DEVELOPMENT AND PLASTICITY OF CORTICAL AREAS AND NETWORKS

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The development of cortical layers, areas and networks is mediated by a combination of factors that are present in the cortex and are influenced by thalamic input. Electrical activity of thalamocortical afferents has a progressive role in shaping cortex. For early thalamic innervation and patterning, the presence of activity might be sufficient; for features that develop later, such as intracortical networks that mediate emergent responses of cortex, the spatiotemporal pattern of activity often has an instructive role. Experiments that route projections from the retina to the auditory pathway alter the pattern of activity in auditory thalamocortical afferents at a very early stage and reveal the progressive influence of activity on cortical development. Thus, cortical features such as layers and thalamocortical innervation are unaffected, whereas features that develop later, such as intracortical connections, are affected significantly. Surprisingly, the behavioural role of 'rewired' cortex is also influenced profoundly, indicating the importance of patterned activity for this key aspect of cortical function.

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The mammalian neocortex, a folded sheet that in humans contains over 10 billion neurons, is the seat of our highest sensory, motor and cognitive abilities. Understanding how it develops and how it changes is central to our understanding of brain function and is crucial to the development of treatments for neurological disease. Cortical development involves the formation of many discrete areas that uniquely process different kinds of information. Individual areas are characterized by specific sets of inputs, by intrinsic processing networks and by specific outputs. In addition, there are small but potentially significant differences in laminar detail between areas. Cortical specification refers to defining the ways in which these various features are set up during development; each of these features involves a combination of intrinsic factors and extrinsic events. Intrinsic factors in cortical development refer to genes and molecules expressed within the tissue. The nature of extrinsic factors differs depending on the time and stage of development. However, it is not possible to separate cleanly between intrinsic and extrinsic aspects of developmental programmes — no gene acts independently of an environment, and the environment always needs a scaffold on which to act.

Much discussion has focused on whether there is detailed specification of cortical areas by genes and molecules that are expressed early in the ventricular zone in a manner that recapitulates cortical parcellation — the protomap hypothesis[1] — or whether the cortex is a *tabula rasa* whose identity is bestowed on it by thalamic afferents — the protocortex hypothesis[2]. We propose instead that the development of layers, areas and networks each derives from a combination of factors that are present in the cortical mantle and are regulated by thalamic input.

Formation of cortical layers

The adult neocortex consists of six layers. These are generated by a heterogeneous population of precursor cells that is present in the ventricular and subventricular zones. It is well established that the time of neurogenesis in the ventricular zone regulates laminar location[3–5]. Cells that leave the cell cycle earlier form the deeper cortical layers, whereas cells born later form progressively more superficial layers (FIG. 1). There is a

