Neuronal circuits are exceptionally sensitive to being shaped by patterns of cellular activity during early brain development called critical periods (Hensch 2005a). The critical period (CP) refers to a defined developmental window when the system is especially sensitive to environmental stimuli and experience produces permanent, large-scale changes to neural circuits. CPs are known to be present in sensory systems such as binocular vision in the visual cortex, barrel representation of whiskers in somatosensory cortex, and tonotopic map refinement in auditory cortex. They are also present in motor systems and even areas of higher cognitions in the brain such as human language acquisition in the Broca’s area (O’Leary et al. 1994; Hensch 2004, 2005a; Knudsen 2004; Daw 2006; Hooks and Chen 2007).

The aim of studies investigating mechanisms underlying activation and regulation of CPs in the central nervous system (CNS) are to identify mechanisms that may allow for reactivation of neural circuit plasticity in adulthood when these circuits are no longer plastic. An important application would be to aid rewiring of neural circuits after damage to the CNS such as in the case of stroke to regain normal function. In children with neurodevelopmental disorders involving synaptic plasticity, understanding mechanisms to reactivate critical period can also potentially help to correct alterations in neural circuits via pharmacological intervention.

The visual cortex is the best-studied experimental model used to study critical period as it is easy to manipulate visual experience independently in each eye and measure changes in plasticity. Direct electrophysiological measurements of neuronal function measure ocular dominance, a phenomenon whereby visual cortical neurons are activated to different degrees by the presentation of visual stimuli to one eye versus the other. During the CP, cortical responses can be manipulated by deprivation of sensory inputs via the closure of one eye, known as monocular deprivation (MD), leading to irreversible synaptic reorganization of neural circuits. This

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in turn results in the decrease in ability of the deprived eye to elicit cortical neuronal responses and in the increase in number of neurons responsive to the open eye. This phenomenon is known as the ocular dominance plasticity, first described in kittens by Nobel award winners Hubel and Wiesel (Hubel and Wiesel 1959, 1962). Aside from MD, there exists CPs and plasticity for orientation and direction selectivity (Wang et al. 2010). The closure for the CP of direction selectivity occurs prior to ocular dominance plasticity; however, it is unclear if vision plays an essential role to maintain the orientation selectivity (Butz et al. 2009). Pharmacological studies have shown that manipulating the inhibitory–excitatory circuitry can either modify or eliminate directional and orientation selectivity in primary visual cortices of cats (Sillito 1979; Sillito et al. 1980; Eysel and Shevlev 1994; Monier et al. 2003). The visual cortical circuits exhibit maximal plasticity in young animals during CP and this is lost after this unique period as prolonged visual deprivation in adults does not cause changes in visual cortical responses (Hensch and Fagiolini 2004). Furthermore, the young animals that underwent MD lost visual acuity in the deprived eye permanently, despite exposure of the closed eye to subsequent visual experience (Berardi et al. 2000).

Different brain regions, such as the somatosensory cortex and the auditory cortex, have also been used to study other forms of experience-dependent plasticity exhibiting a critical period. In the somatosensory cortex, CPs for somatosensory mapping occur at different time points for different layers. Moreover, plasticity can be defined as structural plasticity and functional plasticity but is often used interchangeably in papers as they are more than often coupled. Structural plasticity refers to anatomical changes in connectivity between neurons, that is, synaptic rewiring, whereby new synaptic connections are formed and/or number of neurons or synapses are altered. However, functional plasticity refers to the strength of a single synapse that is either strengthened by long-term potentiation or weakened by long-term depression thus affecting the function of the existing neurons (Butz et al. 2009). In some conditions, they may have varying CPs but the question remains as to what common factors determine the timing of CP across different brain regions.

One of these factors implicated in the onset of CP plasticity appears to be the development of inhibitory circuits (Fagiolini and Hensch 2000; Hensch and Fagiolini 2004; Huang et al. 2007). Inhibitory interneurons make up ~ 20% of cortical neurons and they secrete the neurotransmitter gamma-aminobutyric acid (GABA) (Markram et al. 2004). They serve to regulate neuronal excitability (Swadlow 2003), integration (Pouille and Scanziani 2001), generate temporal synchrony, and oscillation among a network of excitatory neurons (Somogyi and Klausberger 2005). Even during development, these interneurons regulate cell migration via GABA (Luhmann et al. 2015), differentiation of neurons, and experience-dependent refinement of neuronal connections (Ben-Ari 2002a; Hensch and Fagiolini 2004). Although the GABAergic inhibitory interneurons are made of multiple varied populations, three primary populations: the Ca	extsuperscript{2+}-binding protein parvalbumin (PV), neuropeptide somatostatin, and the ionotropic serotonin receptor 5HT3a (5HT3aR)-expressing interneurons have been shown to account for almost 100% of GABAergic interneurons in the neocortex (Rudy et al. 2011). PV-expressing interneurons make up 40% of the inhibitory interneuron population, with somatostatin and 5HT3aR-expressing interneurons each making up 30% of the population (Rudy et al. 2011). Several studies have pointed to PV-expressing interneurons as the ones involved in critical period plasticity regulation. The expression of PV in interneurons and critical period onset coincide (Del Rio et al. 1994); furthermore, both are accelerated by BDNF over-expression (Huang et al. 1999). Deletion of a potassium current (Kv3.1) that specifically regulates the fast-spiking behavior of PV-expressing interneurons slows the rate of ocular dominance plasticity (Hensch 2005b).

