CRITICAL PERIOD PLASTICITY IN LOCAL CORTICAL CIRCUITS

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Abstract | Neuronal circuits in the brain are shaped by experience during 'critical periods' in early postnatal life. In the primary visual cortex, this activity-dependent development is triggered by the functional maturation of local inhibitory connections and driven by a specific, late-developing subset of interneurons. Ultimately, the structural consolidation of competing sensory inputs is mediated by a proteolytic reorganization of the extracellular matrix that occurs only during the critical period. The reactivation of this process, and subsequent recovery of function in conditions such as amblyopia, can now be studied with realistic circuit models that might generalize across systems.

CRITICAL PERIOD
A strict time window during which experience provides information that is essential for normal development and permanently alters performance.

SENSITIVE PERIOD
A limited time during development, during which the effect of experience on brain function is particularly strong.

AMBLYOPIA
Poor vision through an eye that is otherwise physically healthy due to little or no transmission of the visual image to the brain through circuits that are hard-wired during a developmental critical period. It affects 2–5% of the population.

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doi:10.1038/nrn1787

From polyglots[1] to virtuosi[2,3], human performance reflects the neural circuits that are laid down by early experience. Although learning is possible throughout life, there is no doubt that those who start younger fare better, and that plasticity is enhanced during specific windows of opportunity. An understanding of the neural basis of such CRITICAL or SENSITIVE PERIODS of brain development would inform not only classroom and educational policy, but also drug design, clinical therapy and strategies for improved learning into adulthood. Although which might be the critical periods for higher cognitive functions such as language, music or emotional control is the subject of popular debate, such sweeping questions fail to acknowledge the sequential nature of a multistage process that involves many brain regions. Evidence about the acquisition of these rich human behaviours is largely anecdotal, as the complex environments of everyday life are inherently difficult to quantify and normalize across individuals.

Clear evidence for critical periods has instead been found in the primary sensory systems of several species[4]. Animal models are now revealing, with greater resolution, the molecular, cellular and structural events that underlie experience-dependent circuit refinement. In this review, I focus on the primary visual cortex, which has been the premier model of critical period plasticity for 40 years[5]. During a brief postnatal period (of weeks to years, in proportion to the expected lifespan of the species[6,7]), the closure of one eye (but not both) causes a permanent loss of visual acuity through that eye. AMBLYOPIA occurs despite there being no damage to the retina or its target, the visual thalamus (dorsal lateral geniculate nucleus, dLGN) and is determined in the neocortex (in the visual primary cortex, V1), where the inputs from the two eyes first converge and compete for space[5,6]. Most impressively, the seemingly innocuous act of covering an eye can profoundly alter the physical structure of the brain during the critical period only.

Shaping column size during the critical period

The cortical column is a fundamental unit of organization of the mammalian neocortex. Clusters of thalamocortical axon terminals that serve either the right or left eye tesselate layer 4 of the mature cortex to produce alternating OCULAR DOMINANCE domains[8,9]. Occluding one eye during development yields an expansion of the columns serving the open eye at the expense of those responding to the deprived eye, which become reduced in size and afferent complexity[10,11]. This physical manifestation of early postnatal experience occurs gradually, and is preceded by more rapid changes[12,13] of intracortical circuits outside layer 4, which instruct the hard-wiring of an anatomical fingerprint that is unique to the individual. By extension, the segregation of columns by normal vision during the critical period has

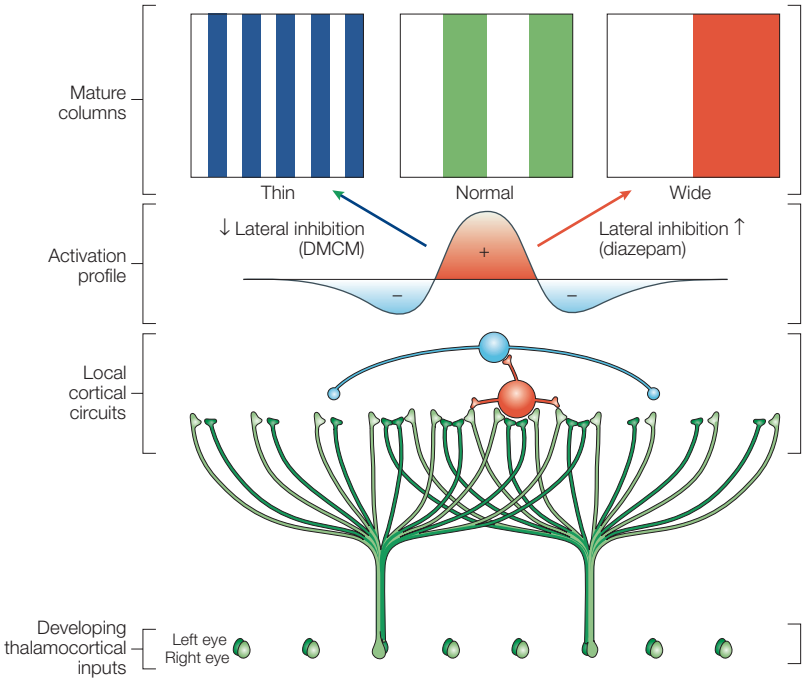


Figure 1 | **Local circuit control of developing columnar architecture in the neocortex.** Activity-dependent models of segregation predict that cortical GABA (γ-aminobutyric acid) circuits are involved in determining the final column spacing from an initially overlapping mosaic[17,18]. Neuronal activity from thalamic inputs serving the right or left eye is spread within the nearby cortex by local excitatory connections (red cell) but is inhibited at greater distances (blue cell), producing a 'mexican hat' activation profile. When this profile is modulated during development by preferentially enhancing or reducing horizontal, long-range inhibition (arrows), columns emerge that are wider or thinner than normal, respectively. This hypothesis was verified *in vivo* in kittens by modulating $GABA_A$ (GABA type A) currents[20] with benzodiazepine agonists (diazepam) or inverse agonists (methyl-6,7-dimethoxy-4-ethyl-β-carboline, DMCM) throughout the critical period[19].

been thought to result from similar activity-dependent rules acting on an initially overlapping continuum of THALAMOCORTICAL AFFERENTS.

This dogma has recently been challenged by the finding that axon terminals of thalamocortical afferents might, in part, be clustered well before the critical period[14]. There is also some evidence that siblings show substantial similarity of visual maps, which supports the idea that molecular cues establish columnar architecture[15]. Nonetheless, it is agreed that sensory experience is important for individualizing ocular dominance maps during the critical period. Even the focal patterns of deprivation that are produced by shadows of blood vessels in a single eye are embossed onto the primary visual cortex[16]. In computational models of self-organization, the recipient cortical circuits largely determine the final spacing of columns[17,18]. Overlapping inputs segregate into clusters ('neurons that fire together wire together') through a neocortical organization that spreads excitation locally but is limited at a distance by farther-reaching inhibition.

FIGURE 1 shows how a central area of excitation surrounded by a larger concentric area of inhibition (the canonical 'mexican hat' profile) of intracortical activation could, in theory, influence thalamic innervation. In particular, lateral inhibition can establish narrow or wide columns in computer simulations of column formation by adjusting the contrast between inputs at nascent border regions during this 'winner-takes-all' competition[18]. These long-standing theoretical predictions have recently been validated *in vivo* through the direct infusion of BENZODIAZEPINES into the kitten visual cortex during the critical period[19]. Such drugs come in three varieties, including agonists such as diazepam, inverse agonists such as the β-carbolines (for example, methyl-6,7-dimethoxy-4-ethyl-β-carboline DMCM), and antagonists that block the actions of both (flumazenil)[20]. All bind to a particular subset of $GABA_A$ (γ-aminobutyric acid type A) receptor, the agonists enhancing and inverse agonists reducing chloride flux. Increasing inhibition throughout the critical period with benzodiazepine agonists leads to a local 30% increase in column width, whereas inverse agonists produce column shrinkage[19] (FIG. 1).