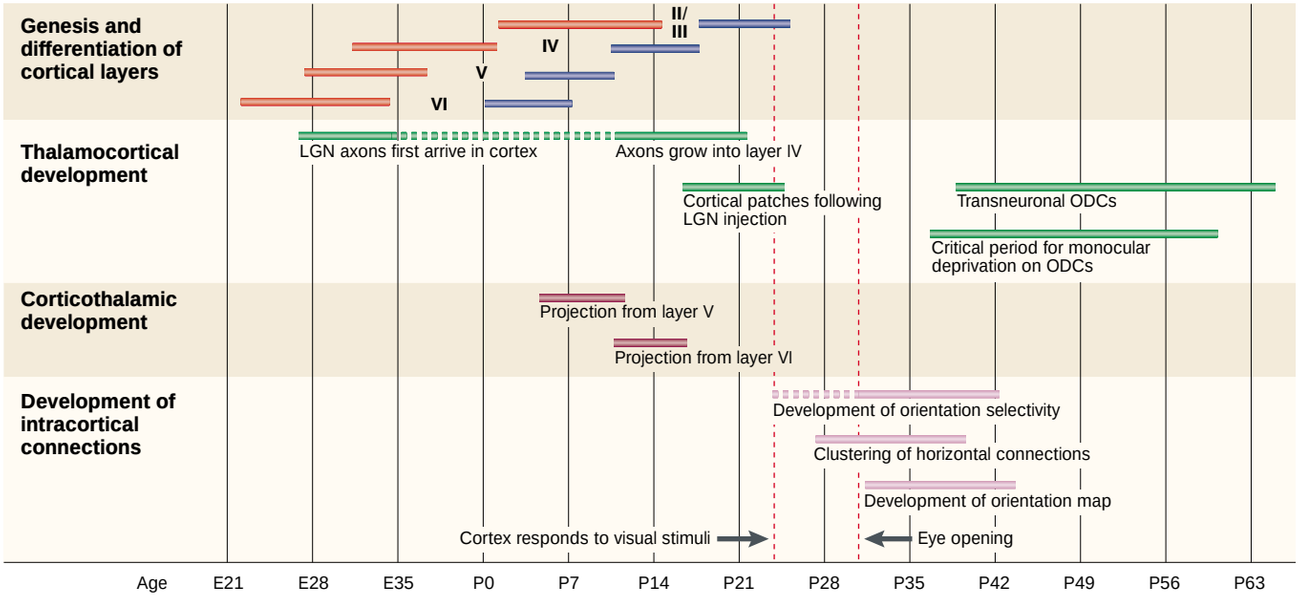


Figure 1 | **Timeline illustrating many of the main events during the development of the visual cortex and its connections with the thalamus in the ferret.** The period of neurogenesis in the cortical layers is shown in red, whereas the time of laminar differentiation is shown in blue. Neurogenesis of the adult layer VI commences on embryonic day (E) 22. Progressively more superficial layers are generated over the following five weeks, with genesis of layers II/III not completed until postnatal day (P) 14; the exception to this is layer I, which is generated both early and late (not shown)[163]. A similar progression of laminar differentiation follows as for neurogenesis[75,163]. The time course of thalamocortical development is shown in green. Axons from the dorsal lateral geniculate nucleus (LGN) first arrive below the developing visual cortex at E27 (REF. 164) and begin their ingrowth into layer IV at around P10, as soon as it differentiates from the cortical plate[165]. Cortical patches following injection of the LGN, which are believed to represent the initial formation of ocular dominance columns (ODCs), are visible from P16 (REF. 49), whereas ocular dominance columns visualized using transneuronally transported tracers from the eyes are not visible until approximately three weeks later[166,167]. The development of corticothalamic connections is shown in pink. The initial projection from the cortex to the thalamus, as shown by the *in vivo* transport of tracers, is formed by layer V neurons a few days after birth. The layer VI projections form about one week later[46]. The development of intracortical connections is shown in purple. A subset of neurons show orientation preference from the onset of visual responsiveness in the cortex, but the adult pattern is not attained until seven weeks after birth[100]. Clustered horizontal connections are present by around P27 (REF. 110), whereas an orientation map as shown by optical imaging can be seen by around P31 (REF. 112).

progressive restriction of cell fate in the precursor population: early progenitors are pluripotent and might give rise to neurons that come to reside in any cortical layer, whereas later progenitors give rise only to neurons of more superficial layers[6–9]. The laminar fate of a neuron is sealed in the late S or G2 phase of the final round of mitosis. Just before this, during the S phase of the final mitotic division, cell fate is more plastic and can be affected by environmental cues[10]. Other extrinsic signals present during the final cell cycle can also influence neuronal phenotype[11].

Events that occur at the ventricular zone can contribute in other ways to regional differences in cytoarchitecture. The dynamics of the cell cycle show regional variation[12,13]. Most notably, the germinal zone of primary visual cortex of the primate — a region with twice the neuronal density of other areas — has a notably higher rate of cell production that is associated with changes in the parameters of the cell cycle[12]. Thalamic afferents can exert a mitogenic effect on cortical progenitors by decreasing the length of the G1 phase and by facilitating the G1/S transition, resulting in an increase in the number of proliferative divisions[14]. The identity of the signal that mediates this mitogenic effect is not known; however, it is known to be a diffusible factor whose effect is blocked by antibodies to basic fibroblast growth factor (bFGF), indicating that bFGF signalling might be involved[14]. The influence of thalamic inputs on cortical development, therefore, starts during very early stages of development with the cell cycle and laminae formation.

Formation of cortical areas

Cortical determinants and thalamocortical matching. There is considerable evidence to suggest that at least the initial broad parcellation of cortex is regulated by molecular determinants that are intrinsic to the proliferative zone of the developing cortex and is, therefore, independent of thalamic influences[15]. For example, evidence from transplantation and co-culture studies indicate that the initial expression of region-specific markers or phenotypes[16–20] is probably not dependent on specific thalamic innervation. Similarly, factors that regulate later cortical connectivity seem to be determined by embryonic day (E)14 (REFS 21,22) in the rat, an age before the arrival of thalamic axons. Several genes, such as *Latexin*[23], *Tbr-1* (REF. 24), cadherins 6 (*Cad6*) and 11 (*Cad11*) (REF. 25), *COUP-TF1*, *CHL1*, *2m3* and *36m1* (REF. 26) are differentially expressed between cortical areas before thalamic afferents seem to have invaded the cortical plate. Similarly, the differential expression of several genes can occur normally in the absence of thalamocortical innervation; for instance, in mice lacking *Gbx2* (REF. 27) or *Mash1* (REF. 25).