The focus of this paper is on the molecular mechanisms regulating post-natal GABAergic circuit development and CP, all the way from protein signaling in the synapse, gene transcription, and epigenetic regulation of gene expression in the nucleus. Expression of genes such as Bdnf, Otx (Sugiyama et al. 2008), and Npas4 (Bloodgood et al. 2013) are crucial for regulating critical period plasticity by regulating and maintaining maturation of inhibitory circuits and the timed expression of these genes are in turn regulated by epigenetic marks rearranging chromosomal DNA for transcription.

**Molecular mechanisms regulating GABAergic development**

**Signaling molecules**

**BDNF**

Brain-derived neurotrophic factor (BDNF) is a growth factor required for the formation of GABAergic synapses in hippocampal and cortical cultures (Rutherford et al. 1997; Vicario-Abejon et al. 1998). To investigate if BDNF also has the same function in vivo, over-expression of BDNF in the visual cortex resulted in accelerated development of GABAergic circuits and inhibition which is correlated with a premature onset and closure of the ocular dominance plasticity (Huang et al. 1999)(Hanover et al. 1999). Furthermore, dark-reared mice treated with BDNF injections to the retina showed normal expression of GABA and GAD65 unlike untreated dark-reared mice that exhibited reduced GABA and GAD65 expression (Lee et al. 2006).

Interestingly, brain slices treated with mature BDNF protein, but not precursor of BDNF (proBDNF) exhibited decreased inhibition (Fierking et al. 1998; Holm et al.
As the *Bdnf* gene can be transcribed via multiple promoters (I–VIII) to produce transcripts with unique 5′ exon (exons I–VIII) that are spliced on to the common 3′ coding exon (exon IX), 9 types of *Bdnf* mRNA transcripts are found in rodents (Aid et al. 2007) and 17 in humans (Prunusild et al. 2007). As unique *Bdnf* mRNAs are expressed during developmental time points and are regulated by different factors, it appears that some transcripts are expressed at basal levels required for neuronal survival and differentiation, while others exhibit experience-dependent *Bdnf* expression responsible for experience-dependent circuit maturation and plasticity (Hong et al. 2008; Sakata et al. 2009). To investigate the role of activity-dependent *Bdnf* expression mediated at promoter IV specifically, Hong et al. generated a mouse line that carried a mutation of the CaRE3/CRE(cAMP/Ca++-response element-like element) in the endogenous promoter IV blocking the its activity-dependent expression. These mice have decreased spontaneous inhibitory postsynaptic currents (sIPSCs) in cortical culture and lesser GABAergic synapses in the cortex (Hong et al. 2008). Another study by Sakata et al. disrupted the promoter IV mediated *Bdnf* transcription by inserting a green flourescent protein-stop cassette after exon IV. The resulting mice had fewer PV-expressing, fast-spiking GABAergic interneurons in the prefrontal cortex, reduced frequency and amplitude of sIPSCs in cortical culture (Sakata et al. 2009). However, the disruption of experience-dependent *Bdnf* transcription from promoter IV in both studies did not affect the structure and function of cortical glutamatergic synapses. These studies show that activity-dependent *Bdnf* transcription is crucial for the development of inhibitory circuits in the cortex.

In order to understand how experience-dependent *Bdnf* expression regulates development of inhibitory circuits, immunohistochemical studies suggest that BDNF produced in cortical neurons act as an intercellular signaling molecule. BDNF communicates pyramidal neuron activity to GABAergic interneurons which express TrkB receptors specific for BDNF (Cellerino et al. 1996; Singh et al. 1997; Holm et al. 2009). To study the effect of BDNF signaling on the GABAergic circuitry, mutant mice that have a specific deletion of TrkB receptor in parvalbumin-expressing, fast-spiking GABAergic (PV+) interneurons were used. These mutant mice exhibited decreased amplitude of glutamatergic inputs to PV+ interneurons and frequency of PV+ interneuron inputs to excitatory pyramidal neurons were also reduced and decreased rhythmic network activity in the gamma frequency band (Zheng et al. 2011). Furthermore, treatment with TrkB inhibitor K252-a showed that the regulation of GABAergic activity was mediated by BDNF signaling via the TrkB receptor (Holm et al. 2009).