Interestingly, increased column spacing has also been reported for STRABISMUS through exotropic deviation of the eyes during the critical period[21]. Both enhanced lateral inhibition by direct intracortical infusion of diazepam and decorrelation of visual input by artificial squint are conditions that favour the maximal segregation of ocular dominance. In summary, local imbalances of neuronal activity influence columnar architecture during normal development, and this cannot be explained solely by genetic instruction. The broad range of column sizes observed in nature[22] might reflect individual differences in the span of local circuit inhibition.

Detection by excitatory–inhibitory balance

Long-range, horizontal inhibitory axons therefore provide a scaffold for discriminating competing sensory input (for example, right or left eye) in the developing neocortex. This is in contrast to the maturing neuromuscular junction in the periphery, where individual motor axons may compete directly with each other for synaptic space on the same end plate[23]. This competition is limited by the global resources (for example, neurotransmitter) that are available within individual presynaptic arbors, each of which might contact multiple muscle fibres[24]. In the tangled circuits of the neocortex[25,26], the action of locally balanced excitation and inhibition first integrates and then detects competition.

Even small changes in the relative amounts of excitation and inhibition can markedly alter information processing[27]. This delicate balance is dynamically adjusted by circuitry in the cortical layers[28–30], where inhibitory connections are developed later than excitatory connections in the pre-critical period for ocular dominance[31]. Drastic pharmacological perturbations of neuronal activity, such as hyperexcitation (by, for example, glutamate[32] or bicuculline[33]) or total silencing (by, for instance, TETRODOTOXIN (TTX)[34], 2-amino-5-phosphonovaleric acid (APV)[35] or muscimol[36,37]), not surprisingly disrupt plasticity, but fail to inform us about intrinsic network behaviour involved in this process. Gentle titration of endogenous neurotransmission by gene-targeted disruption in mice has been instrumental in dissecting the physiological role of

OCULAR DOMINANCE
Relative anatomical or physiological strength of connections from either eye to individual cells in the primary visual cortex.

THALAMOCORTICAL AFFERENTS
Axons from the thalamus (for example, the dLGN) that relay sensory input from the periphery (for example, the retina) to layer 4 of the neocortex.

BENZODIAZEPINES
Modulate chloride flux through $GABA_A$ receptors that contain the γ2 and any combination of α1, α2, α3 or α5 subunits. Benzodiazepine agonists enhance and inverse agonists decrease GABA efficacy.

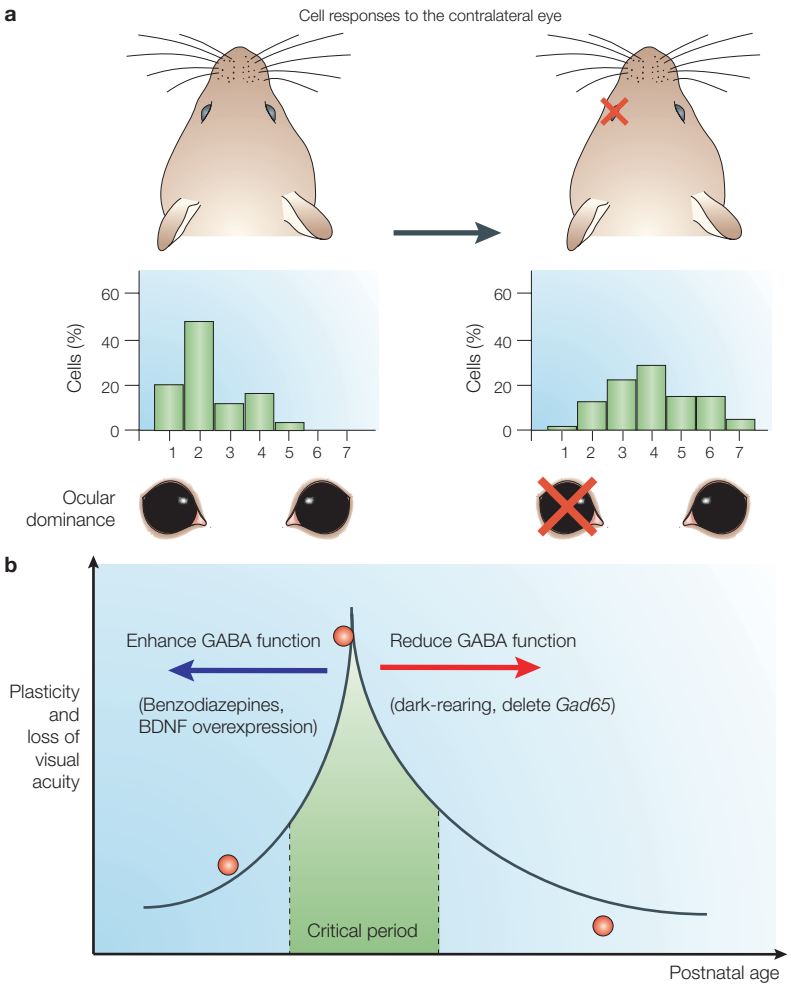


Figure 2 | **GABA-mediated control of the critical period. a** | Monocular deprivation produces a loss of response to the deprived eye and a gain of open-eye input, as measured by the neuronal discharge of single units from the mouse visual cortex[38]. The ocular dominance of cells, rated on a seven-point scale of neuronal responsiveness, indicates a typical bias toward the contralateral eye (1–3) in the rodent (top left). After 3 or more days of monocular deprivation, the distribution shifts toward the open, ipsilateral eye (4–7; top right). **b** | Sensitivity to monocular deprivation is restricted to a critical period that begins, in mice, about 1 week after the eyes open (at postnatal day 13) and peaks 1 month after birth[38]. Monocular deprivation causes amblyopia only during the same critical period. Red circles indicate the onset, peak and end of amblyopia resulting from monocular deprivation[39]. The onset of plasticity can be delayed by directly preventing the maturation of GABA (γ-aminobutyric acid)-mediated transmission by gene-targeted deletion of *Gad65*, which encodes a GABA-synthetic enzyme[43], or by dark-rearing from birth (red arrow)[50–53]. Conversely, the critical period can be brought forward by enhancing GABA transmission directly with benzodiazepines just after eye-opening[44–46] or by promoting the rapid maturation of interneurons through excess brain-derived neurotrophic factor (BDNF) expression (blue arrow)[47,48].

local circuit elements. As in other species[5–9], MONOCULAR DEPRIVATION (MD) shifts the spiking response of neurons in the mouse V1 towards the open eye[38], but, again, only during a critical period for behavioural amblyopia[39] (FIG. 2a; see also BOX 1).

The primary inhibitory neurotransmitter in the brain, GABA (γ-aminobutyric acid), is synthesized by glutamic acid decarboxylase produced by two distinct genes, *Gad65* and *Gad67*. Of these, *Gad65* is concentrated in axon terminals and bound to synaptic vesicles whereas *Gad67* is found throughout the cell[40]. Deletion (knockout) of *Gad67* is lethal and eliminates most cortical GABA content[41], but *Gad65*-knockout mice are viable and show poor GABA release only on strong stimulation[42,43]. Baseline receptive field properties are normal in the absence of GAD65, but ocular dominance plasticity is prevented until inhibition is acutely restored with diazepam[43]. When infused directly into V1, the use-dependent nature and rapid breakdown of benzodiazepine agonists ensures that only those local inhibitory circuits that are normally engaged by monocular deprivation will be boosted. Remarkably, rescue of plasticity is possible at any age in *Gad65*-knockout mice, which indicates that the critical period is dependent on the proper level of inhibitory transmission (FIG. 2b)[44].