Other evidence indicates that gradients of gene expression in the neuroepithelium of different cortical areas might regulate the initial arealization of the neocortex. For example, *Pax6* is usually expressed in a low-caudomedial–high-rostrolateral gradient[28,29]. In *Pax6* homozygous mutants, caudolateral areas are expanded and rostrolateral areas are contracted[30]. Conversely, *Emx2* is expressed in a low-rostrolateral–high-caudomedial gradient[31,32] and the mutants show shrinkage of caudomedial cortex and an expansion of rostrolateral cortex. These shifts are shown both by the staining patterns of molecular markers and, importantly, by the pattern of anatomical connectivity with the thalamus[30,33]. Thus, genes that control the initial arealization of the neocortex can also affect targeting of thalamocortical and corticothalamic axons.

The EphA receptor tyrosine kinases and their ligands also show differential gradients of expression in the cortex before thalamic innervation[34,35]. The subtypes of EPHRINS examined so far have been shown to regulate sizes of areas: deleting ephrin-A2 and ephrin-A5 affects the targeting of thalamocortical axons to neocortical regions *in vivo*, as lateral portions of the body map in somatosensory cortex are enlarged and distorted[36]. Matching of thalamic afferents with cortical gradients to produce specific areas is indicated by experiments that involve the early ablation of large portions of cortex in marsupials[37]. Here, afferents from all of the thalamic sensory relay nuclei still innervate cortex and form cortical areas that are in the appropriate regional relationship, although they are of reduced size and show some overlap.

In the transgenic mouse line H-2Z1, the lacZ reporter is expressed in layer IV neurons of the postnatal somatosensory cortex[17]. The expression of this marker is regionalized specifically to the somatosensory cortex from as early as E11.5 (REF. 20). However, postnatal thalamic innervation serves to alter and match the zone of expression with the zone of thalamic innervation[38]. Other work has shown that the expression of latexin, a carboxypeptidase A inhibitor that specifically marks a subset of neurons in the lateral cortex[23], can be temporally regulated by regional environmental cues[39]. So, whereas the molecular phenotype of a cortical region can appear early, the extent to which this phenotype is expressed can be affected by local environmental signals.

Thalamic and local influences. Whereas intrinsic markers might delineate broad areas of cortex at very early stages of development, thalamic afferents can subsequently influence the size and even the identity of specific areas. Transplants of extremely immature cortex (E12 in rats) can take on inputs and express molecules characteristic of the host region rather than the region of origin[16,40]. BARRELS — a characteristic of rodent somatosensory cortex — have been reported to develop in occipital cortex transplanted to the parietal region[41]. However, more recent work shows that occipital to parietal transplants at E16 do not develop barrels or substantial connections with the somatosensory thalamus, although they do form connections with the dorsal lateral geniculate nucleus (LGN)[21]. Work from the same group has shown that occipital to frontal transplants at E12 can form projections to the spinal cord. However, this capacity has been lost by E14 and tectal projections — a characteristic of the region of origin — are formed instead[22]. Interestingly, a similar age-dependent switch between E12 and E14 influences the cortico-cortical connections made by transplanted perirhinal cortex into the parietal region[42]. This indicates that there might be an early time window during which the input and output connections of a cortical area can be sculpted by thalamic and local areal signals to produce an area-specific phenotype. It is therefore likely that cortical areas arise by progressive specification of their region-specific phenotype from a multipotent phenotype.

Consistent with the role of thalamic influences on cortical differentiation, reduction of thalamic inputs by binocular enucleation alters cortical area fate by creating a hybrid visual cortex in place of area 17 (REFS 43,44). Similarly, early thalamic ablation leads to the development of a thinner cortex and of cortical areas that are reduced in size[45]. Together, the evidence presented above indicates that specification of cortical areas requires multiple cues that involve the regional and/or graded expression of molecules along with spatial and temporal signals regulated by thalamic afferents. The influence of thalamic inputs has been studied intensively in the formation of thalamocortical patterns and intracortical connections and is discussed next.

Formation of cortical networks

The cortex differentiates progressively into layers and, as layer IV appears in the cortical plate, thalamic innervation specifies the principal sensory areas (FIG. 2). Concurrently, descending projections from cortex innervate specific thalamic nuclei, primarily by the targeting of layer V axons to principal and/or association nuclei, followed by the development of layer VI projections to principal relay nuclei[46,47]. Thus, a thalamocortical loop is set up very early in development (FIG. 2), and the initial specification of cortical areas is fundamentally a specification of unique feedforward and feedback connections between thalamus and cortex. The development of intracortical circuitry (indicated in FIG. 2 as horizontal connections in layer II/III) follows thalamic innervation, although some evidence indicates that cortical networks might develop early and be matched to peripheral input. Considerable recent evidence, primarily from the visual cortex, points to a combination of intrinsic and extrinsic factors as being responsible for the formation and maintenance of specific thalamocortical and intracortical connections. In particular, the importance and role of electrical activity has been clarified, and the sum of evidence indicates a progressive role for activity. Its presence is sufficient for early thalamocortical innervation and its specific spatiotemporal pattern is necessary for instructing late intracortical networks.