**GABA**

Unsurprisingly, another signaling molecule that up-regulates GABAergic synapse maturation is GABA. During early development, GABA is excitatory because of high concentration of intracellular chloride ions. It later transits to become inhibitory via the delayed expression of a specific K+-Cl−-coupled co-transporter whose expression leads to a negative shift in the reversal potential for chloride ions (Ben-Ari 2002b). As the GABAergic and glutamatergic synapses are formed sequentially, inhibition eventually becomes necessary for normal function. During this time, intracellular chloride ions are expelled in an activity-dependent manner and GABA starts to function as an inhibitory neurotransmitter rather than being excitatory (Ben-Ari et al. 1989; Wang and Kriegstein 2009).

GABA is synthesized by two forms of glutamic acid deoxycarboxylase – GAD65 and GAD67, the deletion of either gene reduces GABA levels (Asada et al. 1997; Hensch et al. 1998). GAD67 is primarily expressed early in development, in the cell body and nerve terminals contributing to ~ 90% of GABA synthesis, whereas the remaining ~10% is synthesized by GAD65 that is expressed later in development and localized to pre-synaptic terminals (Pinal and Tobin 1998). Previous studies have shown that knockdown of GAD67 in mice resulted in aberrant perisomatic synapse maturation (Chattopadhyaya et al. 2007), whereas knockdown of GAD65 results in deficiency for maintaining stable perisomatic synapses (Hensch et al. 1998). These results lead the authors to conclude that GABA is required for inhibitory synapse formation. However, in a more recent study, Wu et al. demonstrated that knocking out genes encoding for GAD67, GAD65 and vesicular GABA transporter specifically in single basket interneurons, lead to increased bouton and axon density with normal synapse structures when compared to the wildtype interneurons (Wu et al. 2012). This study suggests that instead of forming inhibitory synapses, GABA acts to eliminate subsets of synapses in an activity-dependent manner, while promoting the maturation of other synapses. As GAD67, GAD65 expression is activity-dependent (Patz et al. 2003), GABA functions as an experience-dependent regulator of inhibitory synapses.

Not only is GABA required for the development of GABAergic synapses, the receptors controlling GABA signaling are also important for synapse development and interneuron axon arborization. GABA signaling is largely mediated by ionotropic GABA<sub>A</sub> receptors, and to a smaller extent by metabotropic GABA<sub>B</sub> receptors activated by endogenous release of GABA (McLean et al. 1996). Recent studies have shown that GABA<sub>A</sub> receptors display an excitatory signaling mechanism in Down syndrome and its reversal restores synaptic plasticity in mice (Deidda et al. 2015). Also, treatment with GABA<sub>A</sub> or GABA<sub>B</sub> receptor agonists, resulted in recovery of perisomatic synapses in GAD67<sup>−/−</sup> mice (Chattopadhyaya et al. 2007). These results suggest the significance of GABA receptors in synapse development. As these receptors are present on post-synaptic neurons, GABA axon terminals and surrounding glial...
processes, cell-autonomous activation of pre-synaptic GABA<sub>a</sub> receptors (modulating Ca<sup>2+</sup> channels and GABA release) influences growth cone motility and bouton stability. Furthermore, GABA signaling through post-synaptic or glia receptors could trigger retrograde factors, promoting axon branching and synapse formation. Fiorentino et al., demonstrated that one of the possible mechanisms utilized by GABA to regulate synapse formation is via the metabotropic GABA<sub>b</sub> receptors on pyramidal neurons that trigger secretion of BDNF and promotes the development of perisomatic GABAergic synapses in hippocampal neurons (Fiorentino et al. 2009). In addition, GABA<sub>a</sub> receptors appear to be negatively regulated by the precursor of BDNF (proBDNF) – p75 signaling pathway. The presence of proBDNF results in degradation of GABA<sub>a</sub> receptors and repression of its synthesis resulting in decreased inhibitory transmission. The cleavage of proBDNF to mature BDNF is mediated by tissue-type plasminogen activator and the expression of tissue-type plasminogen activator is found to be implicated in experience-dependent plasticity in the visual system (Mataga et al. 2004). Insofar, these studies suggest that there is a positive interplay between experience-dependent activity, BDNF, and GABA signaling for the maturation of GABAergic synapses.