Conversely, the onset of the critical period can be accelerated by prematurely enhancing inhibition with benzodiazepines just after eye opening[44–46], as well as by transgenic overexpression of brain-derived neurotrophic factor (BDNF) to promote the maturation of GABA neurons[47,48] (FIG. 2b). A close relationship between neuronal activity, BDNF release and GABA function also explains the classic effect of dark-rearing. Raising animals without visual experience from birth naturally reduces BDNF levels[49] and GABA-mediated transmission in the visual cortex[50,51], and delays the peak of plasticity into adulthood[45,52,53]. Direct diazepam infusion[45], or BDNF overexpression[54] or secretion by enriched environments[55] in complete darkness abolish the expected delay of the critical period. These striking results indicate that tonic GABA release is sufficient to trigger the eventual closure of the plastic state, even in the total absence of visual input.

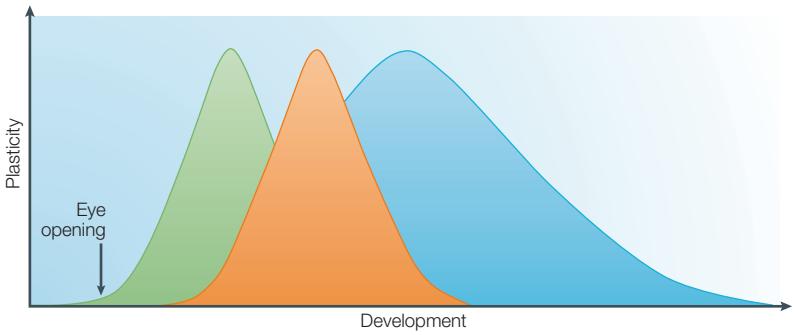
Specific GABA circuits for plasticity

Interestingly, not all GABA circuits are involved in critical period regulation. Several lines of evidence point towards a single class of interneuron that has the potential to mediate long-range inhibition and synchrony in the visual cortex. Among the many types of GABA-positive interneuron[56–58] (FIG. 3b), neurochemical markers, such as calcium-binding proteins, have been used to reveal that the onset of the critical period corresponds closely to the emergence of PARVALBUMIN-positive cells[59] and both events are accelerated by BDNF overexpression[47]. The specific blockade of a potassium channel (Kv3.1) that uniquely regulates the fidelity of FAST-SPIKING behaviour (and thereby GABA release) from parvalbumin-positive interneurons[60–62] slows the rate of ocular dominance plasticity (Y.-T. Matsuda *et al.*, unpublished observations). To date, the molecular biology of benzodiazepine action has provided the deepest insight into the local circuits that underlie plasticity.

The α-subunits of $GABA_A$ receptors determine benzodiazepine binding through a single amino acid residue in their amino terminus[20,63] (FIG. 3a). In mice, knock-in of a point mutation at this site renders individual $GABA_A$ receptor subtypes insensitive to benzodiazepines[64]. Weak inhibition in the visual cortex in early life (as observed for *Gad65* deletion) prevents experience-dependent plasticity[44,45]. Loss of responsiveness to an eye deprived of vision can be

STRABISMUS
Deviation of the two eyes due to a weakening of extraocular musculature that results in either an inward (esotropic) or outward (exotropic) rotation of one orbit and consequent amblyopia.

Box 1 | **Critical periods: gateway to lifelong plasticity**



Ocular dominance is one of several thalamocortical circuit properties in the primary visual cortex (V1) that develop in an experience-dependent manner during early life[4,186]. These might show different postnatal profiles (see panel) with, for example, orientation or direction selectivity (green) being shaped earlier than ocular dominance[7,44,53] (orange), or slow-wave sleep oscillations[169] (dark blue). Surprisingly, the detailed molecular machinery underlying each receptive field property may also differ[53]. Recent gene expression profiling supports the idea that the critical period for ocular dominance offers a specialized molecular milieu for plasticity[170,171], which is consistent with dendritic spine and axonal rearrangement being limited to this time in life[10,85,86].

Recently, monocular deprivation in adult animals has been reported to produce subthreshold synaptic plasticity[172–174], which has no further impact on spiking output[38,44,175] spines[85,86] or visuospatial acuity[7,39]. This suggests that the closure of the critical period might reflect sequential 'locks' that are placed on the molecular pathway as it flows from mature GABA (γ-aminobutyric acid)-mediated detection towards structural consolidation (FIG. 6). Functional plasticity may persist throughout life in many other systems (such as the somatosensory cortex[154,176] and the barn owl tectum[149]). Interestingly, limited plastic states can be greatly facilitated (to near critical period levels) by the judicious activation of neuromodulatory systems in adulthood[177,178]. A potent endogenous regulator of neuromodulation is sleep, which plays an intriguing part in enhancing adult learning[179].

Neuromodulators signal through second-messenger systems (FIG. 6), which can acutely reset the excitatory–inhibitory balance[180,181]. Full reactivation of the critical period may further require the 'undoing' of hard-wired neuronal structures[72,73]. The non-permissive growth environment of mature myelin is an especially promising target for rekindling plasticity, as it relates broadly to the acquisition of visual[182], linguistic[183] or musical[184] abilities. Better still, laying down multiple anatomical traces through rich childhood experiences might also expand the capacity for plasticity in adulthood[147,150].

initiated prematurely by enhancing GABA-mediated transmission with zolpidem (FIG. 4a), a $GABA_A$ α1-, α2- and α3-subunit selective ligand[46]. Systematic use of the mouse 'knock-in' mutation has further shown that only one of these subtypes, the α1-subunit-containing circuits, drives cortical plasticity (FIG. 4b). Diazepam fails to trigger premature plasticity in α1-subunit-mutants, although they are fully capable of undergoing plasticity at the proper age (postnatal day (P) 25) even without drugs[46], as they form normal α1- subunit-containing GABA receptors at the appropriate time.

Importantly, GABA-releasing interneurons in the neocortex show precise connectivity[25,58] (FIG. 3b). Synapse formation by parvalbumin-positive cells is largely mediated through molecular cues and then refined by neuronal activity[65,66]. These cells include axon-ensheathing CHANDELIER CELLS and soma-targeting LARGE BASKET CELLS. The latter extend the wide-reaching, horizontal axonal plexus (FIG. 1), which has been shown to span ocular dominance columns in the cat[67]. The use of immuno-electron microscopy has further indicated that individual $GABA_A$ receptor α-subunits are trafficked to discrete postsynaptic sites on the pyramidal cell axon, soma and dendrites (FIG. 3b). For example, α2-subunits are preferentially enriched at the axon initial segment and at short-range basket cell synapses that are innervated by CHOLECYSTOKININ-positive axon terminals[68,69]. Although α2-subunit-containing connections do regulate neuronal firing, they have no effect on the induction of plasticity[46]. This dissociation has implications not only for models of brain development, but also for the safe design of benzodiazepines for use in human infants (see below).

The α1-subunit-containing $GABA_A$ receptors are instead localized to receive parvalbumin-positive (but not cholecystokinin-positive) synapses on the soma[68,69], further implicating these large basket cell circuits in the control of the critical period. With age, large parvalbumin-positive cells are preferentially enwrapped in PERINEURONAL NETS of extracellular matrix (ECM) molecules and sugars[70]. When these are disrupted, perisomatic inhibition of their targets is reduced[71], and ocular dominance shifts can once again be induced by monocular deprivation, even in adulthood[72]. This might be the result of resetting and tapping the original GABA-mediated trigger[44] (FIG. 5b), as perineuronal nets probably control the extracellular ionic milieu (for example, potassium concentration[70]) that surrounds parvalbumin-positive cells, allowing them to establish their fast firing efficiency[60–62], or might otherwise sequester molecular regulators of parvalbumin-positive cell maturation (S. Sugiyama *et al.*, unpublished observations). The identification of a cellular critical period trigger holds great promise as a therapeutic target and for the development of strategies for lifelong learning.