Thalamocortical patterning. Ocular dominance columns — regions within layer IV of the visual cortex that receive input exclusively from one eye through the LGN — are set up during very early development. In

EPHRINS AND EPH RECEPTORS
Two families of molecules that mediate cell-contact-dependent signalling, and are primarily involved in the generation and maintenance of patterns of cellular organization. They accomplish this goal by the control of repulsion at a boundary or gradient, or by upregulating cell adhesion.

SOMATOSENSORY BARRELS
Discrete functional units present in layer IV of the rat cortex, which process tactile inputs derived from a single whisker.

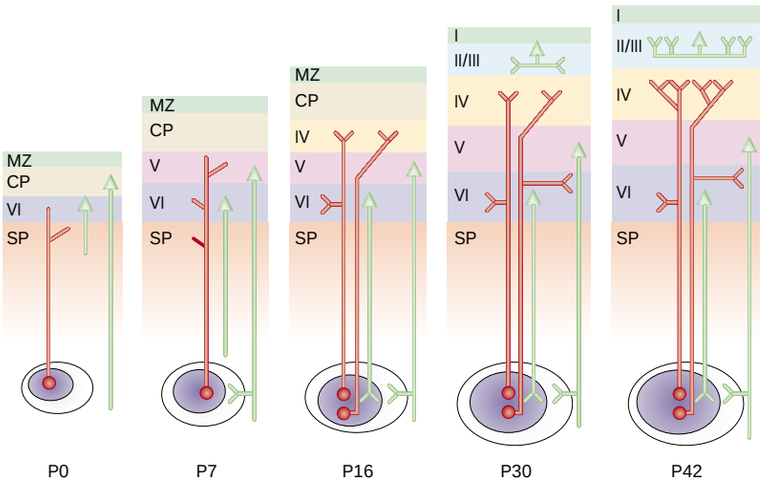


Figure 2 | **The development of the ferret's visual cortex and its interconnections with the thalamus.** By the day of birth (P0), axons from the dorsal lateral geniculate nucleus (LGN) have arrived below the developing visual cortex[164] and have begun to probe the base of the cortical plate (CP)[165]. At this stage the CP consists of an undifferentiated region containing predominantly the neurons that will form layer V, and a differentiated region below which is the developing layer VI (REFS 75,163). Corticothalamic projections have not yet formed[46]. By postnatal day (P) 7, layer V is visible below the undifferentiated CP, and the initial corticothalamic projection has been formed by collateral branches of layer V neurons that have grown past the thalamus. By P16, layer IV has differentiated and thalamic axons have grown in and established synaptic contacts[165] that are segregated into patches reminiscent of ocular dominance columns[49]. The layer VI projection to the thalamus has also formed. By P30, layer II/III has differentiated and horizontal connections have begun to form[110]. These connections show a more mature clustered pattern by P42 (MZ, marginal zone; SP, subplate).

primates they are present at birth, suggesting that visual experience is not required for their formation[48]. Recent work indicates that they might also be set up before eye opening in ferrets[49] and in cats[50], soon after geniculocortical axons innervate layer IV. Surprisingly, they might not even require the presence of the eyes for their initial establishment[51]. Monocular enucleation does not degrade these early columns immediately[49], and binocular lid suture does not reduce their development in cats for the first three weeks[52]. One possibility is that ocular dominance columns are set up initially by the molecular matching of inputs from different layers of the LGN (each layer representing a given eye) with appropriate target regions in V1.

An alternative view is that ocular dominance columns are set up by activity-based developmental rules. Thus, correlated inputs from one eye and uncorrelated inputs from the other eye can lead to cortical stripes that resemble ocular dominance columns[53]. The application of a HEBBIAN rule for strengthening and weakening connections, together with local excitation and long-range inhibition in the cortex in a manner formally similar to Turing's formulation[54] can indeed account for the formation of the columns. Correlated inputs in the form of spontaneous waves of activity exist in the retinae before eye opening[55,56]. This activity can drive cells in the LGN to fire bursts of action potentials *in vitro*[57] and recent work in ferrets has found that this is also the case *in vivo*[58]. Here it has been shown that the firing of neurons within a given eye-specific layer of the LGN is well correlated, whereas correlation between eye-specific layers is much less evident. Interestingly, removal of inputs from the eyes while leaving corticothalamic inputs intact sustains correlated bursts. The pattern of electrical activity transferred to the cortex, therefore, seems to be strongly regulated by interactions between the thalamus and cortex, and activity in the thalamocortical loop might be sufficient for eye-specific patterning. However, two issues remain unanswered. First, the contralateral eye drives LGN activity far more strongly than the ipsilateral eye[58], posing a problem for purely Hebbian models of ocular dominance development. Second, the LGN activity has been examined during the fourth postnatal week whereas ocular dominance columns appear to be already present by the third week. So experiments at earlier ages are required. At the same time, significant support for the hypothesis that ocular dominance columns can arise by activity-dependent sorting of eye-specific inputs comes from the finding that eye-specific stripes form in the optic tectum of 'three-eyed' frogs. In frogs, the optic tectum usually only receives input from the contralateral eye so no stripes are present normally in the tectum. However, implantation of a third eye forces one tectum to receive input from two eyes and the terminals segregate into eye-specific bands[59]. Exposure of the tectum in these animals to NMDA (*N*-methyl-D-aspartate) receptor antagonists results in desegregation of the eye-specific stripes[60], further showing the importance of activity-dependent mechanisms in this process.