Aside from receptors, GABA transporters regulate signaling between synapses. GABA released by pre-synaptic terminals is not enzymatically broken down and instead, its clearance depends completely on diffusion and its uptake by specific transporters, which therefore regulates the activation of GABA receptors (Scimemi 2014). In mice, there exist four pharmacologically distinct GABA transporters (GAT1 – GAT4), of which GAT1 and GAT4 are brain specific. Early studies show that GAT1 and GAT4 expression correlates with the z1 subunit of GABA receptors (Jursky and Nelson 1996), which is found to drive cortical plasticity (Fagioli et al. 2004). In rats, GAT 1 and GAT3 display post-natal changes that reflect the maturation of GABAergic inhibition (Vitellaro-Zuccarello et al. 2003). These observations together suggest that the transporters may have an implication of the maturation of GABAergic innervation and synaptic plasticity; however, much research has not been conducted to further elucidate its association.

**Endocannabinoid signaling**

Endocannabinoids are produced and released post-synaptically and act as retrograde negative regulators of pre-synaptic neurotransmitter release (Chevaleyre et al. 2006; Lovoinger 2008; Kano et al. 2009). They bind to cannabinoid receptors (CB1R) pre-synaptically and mediate long-term depression of inhibitory transmission (iLTD) underlying the decrease in release probability at inhibitory synapses of fast-spiking PV+ interneurons during development in the visual cortex (Jiang et al. 2010a). iLTD was found to be induced only during experience-dependent critical period of the layer II/III visual cortex. When antagonists against CB1R were applied or CB1RKO mice were used, absence of endocannabinoid-induced iLTD prevented the characteristic decrease in release probability, short-term depression, and response variability in mature cortical GABAergic inhibition (Jiang et al. 2010a).

In a follow up study, the authors found that there exists a laminar difference in sensitivity to endocannabinoids in the visual cortex (Jiang et al. 2010b; Sun et al. 2015). They showed that GABAergic synapses in layer II/III and layer V were more sensitive to the CB1R agonist showing precocious maturation and this was not observed in transgenic CB1R knockout mice, demonstrating that endocannabinoid signaling is responsible for iLTD. However, in layer IV, administration of CB1R agonist at any age did not result in precocious maturation. This suggests that although endocannabinoids do not play a role in maturation of GABAergic inhibition in layer IV of the visual cortex, they may be partly responsible for maturation of GABAergic inhibition in layer II/III and V. These findings also provide an explanation for the differences in timing in maturation of GABAergic inhibitory circuits between layer IV and layers II/III and V (Jiang et al. 2010b; Sun et al. 2015).

Recent studies have shown that BDNF can induce endocannabinoid release and there exist cross-talk between BDNF and endocannabinoid signaling. Evidence of interaction between endocannabinoids and BDNF interaction are found in the visual cortex (Huang et al. 2008), hippocampus (Khaspekov et al. 2004), and cerebellum (Maison et al. 2009). In addition, studies have also shown that TrkB receptors and CB1R are strongly colocalized throughout the forebrain, layer II/III and V of the cortex (Cabelli et al. 1996; Fryer et al. 1996; Miller and Pitts 2000), with the highest levels of CB1R found in layer II/III (Matsuda et al. 1993; Tsou et al. 1998; Marsicano and Lutz 1999; Egertová et al. 2003). Endocannabinoid synthesis and release was found to be mobilized by BDNF-TrkB signaling, acute application of BDNF in the cortex suppressed pre-synaptic GABA release, causing decreased GABAergic transmission. This decrease in GABA release was because of retrograde signaling of endocannabinoids from the post-synaptic pyramidal neuron (Fig. 1) (Lemtri-Chlieh and Levine 2010). The production of endocannabinoid synthesis is independent of mGluR and is initiated by post-synaptic TrkB signaling followed by downstream Phospholipase C (PLC) signaling (Zhao and Levine 2014). Endogenous BDNF-TrkB signaling is required for inducing endocannabinoid-mediated iLTD that occurs during the critical period for the maturation of GABAergic inhibition. Blockade of both the TrkB receptors and the activation of diacylglycerol lipase (DAG-lipase, DGL) abolished iLTD at layer II/III cortical inhibitory synapses suggesting that the endocannabinoid 2-arachidonoylglycerol (2-AG) is involved in the signaling pathway (Zhao et al. 2015). However, sufficient evidence is not available to completely rule out the involvement of other endocannabinoids such as anandamide.
**The extracellular matrix (ECM): holding it all together**

The extracellular matrix makes up a huge portion of the brain volume (Ruoslahti 1996). The extracellular matrix (ECM) not only provides physical support for the cells in the nervous system, they are also hypothesized to play crucial roles in neurotransmission of signals. A remarkable feature of the brain is its capacity to remodel itself to changing neuronal activity. As a result, remodeling or pruning occurs at the level of synapses. A major role of these ECM is to modulate plasticity by rapid reorganization of synaptic connections during the critical period of development. Such is the importance of the ECMs that artificial removal by pharmacological intervention leads to reactivation of neural plasticity. Here, we describe two groups of molecules that interact with the extracellular environment to regulate synaptic remodeling.