Expression by proteases: structural rewiring

The ECM is increasingly being recognized as a potent site for critical period plasticity[73]. To convert physiological events (altered vision) into structural refinements, connections must ultimately be broken and neuronal wiring rerouted. Proteases are ideally suited to clear the way for growing neurites[74]. TISSUE-TYPE PLASMINOGEN ACTIVATOR (tPA) is the main serine protease in the postnatal mammalian brain[75,76], and was originally identified there as an IMMEDIATE EARLY GENE activated by hippocampal seizures[77]. Proteolysis by tPA is gradually upregulated in V1 within 2 days of monocular deprivation during the critical period (FIG. 5a), but not in adults or *Gad65*-knockout mice[78]. Interestingly, at least 2 days of diazepam treatment are required to rescue plasticity in the absence of GAD65 (REF. 45). Functional ocular dominance plasticity is impaired when tPA action is blocked[78–80] and can be rescued by exogenous tPA (but not diazepam)[78].

Permissive amounts of tPA might, therefore, couple functional to structural changes downstream of the excitatory–inhibitory balance that triggers visual cortical plasticity. The second messenger systems, which are known to be recruited during ocular dominance

TETRODOTOXIN (TTX). A voltage-dependent sodium channel blocker that can be used to silence all neural activity except spontaneous neurotransmitter release.

MONOCULAR DEPRIVATION (MD). Imbalanced visual input due to the occlusion of one eye by patching, eyelid suture or intraocular TTX injection.

PARVALBUMIN
One of three calcium-binding proteins, which, together with calretinin and calbindin, are expressed in most GABA-mediated neurons in the neocortex in largely non-overlapping groups.

FAST-SPIKING
Ability of parvalbumin-positive cells to fire non-adapting action potentials at rates of up to several hundred Hertz, due, in part, to unique potassium conductances (Kv3 class).

CHANDELIER CELL
Stereotypical GABA cell of the cerebral cortex that ensheathes the axon initial segment of up to 200 pyramidal cells with 'cartridge' synapses to directly control action potential generation.

LARGE BASKET CELL
Class of GABA cell with long, horizontally-extending axon that makes potent inhibitory contacts on the soma and proximal parts of the dendrites of target pyramidal cells.

CHOLECYSTOKININ
(CCK). A neuropeptide that is found in non-fast-spiking large basket cells that contact the soma of target pyramidal cells at synapses enriched in $GABA_A$ receptor α2-subunits.

PERINEURONAL NET
A conglomeration of chondroitin sulphate proteoglycans, extracellular matrix and cell-adhesion molecules that condenses around particular large-basket cells with age.

TISSUE-TYPE PLASMINOGEN ACTIVATOR
(tPA). The major serine protease in the brain, well known as an anti-clotting agent that works by cleaving fibrin in the blood.

IMMEDIATE EARLY GENES
Transcription factors that are induced within minutes of intense neuronal activity. Examples include zif268 and c-fos.

PLASMIN
The active form of plasminogen, which is the primary target of tPA action, and itself a protease that is known to cleave extracellular matrix molecules (for example, laminin and phosphacan).

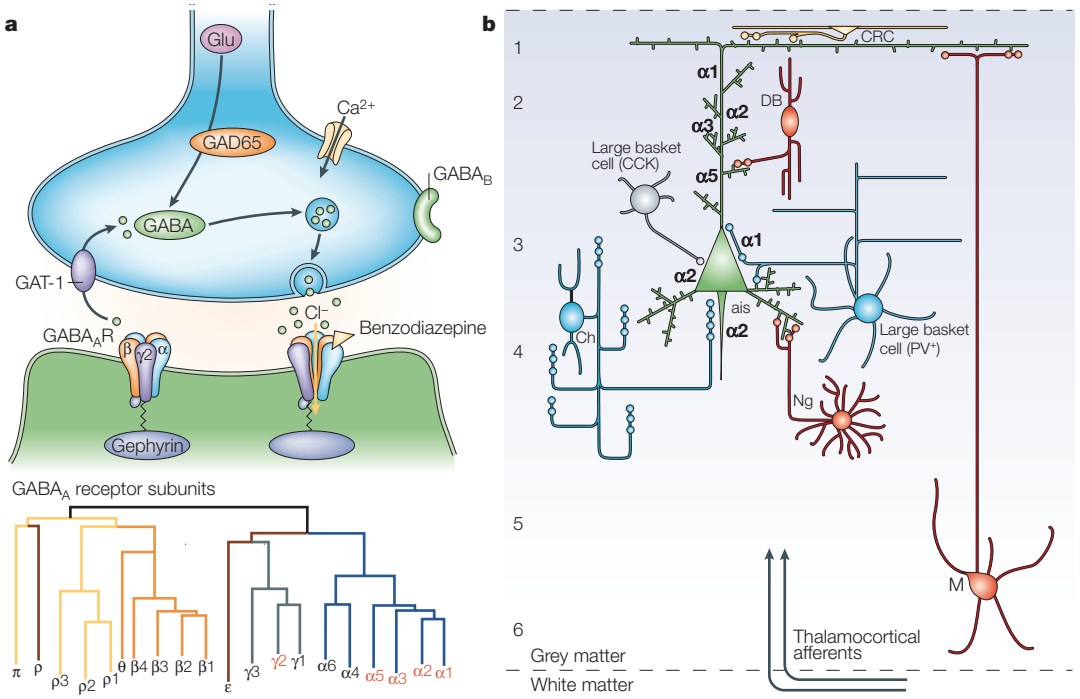


Figure 3 | **Heterogeneity of local GABA circuits in the neocortex. a** | Inhibitory synaptic transmission is mediated by GABA (γ-aminobutyric acid) synthesized by glutamic acid decarboxylase 65 (GAD65) in the presynaptic terminal during strong stimulation. The postsynaptic effect of released GABA is modulated by exogenous benzodiazepines acting on specific postsynaptic receptors. Among the 20 identified subunits that the $GABA_A$ (GABA type A) receptor ($GABA_AR$) may comprise[20,63], the α1-, α2-, α3- and α5-subunits contain an amino acid residue, histidine, that is vital to the benzodiazepine binding site[20,64]. Benzodiazepine (but not GABA) binding is lost when this amino terminus histidine is mutated to arginine (causing the α1-, α2-, α3- and α5-subunits to mimic the naturally benzodiazepine-insensitive α4- and α6-subunits. **b** | Many subtypes of GABA-releasing inhibitory interneuron can be identified in the neocortex on the basis of morphology, connectivity, expression of calcium-binding proteins or neuropeptide content[56–58,25]. Moreover, specific contacts are preferentially enriched in specific $GABA_A$ receptor α-subunits[63,64]. The perisomatic localization of different subunits is shown next to the central pyramidal neuron. All subunits are found diffusely along the dendrite. ais, axon initial segment; CCK, cholecystokinin expressing; Ch, chandelier cell; CRC, Cajal–Retzius cell; DB, double bouquet cell; M, Martinotti neuron; N, neurogliaform neuron; PV^+, parvalbumin positive. Lower part of panel **a** modified, with permission, from REF. 63 © (2001) Elsevier Science.

plasticity[81] (FIG. 6), lie along a molecular cascade that links neuronal activity to tPA release[4,78], the structural consequences of which have recently been clarified. Thalamocortical axon rearrangement is a classical outcome of critical period plasticity (FIG. 1), but is much too slow to explain the rapid shift of ocular dominance that occurs within days of monocular deprivation[10–13,82]. Morphological plasticity is initiated postsynaptically along the apical dendrites of target pyramidal cells in the cerebral cortex, where spines serve as pleiomorphic sites of excitatory synaptic connection.