Whereas the role of electrical activity in instructing the formation of ocular dominance columns in V1 is not totally clear, there is convincing evidence that electrical activity is required to maintain them. Just a few days of monocular lid suture leads to shrinkage of columns from the closed eye[61]. Activity within the target cells of the cortex itself regulates the direction of this plastic change. Blocking cortical activity by infusion of the GABA (γ-aminobutyric acid) receptor agonist muscimol[62] results in dominance of cortex by the closed eye, along with shrinkage of columns from the open eye[63,64]. In principle, such evidence is in agreement with a Hebbian model of strengthening presynaptic inputs that are correlated with postsynaptic activity and weakening of non-correlated inputs. LONG-TERM POTENTIATION (LTP) and LONG-TERM DEPRESSION (LTD) are postulated to be the cellular correlates of plasticity in the visual cortex[65,66]. In this model, NMDA receptors act as detectors of correlated neural activity. Blockade of NMDA receptors prevents plasticity commonly associated with monocular lid suture[67]. NMDA-receptor blockade might also reduce cortical activity nonspecifically[68]; however, infusing antisense DNA for NMDA receptor subunit mRNA into V1 preserves cortical responses while blocking NMDA-receptor function, and also prevents ocular dominance plasticity[69].

Activity-dependent plasticity might reflect competition for a trophic factor that is produced by the target cell and is only available in limited amounts to active inputs. Current evidence indicates that the neurotrophins might be such a factor. Decreased retinal activity results in a

HEBB'S RULE
"When the axon of cell A excites cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells so that A's efficiency as one of the cells firing B is increased."

LONG-TERM POTENTIATION AND DEPRESSION
Long-lasting activity-dependent changes in the efficacy of synaptic transmission.

decrease in the expression of brain-derived neurotrophic factor (BDNF)[70,71] and blockade of BDNF receptors prevents ocular dominance column formation[72]. Neurotrophins are also known to have laminae-specific effects on dendritic remodelling[73]. Intriguingly, the infusion of BDNF into the visual cortex of monocularly deprived kittens actually results in a shift in ocular dominance towards the closed eye[74], similar to the effect of increasing cortical inhibition mentioned above. There is accumulating evidence to indicate a link between BDNF, the maturation of inhibition and the critical period for ocular dominance plasticity (FIG. 1). The maturation of inhibition lags behind excitation and, in ferrets, there is a late peak in GABA neuron density[75] that correlates with the end of the critical period for monocular deprivation[76]. Rearing animals in complete darkness delays both the end of the critical period and the maturation of GABA-mediated inhibition[77,78]. BDNF has been shown to promote GABA release from cortical synaptosomes[79]. In transgenic mice that overexpress BDNF, there is an accelerated rate of maturation of the GABA system; this is accompanied by an earlier than normal end to the critical period[80,81]. Conversely, in transgenic mice with reduced GABA function there is no endogenous critical period[82]. However, a critical period can be induced at any age by artificially enhancing GABA-mediated inhibition[77]. Other work has suggested that a switch in NMDA receptor subunits from NR2B to NR2A might also be involved[83]. It is very likely that several of these factors work in concert to regulate ocular dominance plasticity (FIG. 1).

In the somatosensory cortex of the rodent, there is also an early critical period during which whisker removal prevents the formation of cortical barrels[84]. As in the visual system, there is a correlation between this susceptibility to peripheral influences and the ability to induce LTP and LTD in the thalamocortical projection[85,86]. There is also a developmental increase in the proportion of cells expressing the NR2A receptor subunit during this period[87]. Interestingly, whereas earlier work had suggested that activity might have little role in barrel formation — barrels form even when peripheral[88] or cortical activity is blocked[89] — recent work with transgenic mice lacking cortical NMDA receptors indicates that NMDA receptors are indeed crucial for the formation of barrels[90].

NMDA receptors, at least in the cortex of adult cats and kittens *in vivo*, are often engaged at resting membrane potentials and contribute significantly to cortical responses to natural stimuli[68,91,92]. It is therefore possible that the crucial role of NMDA receptors in the early patterning of thalamocortical inputs in both the visual and somatosensory cortex is primarily to flux calcium rather than to detect correlated activity. If so, activity might be permissive for the development of thalamocortical patterns, including ocular dominance columns in V1 and barrels in somatosensory cortex. That is, the presence of activity and of activity-dependent factors (such as neurotrophins) are important for the maintenance, and probably the initial development, of these patterns, but the specific correlations of inputs might be less important.