**Polysialic acid (PSA) – NCAM**

Neural cell adhesion molecule (NCAM) is a key player in cell–cell adhesion of neuronal circuits (Rutishauser 2008). In the mammalian brain, NCAM is a unique substrate for poly-sialytransferases (PST). PST attaches polymers of α-2,8-linked sialic acid onto NCAMs, causing the NCAMs to lose its adhesive properties (Cunningham et al. 1983; Sadoul et al. 1983). Addition of polysialic acid (PSA) onto NCAMs has been implicated in many neuronal processes, such as migration (Ono et al. 1994), axon guidance (Tang et al. 1992; Seki and Rutishauser 1998; El Maarouf and Rutishauser 2003), and synaptogenesis (Dityatev et al. 2004). It is hypothesized that PSA acts as a switch, functionally switching NCAM between a cell adhesion molecule and a signaling molecule. In early development, PSA binds to NCAMs, permitting cell migration to happen. This is followed by the development of neurite processes and even synaptogenesis. Once these developmental processes are completed, there is an accompanying reduction in expression of PSA. As a signaling molecule, NCAMs are known to interact with a host of signaling molecules, which include Fibroblast growth factor (FGF) receptors (Doherty and Walsh 1996; Rønn et al. 1999), Glial cell line-derived neurotrophic factor (GDNF) (Paratcha et al. 2003), and neurotrophin receptors such as BDNF (Muller et al. 2000).

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**Fig. 1** Endocannabinoid-mediated long-term depression of inhibitory transmission (iLTD) in GABAergic pre-synaptic terminal induced by endogenous brain-derived neurotrophic factor (BDNF)-TrkB signaling during the critical period. Retrograde signaling of endocannabinoids from post-synaptic pyramidal compartments negatively regulates GABA release from the pre-synaptic membrane and subsequently causes maturation of the inhibitory circuitry through long-term depression of inhibitory transmission (iLTD). An acute increase in endogenous BDNF decreases GABA release and promotes iLTD. Phospholipase C (PLC)-diacylglycerol lipase (DGL) pathway generates the CB1R agonist 2-arachidonoylglycerol (2-AG). First, the precursor of 2-AG, diacylglycerol (DAG) is generated by membrane-associated PLC that cleaves the phosphate group from the membrane phospholipid precursors when in contact. DAG is then hydrolyzed by DGL to form 2-AG which is released from the post-synaptic compartment for retrograde signaling in the pre-synaptic terminal. The exact mechanism for its release is still unclear. The endocannabinoids then bind to CB1R and sends feedback to decrease the secretion of GABA neurotransmitters.
Mouse models of NCAMs or PSTs deletion have been shown to cause deficits in synaptic plasticity and cognitive function. This makes PSA-NCAMs an attractive candidate in the study of synaptic plasticity. In a study published by Di Cristo et al., the authors discovered that PSA is down-regulated after visual experience but dark-rearing attenuates this down-regulation. Moreover, enzymatic removal of PSA causes early onset of critical period in the visual cortex by enhancing inhibitory synaptic transmission. This inverse relationship of PSA expression and timing of maturation of GABAergic innervation (Di Cristo et al. 2007) makes PSA a key player in functional and structural development of GABAergic inhibitory circuits.

Perineuronal nets (PNN)
As described previously, inhibitory circuit maturation is pivotal for critical period plasticity. Studies have shown, in both visual and somatosensory modalities, that a special kind of ECM known as perineuronal nets (PNN) form around inhibitory neurons, specifically PV+ neurons (Brückner et al. 1993; Härtig et al. 1994). Perineuronal nets are extracellular structures made of many glycoprotein components, namely chondroitin sulfate proteoglycans, hyaluron, and tenascins (TnR and TnC) (Köppe et al. 1997; Carulli et al. 2006; Deepa et al. 2006). PNNs form around the soma and proximal dendrites of PV interneurons and they influence the synapse development. This is functionally important as the PNNs consolidate the connections established during development and prevents any changes to the synapses. Studies have shown that components of the PNNs have activity-dependent expression (Sur et al. 1988; Lander et al. 1997; Kind et al. 2013; Ye and Miao 2013), suggesting the important role that they play in maintaining synapses and neurotransmission. Interestingly, the expression of PNNs is concomitant to a decrease in plasticity, suggesting that PNNs consolidate the matured state of synaptic connections (Hensch 2003) by acting as a structural brake. Not surprisingly, if one were to reduce or remove activity by deprivation paradigms, such as dark-rearing (Hockfield et al. 1990) or monocular deprivation (Sur et al. 1988; Pizzorusso et al. 2002, 2006) and whisker trimming (McRae et al. 2007; Nakamura et al. 2009; Nowicka et al. 2009), PNN expression will be reduced and plasticity is maintained. This is supported by evidence that removal of PNNs recovers ocular dominance plasticity in the visual system (Pizzorusso et al. 2002) of adult rats.