Spine shape has been shown to be highly dynamic using two-photon laser scanning microscopy in living transgenic mice expressing green fluorescent protein (GFP) in a subset of layer 5 cells. The motility of spines decreases with age in the visual cortex[83,84], but, during the critical period, can be transiently elevated by 2 days of monocular deprivation[85] (FIG. 5a, step 1). This occludes the motility that can be induced by the direct application of tPA to naive brain slices, which indicates that tPA and its substrate, plasminogen, might be the endogenous mediators of experience-dependent spine motility. Even along the same apical dendrite[85], spines are set in motion by brief monocular deprivation only in layers 2, 3 and 5, consistent with early extragranular changes that instruct later events in layer 4 (REF. 12).

After 2 days of monocular deprivation, increased proteolysis degrades ECM and cell-adhesion proteins before any physiological ocular dominance shift is detectable[38,78]. Consequently, spines are eliminated by 4 days of monocular deprivation, which corresponds to the rapid, complete loss of functional responsiveness[86] (FIG. 5a, step 2). After this postsynaptic pruning, axons carrying input from the deprived eye retract before afferents serving the open eye can migrate to spaces cleared by tPA–PLASMIN along the dendrite (FIG. 5a, step 3)[10,11]. As expected for a true critical period event, spine density is not reduced by brief monocular deprivation in adulthood or in mice that lack tPA or GAD65 (REF. 86). The reduction in spine density can be restored in tPA- or *Gad65*-knockout mice by exogenous tPA or diazepam infusion, respectively. Importantly, spine motility and pruning faithfully reflect competitive interactions between the two eyes, as they fail to occur in the adjacent monocular segment that receives input solely from the contralateral eye[85,86].

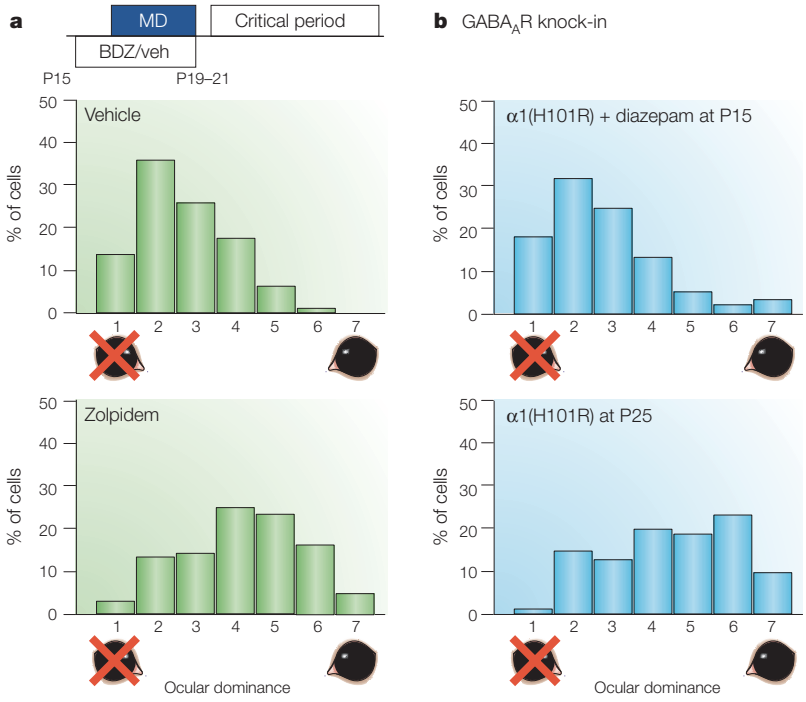


Figure 4 | **Specific GABA$_A$ circuits for visual cortical plasticity. a** | Ocular dominance shifts, as rated by the neuronal discharge of single units from the mouse visual cortex on a scale from 1 (contra) to 7 (ipsi) eye input, can be induced by monocular deprivation (MD) before the critical period in the presence of zolpidem[46], a benzodiazepine (BDZ) agonist that is selective for α1-, α2- or α3-subunit-containing GABA$_A$ (γ-aminobutyric acid type A) receptors (GABA$_A$Rs)[20]. **b** | Conversely, premature plasticity cannot be induced in mice with a point mutation that renders the α1-subunit insensitive to the benzodiazepine diazepam[46] (α1(H101R)). Importantly, GABA$_A$ receptor expression and localization occur normally, as the knock-in mice show robust plasticity (without drugs) at the typical critical period (postnatal day (P) 25). Figure modified, with permission, from REF. 46 © (2001) Elsevier Science.

Ultimately, the territory that represents the open eye grows[9–11] (FIG. 5a, step 3, right), and this requires cortical protein synthesis[87]. Cleavage of secreted pro-neurotrophins by tPA–plasmin to yield active mature forms such as BDNF might contribute to the elongation of neurites[88,89]. As proteolytic activity slowly wanes after a week of monocular deprivation[78], axons serving the open eye expand[10,11], spines grow out to meet them and their density largely recovers[86] (FIG. 5a, asterisks). Curiously, spine loss is most robust near the soma of layer 2/3 pyramidal cells. Competition detected by inhibitory circuits impinging on pyramidal cell somata might, therefore, be translated into structural changes mediated by a multistep proteolytic action of the extracellular tPA–plasmin cascade.

The homosynaptic view

It is tempting to speculate that the loss or gain of visual responsiveness of neurons in V1 during the critical period is simply the result of homosynaptic LONG-TERM DEPRESSION (LTP) or POTENTIATION (LTP) somewhere in the visual circuit (the homosynaptic view). On theoretical grounds, homosynaptic rules of excitatory synaptic plasticity alone are insufficient to produce a competitive outcome[90], as they require the involvement of other complex mechanisms, such as sliding thresholds or metaplasticity. Although correlative evidence has been presented to support homosynaptic rules for plasticity *in vivo*, the fact that direct comparisons are not supportive is often overlooked.

In favour of the homosynaptic view, changes in phosphorylation state and membrane trafficking of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptor subunits — events that seem to underlie LTP or LTD at central synapses[91] — have been observed in the primary sensory cortex after natural sensory experience *in vivo*. For example, whisker stimulation at P12–14 in rats drives a recombinant AMPA receptor subunit (GluR1) into synapses from layers 4 to 2/3 in the somatosensory barrel cortex[92]. Expression of the GluR1 cytoplasmic tail, which inhibits the synaptic delivery of endogenous receptors during LTP *in vitro*, blocks this insertion and subsequent synaptic potentiation *in vivo*. Whisker deprivation produces both an expansion of neighbouring input from spared barrels and a loss of response to the principal whisker. The latter largely occludes induction of NMDA (*N*-methyl-D-aspartate) receptor-dependent LTD by low-frequency stimulation (LFS) along the principal ascending pathway[93], which supports the idea that the mechanisms mediating changes in barrel cortex responsiveness are the same as those that mediate LTD.

Similarly, in the visual cortex, 24-h monocular deprivation (too short a time period to shift ocular dominance *in vivo*[38]) reduces the saturation level of LTD in response to repeated LFS, and leads to numerous changes in the GluR1 phosphorylation status, which are akin to those that occur during hippocampal LTD[94]. The main difficulty with correlative studies is that they can never demonstrate causality. Ostensibly similar molecular pathways (FIG. 6) might be used differently by LTP/LTD and by critical period mechanisms subserving circuit function *in vivo*. For example, the late onset and experience-dependent profile of NMDA receptor 2A (NR2A) subunits[95–98] — known to determine LTP levels in the hippocampus[99,100] — is irrelevant to critical period expression in the visual cortex[53]. A decline in LTP/LTD magnitude and slow emergence of NR2A at thalamocortical synapses in the barrel cortex during the anatomical critical period in the first postnatal week might also be coincidental[101,102]. Barrel shrinkage and expansion on whisker cauterization at birth is impervious to cortical NMDA receptor deletion[103] and might reflect changes at subcortical levels, before thalamic axons segregate in layer 4 (REF. 104).

