, H., Hornby, Z. D. and Malenka, R. C. (2001) An ER retention signal explains differences in surface expression of NMDA and AMPA receptor subunits. *Neuropharmacology,* **41,** 714-723.

Xu, T., Yu, X., Perlik, A. J., Tobin, W. F., Zweig, J. A., Tennant, K., Jones, T. and Zuo, Y. (2009) Rapid formation and selective stabilization of synapses for enduring motor memories. *Nature,* **462,** 915-919.

Yamagata, N., Hiroi, M., Kondo, S., Abe, A. and Tanimoto, H. (2016) Suppression of Dopamine Neurons Mediates Reward. *PLoS Biol,* **14,** e1002586.

Yang, G., Pan, F. and Gan, W. B. (2009) Stably maintained dendritic spines are associated with lifelong memories. *Nature,* **462,** 920-924.

Yang, Y. and Calakos, N. (2013) Presynaptic long-term plasticity. *Front Synaptic Neurosci,* **5,** 8.

Yang, Y. and Lisberger, S. G. (2014) Purkinje-cell plasticity and cerebellar motor learning are graded by complex-spike duration. *Nature,* **510,** 529-532.

Yger, P. and Gilson, M. (2015) Models of Metaplasticity: A Review of Concepts. *Front Comput Neurosci,* **9,** 138.

Yin, H. H., Mulcare, S. P., Hilario, M. R., Clouse, E., Holloway, T., Davis, M. I., Hansson, A. C., Lovinger, D. M. and Costa, R. M. (2009) Dynamic reorganization of striatal circuits during the acquisition and consolidation of a skill. *Nat Neurosci,* **12,** 333-341.

Zarnadze, S., Bauerle, P., Santos-Torres, J., Bohm, C., Schmitz, D., Geiger, J. R., Dugladze, T. and Gloveli, T. (2016) Cell-specific synaptic plasticity induced by network oscillations. *Elife,* **5**.

Zellner, M. R., Kest, K. and Ranaldi, R. (2009) NMDA receptor antagonism in the ventral tegmental area impairs acquisition of reward-related learning. *Behav Brain Res,* **197,** 442-449.

Zhang, L. I., Bao, S. and Merzenich, M. M. (2001) Persistent and specific influences of early acoustic environments on primary auditory cortex. *Nat Neurosci,* **4,** 1123-1130.

Zhou, Q., Homma, K. J. and Poo, M. M. (2004) Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. *Neuron,* **44,** 749-757.

Ziemann, U., Ilic, T. V., Pauli, C., Meintzschel, F. and Ruge, D. (2004) Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *J Neurosci,* **24,** 1666-1672.

Zito, K., Scheuss, V., Knott, G., Hill, T. and Svoboda, K. (2009) Rapid functional maturation of nascent dendritic spines. *Neuron,* **61,** 247-258.

Figure 1: Synapse-to-nucleus communication and local proteostasis in synaptic plasticity. (1.) LTP induces postsynaptic AMPAR (green) insertion, enabling elevated calcium (Ca^{2+}) influx through NMDAR (blue) activity. Increased Ca^{2+} levels lead to autophosphorylation and activation of CAMK-IIα, which acts as a scaffold translocating the 26S-proteasome to the synapse, thereby inducing degradation of polyubiquitinated proteins and facilitating protein turnover and synaptic plasticity. Increased Ca^{2+} influx further activates PP2B/calcineurin (CaN), which dephosphorylates CRTC-1, a transcriptional coactivator that mediates CREB-dependent transcription. CRTC-1 thus binds to importin and translocates to the nucleus. Activation of GPCRs coupled to Gs stimulate adenylyl cyclase (AC) to produce cAMP, thereby leading to activation of cAMP-dependent protein kinase (PKA). PKA phosphorylates CREB-1, which together with nuclear CRTC-1 induces transcription of pro-LTP factors. These newly produced mRNAs may be stored in ribonucleoprotein granules (RNPs) and transported to Golgi and endoplasmic reticulum (ER) outposts or to free polysomes at synapses, where they will be locally translated. (2.) On the other hand, LTD-dependent reduction in postsynaptic AMPARs decreases Ca^{2+} influx and facilitates CREB-2 translation. Furthermore, mGluRs are activated, leading to modulation of translation factors with additional induction of CREB-2 translation. CREB-2 translocates to the nucleus via binding to importin, drives LTD-dependent transcription and antagonizes the actions of CREB-1, thus reducing pro-LTP gene expression.

Figure 2: Hebbian and non-Hebbian forms of synaptic plasticity. During basal state, synapses process stimuli via AMPARs (A, upper panel), leading to a defined firing rate (A, lower panel). LTP induces Hebbian plasticity, during which synapses increase the number of AMPARs in an input-specific fashion (B, upper panel), thereby strengthening synapses. Increased stimuli lead to an increased firing rate (B, lower panel). Synaptic scaling, the most studied form of non-Hebbian plasticity, acts via post-synaptic reduction of AMPARs (C, upper panel) through weakening synapses adjacent to the potentiated synapse to restore homeostasis and optimal global firing rate (C, lower panel).