Besides acting as a structural brake, PNNs also have a role in providing a microenvironment for molecular cues such as Semaphorin 3A (Vo et al. 2013) and orthodenticle homeobox 2 (Otx2) (Sugiyama et al. 2008; Beurdeley et al. 2012). Otx2 will be discussed further in the section below.

Taken together, the ECM provides permissive cues for plasticity in the brain by physical methods and also provides the platform for instructive cues such as transcription factors to act on the cell.

Transcription factors

Orthodenticle homeobox 2 (Otx2)
Otx2 is a transcription factor whose expression is selectively in the retina and then when triggered by visual experience is transferred from cell to cell until it reaches the PV interneurons and is accumulated (Sugiyama et al. 2008). When the visual cortex was infused with Otx2, PV interneuron maturation and critical period closure were both accelerated. However, conditional removal of Otx2 from the visual pathway resulted in the loss of critical period plasticity (Sugiyama et al. 2008). This suggests that Otx2 is also required for opening the critical period.

Otx2 bind to the aforementioned PNNs wrapped around the surface of the PV interneurons. These PNNs constitutively capture Otx2, enabling the accumulation of Otx2 in PV interneurons. The action of PNNs was demonstrated by hydrolysis of PNNs by chondroitinase ABC and via blockade of the binding motif of Otx2 to PNNs. Preventing Otx2 from binding to PNNs resulted in the reactivation of critical period plasticity in adult mice (Fig. 2). Hence, constant accumulation of Otx2 is required to maintain the closure of the critical period (Beurdeley et al. 2012).

NPAS4
NPAS4 is a transcription factor whose expression is activated by excitatory synaptic activity. Subsequently, it triggers downstream gene expression for the formation and maintenance of inhibitory synapses on excitatory neurons and regulates experience-dependent GABAergic synapse development (Lin et al. 2008). The expression of NPAS4 parallels that of visual cortical plasticity and over-expression of NPAS4 reactivated critical period plasticity in adult mice (Fig. 2). However, when NPAS4 was knocked down in combination with fluoxetine, the reactivation of plasticity in adulthood initially caused by fluoxetine, was prevented. The results suggest that NPAS4 regulates downstream expression of synaptic plasticity genes essential for reactivation (Maya-Vetencourt et al. 2012).

Clock
Clock is a transcription factor known to regulate circadian rhythms that regulate many physiological processes (Lowrey and Takahashi 2011). A recent study has shown that it is also implicated in timing the maturation of PV interneurons (Kobayashi et al. 2015). In Clock knockout mice, not only was circadian gene expression decreased but the maturation of PV interneurons was also delayed. These transgenic mice additionally exhibited late onset and extended critical period plasticity. To study if Clock directly regulates PV interneurons, specific deletion of Clock in PV neurons only displayed the same outcome as Clock knockout mice resulting in the late onset of critical period (Fig. 2) (Kobayashi et al. 2015). Collectively, these results show that Clock impacts PV interneurons directly and affect their maturation.
Epigenetics: more than ATGC
There is a dynamic interplay between genes and experience, nature versus nurture, a clearly delineated and biochemically driven mechanistic interface known as epigenetics.

Epigenetics allows post-mitotic, non-dividing neurons to dynamically regulate chromatin state. The state of chromatin packing determines how accessible gene regulatory elements are and how they can be regulated in response to