In the absence of NR2A, the depolarizing action of NMDA currents is prolonged. Like *Gad65* deletion[43], this tips local circuit equilibrium towards excitation, weakening ocular dominance plasticity that can be restored by diazepam[53]. Counter-intuitive to an LTP perspective[99,105], inhibition is required for plasticity *in vivo* when NMDA receptor function is high. Conversely, although LTD is blocked by NMDA-receptor antagonists, high doses of APV[35] promote a paradoxical loss of open eye input, as does strong postsynaptic activation of GABA$_A$ receptors with muscimol[36,37]. Although maturation of other receptive field

LONG-TERM DEPRESSION (LTD). A persistent reduction of synaptic transmission in response to weak, poorly-correlated input.

LONG-TERM POTENTIATION (LTP). A persistent strengthening of synaptic transmission in response to strong, correlated input.

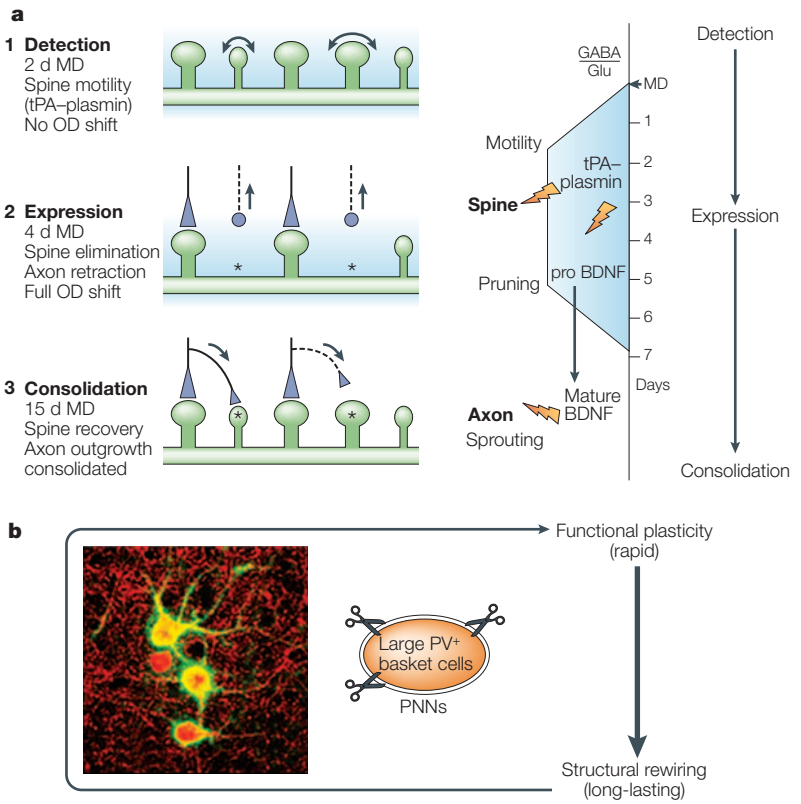


Figure 5 | **Structural consolidation during the critical period. a** | Once functional detection of competing inputs is made possible by the maturation of relevant GABA (γ-aminobutyric acid) circuits[43–48], a series of structural rearrangements accompanies sensory deprivation. Shortly (2 days) after monocular deprivation (MD), the motility of spines (two-headed arrows)[85] is increased on apical dendrites of excitatory pyramidal neurons by an increase in tissue-type plasminogen activator (tPA)–plasmin proteolytic activity (blue background)[78]. No shift in ocular dominance (OD) can be detected at this stage[38] (1). The total number of spines on pyramidal cell apical dendrites is transiently and significantly decreased owing to their elimination (asterisks), with a time course that corresponds to the loss of cellular responses of the deprived eye 4 days after monocular deprivation[86]. This is followed by a retraction of thalamocortical axons[10,11] as extracellular tPA–plasmin activity remains high[78] (2). After long-term monocular deprivation, new spines emerge (asterisks) to receive synaptic input from sprouting axons carrying input from the open eye (triangles)[10,11,13] as tPA–plasmin activity subsides[78] (3). **b** | These results predict that structural modification is necessary to reactivate critical period plasticity in adulthood. Infusion of chondroitinases (scissor symbols) to break up perineuronal nets (PNNs) in the extracellular matrix restores ocular dominance shifts to adult rats[72]. Interestingly, these nets preferentially enwrap large, parvalbumin-positive (PV^+) basket cells[70], which control perisomatic inhibition[71] and trigger the endogenous critical period. The section depicts parvalbumin-positive basket cells stained with monoclonal antibody (red) and perineuronal nets stained with *Wisteria floribunda agglutin* (WFA; green). Note that small parvalbumin-positive cells are not ensheathed by perineuronal nets. BDNF, brain-derived neurotrophic factor; Glu, glutamate.

properties (such as orientation bias[44,53]) might reflect subunit-specific coupling of NR2A to postsynaptic signalling pathways (like LTP[100]), the yin-yang relationship of excitatory–inhibitory balance is essential for ocular dominance plasticity.

During learning, distinct plasticity mechanisms subserve sequential phases of memory[106]. Local (synaptic and cellular) events are eventually consolidated at a systems (circuit) level by increasing protein synthesis and neurite growth. Excessive emphasis on LTP/LTD alone (which is all-or-none at single synapses[107]) ignores the gradual, long-lasting changes that are the hallmark of critical period plasticity. One day of monocular deprivation does not occlude homosynaptic depression by single LFS[94], and these early forms of synaptic change, which persist in the presence of protein synthesis inhibitors[108], are insufficient to shift ocular dominance *in vivo*[87]. However, multiple spaced conditioning stimuli, used to saturate LTP/LTD[94], activate distinct transcriptional pathways (for example, that of immediate early gene *Zif268*)[109], which are also not required for ocular dominance plasticity[110]. In fact, the role of proteases (tPA) in growth for long-lasting forms of LTP[111,112] is opposite to that for ocular dominance plasticity (spine pruning[86]).

Overall, no consistent correlation has been found between the ability to induce homosynaptic plasticity *in vitro* and amblyopic effects *in vivo*[113–116]. The relationship is not straightforward, as the mechanisms of LTP and LTD might differ depending on cortical layer[117]. Moreover, unlike the very rapid induction of synaptic changes, no loss of visual response or acuity occurs until several days of eyelid suture have elapsed[38,39]. Rapid phosphorylation dynamics of one GluR1 amino acid residue alone are unlikely to explain the complex functional and structural events that constitute the critical period (FIG. 5). Spine shrinkage by LFS is, in fact, mediated by cofilin and is independent of the AMPA receptor dephosphorylation that underlies LTD[118]. At present, there is only limited evidence directly connecting the coincident structural and functional plasticity at spines[119].

Most strikingly, synaptic depression is intact whereas ocular dominance plasticity is lost in mice that conditionally overexpress the protein phosphatase, calcineurin[120]. Underscoring a double dissociation, homosynaptic models based on NMDA-receptor activation stipulate that the maturation of inhibition will terminate plasticity[105], whereas quite the opposite is true: *in vivo*, GABA function is required to trigger the critical period[44]. Given that diazepam[121] and endogenous BDNF[122] block LTD induction in the cortex, their acceleration of plasticity *in vivo*[44–48] is not predicted by homosynaptic models, which are routinely studied *in vitro* in the presence of GABA-receptor blockers. In the end, adjusting local inhibitory circuit function has provided direct control over the critical period (FIG. 2), which LTP-based models have not.