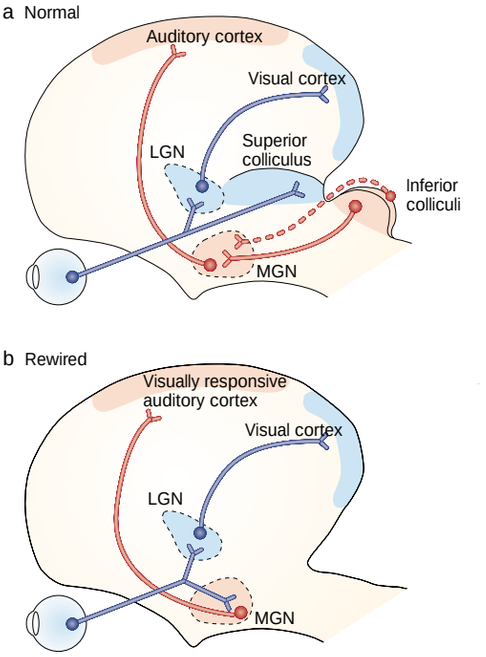
It has been suggested that ocular-dominance development and plasticity are separate processes[49], so that the critical period for plasticity follows the early establishment of ocular dominance columns (FIG. 1). Validating this theory requires proof that the early manipulation of activity has no effect on ocular dominance development. One study that involved very early monocular deprivation indeed showed no effect on eye-specific driving of cortical responses through the first three weeks, followed by a reduction in driving by the closed eye[52]. These data are also compatible with the idea that the development and plasticity of ocular dominance columns are parts of the same process. Activity in the thalamocortical loop allows the initial development of ocular dominance columns, whereas visual inputs are able to provide sufficient drive later[50] and bring on the critical period for plasticity.

Intracortical connections. ORIENTATION SELECTIVITY is created in V1 by aligned thalamic inputs[93] whose activity is amplified by local intracortical connections[94,95]. Orientation selectivity is present in V1 of primates at birth[96], and to a degree in cats and ferrets at or before the time of natural eye opening (FIG. 1), although selectivity increases with visual experience[97–100]. Short-term binocular deprivation impairs, but does not completely prevent, the maturation of orientation-selective responses[100–103], whereas prolonged deprivation leads to a progressive deterioration of specific receptive-field properties[102–104].

Orientation-selective cells in V1 are linked by horizontal intracortical connections in the superficial layers[105] to form an orientation map[106]. The adult pattern of clustered horizontal connections is present at birth in primates[107]. In cats and ferrets, crude clusters appear just before eye opening and are refined after the onset of vision[108–110]; binocular deprivation prevents this refinement[111]. The orientation map, revealed by optical imaging of intrinsic signals, develops in parallel with the development of orientation selectivity in single cells, starting with a map that shows lower signal strength but well-developed size, location and periodicity of orientation domains that remain remarkably constant as development proceeds[112]. Short-term binocular suture does not alter the normal layout of orientation maps[52,113]; however, long-term binocular suture induces a progressive deterioration of the map[52]. In cat area 18 or V2, one week of monocular lid suture after orientation maps have already formed disrupts the map from the closed eye; reverse lid suture restores the map precisely[114]. In addition, matching orientation maps for the two eyes develop even in cats raised under a reverse-suture paradigm from before the natural time of eye opening, so that the two eyes never had common visual experience[115]. Together, these studies indicate that, although visual experience is necessary for orientation selectivity and maps to fully mature, the emergence of orientation-selective responses in single cells and the overall layout of the orientation map does not require patterned vision. At the same time, infusion of the sodium channel blocker tetrodotoxin (TTX) into

ORIENTATION SELECTIVITY
Property of visual cortex neurons that allows for the detection of bars and edges within visual images and the encoding of their orientations. As the cortex is organized in columns, neurons that belong to the same column share the same orientation tuning.

Box 1 | Redirecting afferent axons



Schneider[152] first showed that neonatal lesions of specific subcortical structures in hamsters could cause retinal axons to innervate targets that they do not normally innervate. Since then, cross-modal rewiring has been obtained in several different preparations and between different sensory modalities[153–157]. Sur *et al.*[158] induced retinal axons to innervate the auditory thalamus in the ferret, a carnivore that has a highly organized visual pathway and is born at a very early stage in development, so that cross-modal plasticity can be induced by neonatal (rather than *in utero*) surgery. Furthermore, the routing of retinal projections to the auditory pathway can be induced extremely early in development, allowing one to probe the role of patterned activity in the establishment (and not simply maintenance) of response features and cortical circuitry.