Fig. 2 Factors affecting the onset and reactivation of experience-dependent critical period plasticity. (a) Early manipulations in pre-critical period can allow for the precocious onset of plasticity primarily by hastening the maturation of the GABAergic circuitry. Blue dotted lines indicate the shift in the onset, peak, and closure of critical period to an earlier timing. An increase in either brain-derived neurotrophic factor (BDNF), endocannabinoids, perineuronal nets (PNN) formation, or orthodenticle homeobox 2 (Otx2), or a decrease in polysialic acid (PSA)-neural cell adhesion molecule (NCAM) interaction leads to an increase in inhibition in neuronal circuitry which in turn has shown to trigger the early onset of critical period plasticity. (b) Behavioral and genetic interventions such as dark-rearing (specifically for visual plasticity) and Clock removal during pre-critical period have been implicated in delaying the onset of critical period to a later age as shown by the red dotted lines. (c) Interventions for reactivation of plasticity in adulthood post-critical period during which neuronal circuitry has already been consolidated. Counteracting particular brakes on plasticity through pharmacological approaches (HDAC inhibitors, chondroitinase ABC for PNN breakdown) or genetic approaches (Otx removal, NPAS4 overexpression) has shown to reactivate plasticity as represented by the green dotted lines.

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environmental cues. Besides rapid and dynamic control over gene regulation, it is becoming clearer that epigenetics allows multiple permutations of ‘genetic codes’ without drastically increasing the actual amount of genomic material in each cell. This is supported by the fact that the human genome is no larger than the genome of lesser evolved organisms (Lander et al. 2001; Venter et al. 2001). This ‘epigenome’ alters regulation of genetic material, is reversible, and does not alter the primary DNA sequence. Some examples of common epigenetic marks are DNA cytosine methylation, histone acetylation/deacetylation, protein methylation, and phosphorylation.

In fact, the ENCODE project (Bernstein et al. 2012; Consortium RE, Kundaje A, Meuleman W, et al., 2015) was launched to study the epigenomes of human brain tissues and to uncover the role of ‘neuroepigenetics’ in regulation of neuronal function. As such it is not surprising that the maturation of GABAergic interneurons are dependent on timed expression of various genes. Epigenetic regulators such as DNA methylation, hydroxymethylation, post-translational histone modifications, histone variants, and spatial arrangement of highly condensed DNA play an important role in regulating downstream signaling for the development of GABAergic circuits during the critical period and its maintenance. Here, we describe two interesting and emerging types of epigenetic marks that studies have shown may play important roles in PV+ inhibitory interneuron function.

**HDAC inhibitors**

Many studies on epigenetic mechanisms regulating critical period plasticity are done in the visual cortex. Perhaps, the most well-studied epigenetic mark for critical period regulation is histone acetylation. Histone acetylation levels are kept in equilibrium by histone acetyltransferases and deacetylases (HDACs) that have opposing actions. An experience-dependent epigenetic mark, acetylated histone, is abundant at loose chromatin sites of active gene transcription and these marks also exhibit a correlative decrease as critical period plasticity ends (Putignano et al. 2007). Administration of HDAC inhibitors reactivates critical period plasticity in the visual cortex (Putignano et al. 2007; Vetencourt et al. 2011) and also recovers binocular vision in amblyopic adult mice (Silingardi et al. 2010). Furthermore, the reactivation of critical period plasticity was also accompanied by a decrease in GABAAergic transmission and also increased histone acetylation (H3K9) at Bdnf promoter I (Vetencourt et al. 2011). The reactivation of critical period plasticity in these studies was correlated with increased histone acetylation after treatment with HDAC inhibitors. In another study, it was also found that there is a relationship between extinction of conditioned fear, histone modification by HDAC inhibitors, specifically valproic acid, and regulation of BDNF gene expression (Bredy et al. 2007). Because of the unspecific effects of HDAC inhibitors, it is unclear if the reactivation of plasticity and long-term extinction of fear is a result of increased histone acetylation or as a result of other molecular mechanisms. To investigate if increase in histone acetylation levels is directly responsible for the reactivation of critical period plasticity, transgenic mice with specific HDAC knockout can be used.

**HDAC1**

The effect of HDAC1 on inhibitory circuitry maturation was quite recently explored in the somatosensory cortex of mice. A decrease in experience-dependent activation of S1 revealed a negative regulation of Bdnf and Parvalbumin (Pvalb) genes by HDAC1. Whisker-deprived animals showed an increase in HDAC1 expression and activity with a corresponding decrease in inhibitory synapses of PV interneurons. Chromatin Immunoprecipitation analysis revealed direct associations between HDAC1 and promoter regions of Bdnf and Pvalb which were down-regulated because of the increased histone deacetylation (Fig. 3). A temporal knockdown of HDAC1 recovers Bdnf and Pvalb expression levels in
whisker-deprived animals and also prevented the decrease in inhibitory synapses. These results collectively demonstrate that HDAC1 plays a role in the development of PV interneurons both through Bdnf expression as well as epigenetic regulation of specific genes (Koh and Sng 2016).