Local circuit models of critical period plasticity

That inhibition might enable plasticity in the developing brain seems paradoxical. The identification of a particular GABA circuit that drives the onset of the critical period and the subsequent sequence of anatomical events (FIG. 5) now allows us to construct realistic models with which to target the plasticity process more precisely. Two scenarios centred on the parvalbumin-positive basket cell serve as heuristic examples for further study. One is an 'instructive' model (FIG. 7a), in which powerful, fast somatic inhibition edits one-by-one the action potentials that can pass into the dendritic arbor by back-propagation through the cell body. Recent SPIKE-TIMING DEPENDENT models of synaptic plasticity rely on precise millisecond

SPIKE-TIMING DEPENDENT PLASTICITY
Describes physiological windows for LTP or LTD of synaptic transmission based on the arrival time of incoming action potentials with respect to back-propagated spikes in the target dendrite.

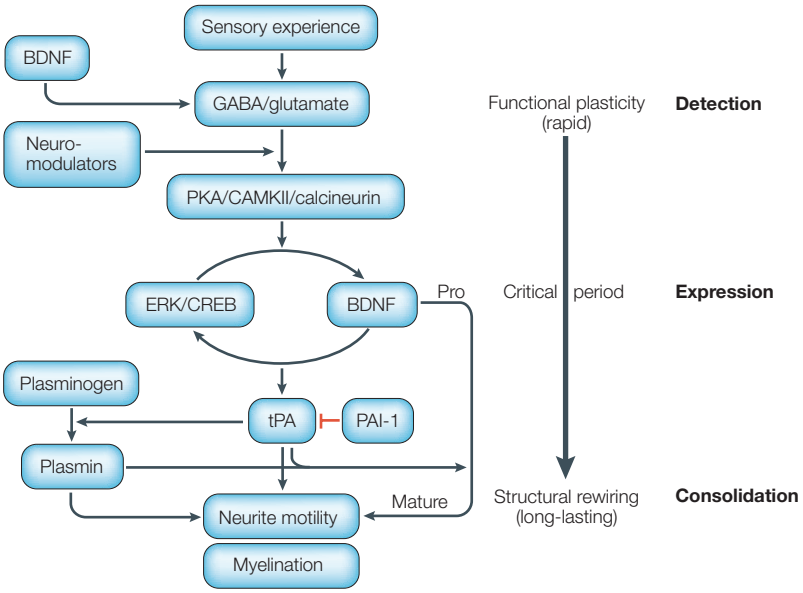


Figure 6 | **Molecular mechanisms of visual cortical plasticity.** Many candidate plasticity factors have been screened using the monocular deprivation protocol — by pharmacology in kittens or by gene-targeted disruption in mice (for a review, see REF. 81). Only a handful of second messenger molecules have been found to have a direct role in plasticity without perturbing global neuronal activity. These include PROTEIN KINASE A (PKA)[181], calcium/calmodulin-dependent protein kinase II (CaMKII), calcineurin[120], extracellular signal-regulated kinase (ERK), cyclic AMP responsive element binding protein (CREB), protein synthesis machinery[87] and the plasmin system (tissue-type plasminogen activator (tPA)–plasmin), which is regulated by its inhibitors (plaminogen activator inhibitor, PAI-1)[78–80]. Brain-derived neurotrophic factor (BDNF) has an early role in plasticity, establishing the GABA (γ-aminobutyric acid) cells that discriminate competing sensory inputs to trigger the critical period[47]. Mature BDNF, which is produced from the cleavage of pro-BDNF by tPA–plasmin [88], in turn stimulates the expression and release of tPA[185]. Both tPA and BDNF can then contribute sequentially to the final anatomical rewiring of the cortical circuit[10,11,13,85,86,89] (FIG. 5). Plasticity might come to an end when permissive factors are gradually lost[86], or when further growth is actively suppressed by late-emerging inhibitory factors (myelin) in the extracellular matrix[7,73,182].

time windows to allow such postsynaptic spikes to meet presynaptic input[123,124]. Sloppy gating by weak inhibition at the soma would prevent a competitive outcome by allowing excess back-propagation and spurious coincident activity with infrequent, deprived inputs from the retina[125]. Identifying a molecular substrate that is unique to spike-timing dependent (as opposed to LFS or tetanus-induced[126]) plasticity will be a prerequisite to testing this scheme *in vivo*.

Both immature (pre-critical period) and *Gad65*-knockout mice show prolonged neuronal discharge that continues well after stimuli have passed through the receptive field of individual cells[43–45]. Chandelier cell 'cartridge' synapses (which use α2 $GABA_A$ receptor subunits) can directly control this excessive spiking at the axon initial segment[46,127]. Surprisingly, plasticity is still triggered prematurely by diazepam when hyperexcitability persists in mice whose α2-subunits can no longer bind benzodiazepines[46]. Fast-spiking, feedforward inhibition mediated by α1-subunit-containing receptors on the soma is then ideally situated to suppress back-propagation of unwanted spikes[125] (FIG. 7a). The model incorporates the wide-reaching, horizontal axons of basket cells that receive input from one eye to inhibit targets of the other eye[67]. This simple contrast enhancement circuit relieves the burden of discriminating competitors by LTP/LTD at single synapses. Alternatively, well-timed spikes in the soma itself might facilitate nuclear calcium entry for gene transcription (and growth) in response to waves of calcium arriving from synapses on dendritic spines.

A second, 'permissive' model emphasizes newfound knowledge of parvalbumin-positive cell biology. Even in adulthood, basket cells can be coupled electrically into groups of 40 or 50 cells[128,129], endowing the network with the ability to detect synchrony[130] (FIG. 7b). Whereas simultaneous inputs (for example, from the same eye) rapidly co-excite cells through gap junctions, even a 2-ms input jitter (for example, between opposite eyes) is sufficient to dampen the coupling by reciprocal $GABA_A$ synapses, which are also enriched in α1-subunits[131]. As a result, these neurons with long, horizontal axonal arbors[67], are maximally active on a columnar scale, time-locked to release growth or plasticity factors when strong synchronous activity arrives in the neocortex. Gap junctional coupling between interneurons also promotes synchronous oscillation among principal cells[132,133]. Validation of the 'permissive' model awaits conditional deletion of connexins in cortical parvalbumin-positive cells alone, as the retina is also rich in gap junctions[134].

This model assumes an extracellular locus of competition to be quite distinct from the intracellular mechanisms of LTP and LTD. Axons and dendritic spines that are co-active with the synchronized parvalbumin-positive cell network can benefit from the rapid, focal creation of a permissive growth environment[78,86,135]. The source and dynamics of tPA–plasmin release in the brain remain unclear owing to the lack of specific reagents. Laminar motility of spines[85] and their rapid pruning[86] by brief periods of monocular deprivation could reflect activity-dependent secretion of proteases[136–138] from the axons of fast-spiking cells themselves, in which parvalbumin is an important contributor to presynaptic calcium signals and synaptic integration[139].

This might explain why spines nearest the soma of layer 2/3 pyramidal cells are most robustly lost during monocular deprivation[86], as they lie nearest the parvalbumin-positive cell-rich layer[59]. Potential synaptic plasticity of GABA-mediated transmission might add a further layer of regulation. How a competitive outcome arises by uniformly bathing dendrites in proteases also needs to be considered. Cell-adhesion molecules can become insensitive to proteases during high levels of activity[140,141]. Less active synapses also release fewer endogenous protease inhibitors[142], tilting the overall balance nearby towards pruning. Therefore, open-eye axons can protect themselves from proteolytic removal in two ways, whereas silent deprived-eye inputs are left defenceless in a sea of tPA–plasmin during monocular deprivation.