In normal ferrets (**a**), the retina projects predominantly to the lateral geniculate nucleus (LGN) and superior colliculus (blue pathway). The LGN projects to the primary visual cortex. The medial geniculate nucleus (MGN) receives most of its subcortical afferents from the ipsilateral inferior colliculus (red pathway), although afferent projections also arise from the contralateral inferior colliculus (red dashed line) as well as from other ipsi- and contralateral brainstem nuclei (not shown). The MGN projects to the primary auditory cortex.

Extensive neonatal deafferentation of the MGN (**b**) induces retinal axons to innervate the MGN[136,159]. This lesion is accomplished by unilaterally destroying the brachium of the inferior colliculus, which conveys ipsilateral inputs from the inferior colliculus to the MGN, along with a lesion of the superior colliculus down to the deep layers, which carries inputs from the contralateral inferior colliculus. Alternatively, the same effect can be obtained by lesioning the inferior colliculus bilaterally. There is a positive correlation between the degree of deafferentation and the extent of rewiring. However, ablation of normal visual targets is neither sufficient nor necessary to induce rewiring. In addition to deafferentation, the factors that influence the ability of retinal axons to invade a novel target include the expression of repulsive membrane-bound molecules such as the ephrins[160] and possibly attractant molecules or diffusible factors.

The novel retino-MGN projection arises from most, if not all, RETINAL GANGLION CELL TYPES, including cells with small somata and fine axons[139,161] and cells with the largest axon calibre normally encountered in the optic tract[159]. Electrophysiological recordings indicate that the novel projection is functional, as cells in the MGN of adult 'rewired' ferrets are visually responsive, as are cells in the main cortical target of the MGN — the primary auditory cortex or A1 (REF. 162). Activity in visual afferents has a very different spatial and temporal structure than activity in auditory afferents. So, visual input is relayed from the MGN to auditory cortex via thalamocortical projections whose physical identity is unchanged but that provide spatiotemporal patterns of electrical activity to auditory cortex that are very different from normal.

V1 reduces both orientation tuning of single cells[100] and clustering of horizontal connections[110]. Thus, spontaneous activity in cortex or in the thalamocortical loop is important for the initial establishment of local and long-range intracortical connections.

The role of patterned electrical activity

Most experiments on the role of activity in the visual pathway have involved reductions in activity — for example, by lid suture or by intraocular injection of TTX. These studies have therefore largely examined the effect of manipulating the amount of activity on cortical networks. Furthermore, it is now clear that in many experiments the manipulation was initiated after ocular dominance or orientation columns had already formed. Therefore, these studies examined the effect of the manipulation on the maintenance of columns rather than on their initial establishment. Few experiments have examined the influence of the pattern of activity on cortical network development and maintenance. Such manipulations include artificial strabismus, optic nerve stimulation, specific rearing paradigms such as stripe-rearing, and routing of visual projections to the auditory pathway.

Strabismus refers to misalignment of the two eyes' optical axes, whereby the images on the two retinae cannot be brought into register. As a result, activity from corresponding retinal loci in the two eyes are no longer temporally correlated, although the total amount of activity that reaches the cortex via each eye is equal and probably similar to that in normal animals. Artificially induced strabismus causes neurons in V1 to become almost exclusively monocular[116–118]. Ocular-dominance columns are more sharply delineated[119] and have altered spacing[120] as compared with normal animals. Long-range horizontal connections within the superficial layers of V1 are also affected. Whereas in normal cats these connections cluster to link regions with similar orientation preference but do not align with ocular dominance columns[105], the connections come to link columns with similar eye dominance[121] and orientation preference in strabismic cats[122]. Thus, correlations in input activity are used to sharpen and organize ocular dominance columns[123], and to shape intrinsic horizontal connections.

Evidence that the temporal pattern of activity has a role in ocular-dominance and orientation development comes from experiments in which the optic nerve is electrically stimulated. Bilateral blockade of retinal activity with TTX in kittens combined with asynchronous stimulation of the two optic nerves causes cortical cells to become predominantly monocular, whereas synchronous stimulation increases the proportion of binocular cells[124]. Stimulation of an optic nerve in ferrets before and just after the time of natural eye opening[125] disrupts

RETINAL GANGLION CELLS
The three main classes of retinal ganglion cells in carnivores are: X cells, which have the smallest receptive fields; Y cells, which have larger receptive fields; and W cells, which have heterogeneous properties.