HDAC2

HDAC2 has previously been shown to regulate synaptic plasticity and formation of memories in hippocampal excitatory neurons; HDAC2 knockout mice have increased synaptic connections and facilitated memory formation (Guan et al. 2009). To find out if the maturation of PV+ interneurons (necessary for the closure of critical period plasticity) is dependent on epigenetic regulation, Nott et al. deleted HDAC2 specifically in PV+ interneurons (Nott et al. 2015). They found that inhibition was reduced and iLTD that typically occurs during the critical period was present in adult mice. These results suggest that HDAC2 is required for the maturation of PV inhibitory interneurons and the closure of the critical period (Nott et al. 2015).

Protein methylation

Protein methylation, specifically, protein arginine methyla-
tion has been implicated in transcriptional regulation, mRNA processing, nuclear-cytoplasmic shuttling, DNA repair, and signal transduction. An important family of enzymes, the protein arginine methyltransferases (PRMT), has been associated with many cellular processes, mainly in cell cycle progression. PRMTs can catalyze the formation of mono- or di-methylated arginine residues. Depending on the type of arginine dimethylation, PRMTs can be classified as a Type I or Type II enzyme (Bedford and Clarke 2009; Wolf 2009). As a consequence of modification to histones, which alters biochemical properties of nucleosomes, chromatin structure and gene regulation is altered.

PRMTs are strongly implicated in stem cell and cancer biology. Also, many groups are beginning to look to PRMTs as potential therapeutic targets (Cha and Jho 2012), such is the importance of PRMTs as a regulatory element. However, the role of PRMTs has not been elicited in neuronal processes such as synaptic plasticity. Of particular interest might be PRMT8, which is specifically located within the central nervous system (Taneda et al. 2007; Kousaka et al. 2009).

PRMT8S

Because of its unique tissue localization, PRMT8 is suspected to play an important role in neurodevelopment and synaptogenesis. There are evidence to suggest that it

Fig. 4 Methylation of arginine residues on histones by protein arginine methyltransferases (PRMT)8. (a) Methylation by PRMTs can either lead to transcriptional activation or transcriptional repression. In the case of the structural protein Tenascin-R (TNR), methylation by PRMT8 suppresses its expression. TNR proteins are crucial in extracellular complexes organization for the formation of perineuronal nets (PNN). PNNs wrap around parvalbumin (PV) interneurons and consolidate neuronal circuitry acting as a structural break for critical period plasticity. (b) PRMT knockouts lack this suppression of the Tnr gene resulting in the increase in TNR protein synthesis. This in effect hastens PNN formation in mice visual cortex resorting to the premature closure of critical period.

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plays a role in early neuronal development (Lin et al. 2013). A recent study has shown that PRMT8 is an epigenetic regulator of specific structural proteins, such as Tenascin-R, that are involved in the formation of perineuronal nets (PNNs). Development of PNNs, as mentioned earlier, closes the critical period plasticity via consolidation of the inhibitory neuronal connections. In Prmt8 knockout mice, Tnr transcription levels were heightened by 1.5-fold resulting in the increased PNN formation (Fig. 4). Also, there was a 10% increase in wrapping of PV interneurons in PNNs, thus affecting dendritic morphology of the interneurons in knockouts compared to wildtype. Lee et al. moreover, showed that the visual acuity of Prmt8 knockout mice were lower than wildtype mice suggesting a premature closure of critical period because of the hastened PNNs formation. These findings suggest that PRMT8 methylation activity is critical for the complete maturation of inhibitory circuitry by regulating the formation of PNNs that essentially act as structural brakes to critical period plasticity (Lee et al. 2017).

Concluding remarks

With more models to study critical period plasticity emerging in different modalities, GABAergic PV expression has been shown to be a key regulator of critical period plasticity. However, experiences can regulate the maturation of PV+ interneurons via different pathways and studying these processes in different modalities may help us to better understand the differences in regulation between modalities. Further work has to be done to find out if similar pathways of regulation are common in different regions of the brain. Neuroepigenetics is an emerging field crucial for the downstream regulation of gene expression required for PV+ interneuron maturation and can perhaps be used as targets of pharmaceutical intervention as lines of evidence show that using HDAC inhibitors have reactivated critical period plasticity in the visual cortex (Putignano et al. 2007; Vetencourt et al. 2011) and improved absolute pitch perception in human subjects (Gervain et al. 2013). In all, increasing our understanding of such molecular mechanisms regulating developmental plasticity in the brain will enable us to design better pharmaceuticals with lesser side effects aimed to reactivate neural wiring after injury and develop targeted pharmaceuticals to correct alterations in the brain of children suffering from neurodevelopmental disorders caused by imbalance of excitatory-inhibitory transmission.

Acknowledgments and conflict of interest disclosure

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