Towards a common brain principle

How general is the idea of local circuit inhibition and critical periods across other systems? Zebra finches acquire a unique song once in life during a critical period for vocal learning that progresses through three stages[4].

PROTEIN KINASE A (PKA). Phosphorylates multiple targets (including AMPA and $GABA_A$ receptors) when cyclic AMP binds its regulatory subunits to release the catalytic domains.

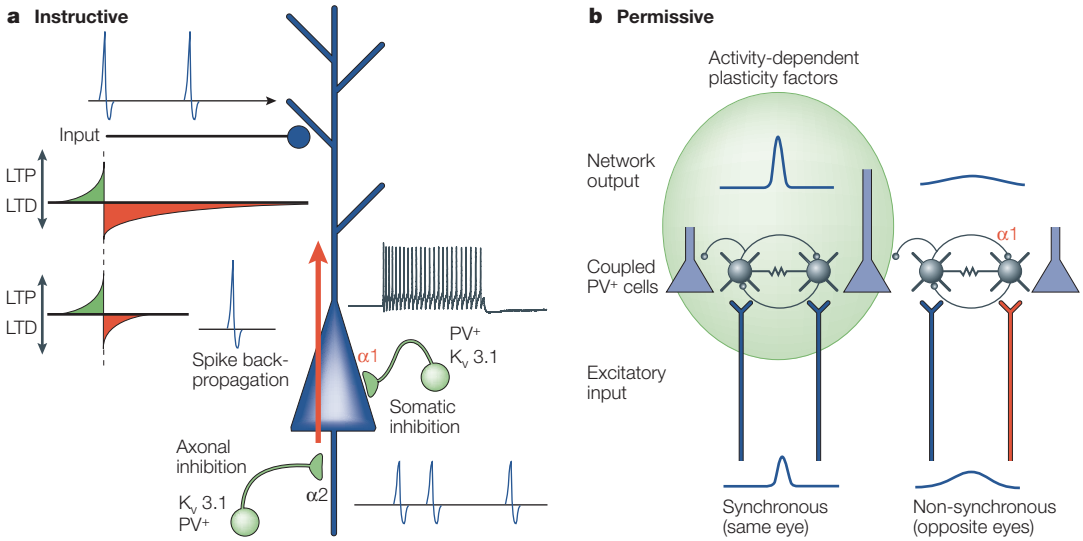


Figure 7 | **Two models for inhibitory control of sensory plasticity. a** | Somatic inhibition by fast-spiking parvalbumin-positive (PV^+) cells (green) expressing the potassium channel Kv3.1 is mediated by the $GABA_A$ (γ-aminobutyric acid type A) α1-subunit, whereas axonal inhibition is mediated by the $GABA_A$ α2-subunit. Somatic inhibition is ideally situated for suppression, or 'editing' of unwanted spikes, preventing them from back-propagating through the cell body into the dendritic tree (red arrow). This is an 'instructive' model, as individual action potentials can produce long-term potentiation (LTP) or depression (LTD) based on precise spike-timing dependent windows at individual synapses of coincident pre- and postsynaptic activity[123,124]. Notably, failure to regulate excess spiking at the axon initial segment can still be differentiated by fast-spiking inhibition at the cell body. **b** | Gap junctional coupling endows networks of parvalbumin-positive (PV^+) interneurons with the ability to detect synchronous input[128–130]. Even a slight jitter in input timing (for example, between eyes) dampens network activity through reciprocal GABA-mediated contacts (enriched with $GABA_A$-receptor α1-subunits[131]). Only synchronous open-eye input will produce maximal, activity-dependent release or uptake of 'permissive' factors for neurite growth (for example, tissue-type plasminogen activator[78,86] and brain-derived neurotrophic factor). Competition is determined extracellularly.

After first memorizing the father's template, birds enter a motor practice phase, followed by song crystallization. In register with the active singing component, a peak in the number of GABA neurons is observed in the motor nucleus robustus archistrialis (RA), where descending auditory and forebrain memory circuits converge onto individual cells[143]. Such a GABA profile is observed only in males, and not in females, which do not produce song. Local inhibitory circuits might allow the proper matching (and discrimination) of template and vocalized sub-song in the RA before consolidation. Indeed, infusion of cannabinoids, which primarily bind presynaptic CB1 receptors to reduce GABA release[144], alters developmental sensorimotor vocal learning but not adult song performance[145].

If barn owls are reared wearing prism lenses to skew their visual world, a learned shift occurs in the auditory map of interaural time differences in the tectum so that it corresponds with the visual input[146]. Multiple maps can be stored in the same tectum if this experience occurs during a critical period[147]. To allow discrimination between conflicting circuits, new GABA-mediated connections are formed to suppress the unused representation[148]. Adult plasticity is limited to incremental displacement of the visual scene within the architectural constraints of axons that were hard-wired during the critical period[149,150].

Conversely, in the barrel cortex GABA circuits are formed and reorganized throughout life[151–153], and are associated with lifelong plasticity[154]. This is also the case in the mammalian olfactory system, where constant neurogenesis is responsible for the underlying memory of odour discrimination in adulthood[155,156]. The newly born cells are GABA-containing granule cells, the functions of which include lateral inhibition and synchronization of neuronal activity[157,158]. This raises the question of whether an olfactory critical period would emerge in the absence of neurogenesis, or whether visual plasticity could be maintained by prolonging cell proliferation in the neocortex.

Most interestingly, the control of visual cortical plasticity by GABA in animal models might also apply to the development of the human brain. In postnatal samples of V1 that were removed post-mortem[159], the maturation of NR2A to 2B is complete within the first 9 months after birth. By contrast, *Gad65* expression and the conversion of $GABA_A$ receptors from α3- to α1-subunit containing occurs more slowly, over several years, which is consistent with the extended length of the critical period for amblyopia in humans[6,7]. Strikingly, the levels of *GAD67* and α2-subunits are constant during the same early postnatal time period[159], consistent with their limited role in plasticity in animals[46]. To avoid the rapid, premature induction of critical period plasticity through α1-subunit-containing receptors[45,46], new benzodiazepine agonists that are selective for α2-subunits should be developed for the control of status epilepticus in human infants[160].

In general, critical periods are a process of selecting the best neural representation available from among the many competing inputs that continually bombard the maturing nervous system. Growth and function of lateral inhibitory circuits offer a rational, cellular substrate to be compared and modelled across regions to gain broader insight into brain development and its disorders[161,162]. Interestingly, cortical lesions or retinal scotomas in adulthood transiently reconfigure local circuit excitation–inhibition to an immature state[163]. This provides a rationale for the administration of diazepam after acute stroke[164] — not only might it reduce excitotoxicity, but it could also aid recovery by triggering plasticity machinery (FIG. 6). The concept of excitatory–inhibitory balance[26] in key neural systems during development might apply to epilepsy[162], autism[161], Rett syndrome[165] and Tourette's syndrome[166], schizophrenia[167] and even the encoding and retrieval of memories[168]. Finding the keys to critical period plasticity could enable the development of novel therapies and training paradigms for education, rehabilitation, recovery from injury and lifelong learning in adulthood.

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Acknowledgements

I thank M. Fagiolini for comments, N. Mataga for immunostaining in figure 5b and all members of the lab for Neuronal Circuit Development (RIKEN BSI) for their dedication to understanding critical period mechanisms.

Competing interests statement

The author declares no competing financial interests.

Online links

DATABASES

The following terms in this article are linked online to:

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
BDNF | *Gad65* | *Gad67* | *Zif268*

OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Rett syndrome | Tourette's syndrome

FURTHER INFORMATION

http://www.brain.riken.jp/

Access to this interactive links box is free online.