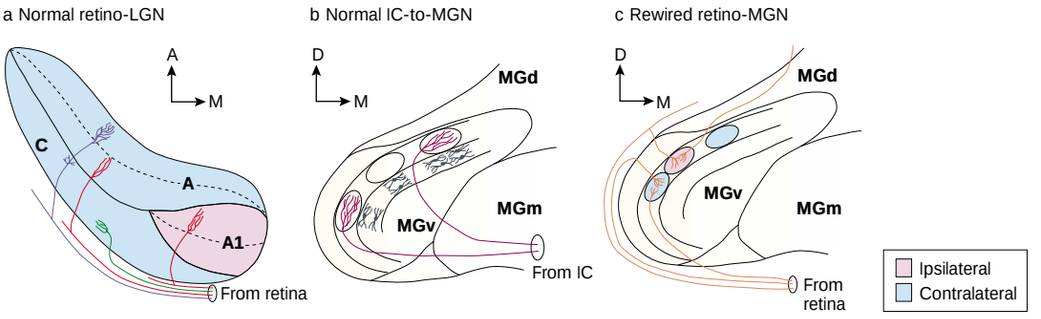


Figure 3 | **Terminal patterns of subcortical afferents to the dorsal lateral geniculate nucleus and the medial geniculate nucleus in normal ferrets, and to the medial geniculate nucleus in rewired ferrets. a** | Retina–LGN (lateral geniculate nucleus) projections in normal ferrets. The LGN is shown in the horizontal plane. A, A1 and C are eye-specific dorsal LGN layers. Dashed lines within the A layers delineate the border between the on and off sublayers. Three main types of retinogeniculate axon are shown: X axons (red) project to the A layers, Y axons (blue) to layers A and C, and W axons (green) to the C layers only. **b** | The projections from the inferior colliculus (IC) to the ventral division of the medial geniculate nucleus (MGv). The MGN is shown in the coronal plane. Afferents from the IC form terminal clusters (ovals) that align within fibrodendritic lamellae. The lamellar pattern in MGv is due to the ordered alignment of its relay neurons. **c** | Retinal projections to the MGv in rewired ferrets. Retinal axons form adjacent but non-overlapping eye-specific terminal clusters (ovals) that align along the MGv lamellae. (MGd, MGm: dorsal and medial divisions of the MGN; A, anterior; D, dorsal; M, medial.) (Adapted from REF. 136.)

the development of orientation and direction selectivity but does not alter orientation maps. Patterned neural activity is therefore required for single cells to achieve their normal adult receptive field selectivity. It is possible that synchronizing activity in one optic nerve did not alter the layout of orientation maps because the stimulation was too intermittent and the protocol was initiated relatively late in development, when some orientation selective responses are already present and are probably already organized in a columnar fashion[126].

Rearing kittens in a visual environment consisting of alternating black and white stripes restricts pattern vision, and seems to shift the orientation preference of cortical cells towards the experienced orientation[127] (but see also REF. 128). Although a shift could be caused by a passive loss of responses to non-experienced orientations[129], there is an expansion of cortical columns devoted to the experienced orientation[130], indicating an instructive effect of patterned visual experience on orientation selectivity and the orientation map.

Rewiring cortex. A different paradigm for investigating the role of patterned afferent activity in the development of cortical circuitry and function is to experimentally redirect afferents that carry information about one sensory modality to central targets and pathways that normally process a different sensory modality (BOX 1).

Rewired ferrets, with retinal projections induced to innervate a novel target — the MGN — provide a unique paradigm for examining how a sensory cortical area develops under the influence of novel spatiotemporal activity patterns. In normal ferrets, retinal axons segregate into parallel eye-specific layers in their normal target — the LGN[131]. Moreover, axons from on-centre and off-centre retinal ganglion cells from each eye further segregate into on and off sublayers within each eye-specific layer[132,133] (FIG. 3a). By contrast, within the ventral division of the normal MGN (MGv), afferents from the inferior colliculus form terminal clusters aligned within fibrodendritic lamellae that each map a narrow range of sound frequencies[134,135] (FIG. 3b). In the MGN of rewired ferrets, retinal axons from the two eyes initially overlap but segregate by the third postnatal week into small eye-specific clusters that are aligned within the MGv lamellae[136] (FIG. 3c). Thus, the segregation of retinal axons into limited eye-specific domains is driven by spontaneous activity in retinal afferents, whereas the size and general layout of the domains is determined by the cellular configuration of the target.

Retinal ganglion cell axons form focal terminal arbours within the MGN in rewired ferrets[137], leading to an orderly retinotopic map[138]. Receptive fields of visually responsive cells within the MGN are monocular and unorientated[139], similar to their retinal ganglion cell input. In rewired animals, the lamination and cell density of A1 appears indistinguishable from normal. Similarly, the structure of thalamocortical arbours within A1 appears not to be affected and is similar to normal MGN axon arbours within A1, but different from LGN axon arbours within V1 (FIG. 4). Thus, patterned activity has little influence on these aspects of cortex even when altered at a very early stage in development.

However, the map of visual space in rewired A1, the generation of orientation- and direction-selective responses, and the map of orientation-selective cells all show the role of patterned activity in shaping cortical networks. An orderly two-dimensional retinotopic map develops in A1 of rewired ferrets[140], an area of cortex that normally maps a one-dimensional surface, the cochlea (FIG. 4). In normal animals, axons of LGN cells are organized anatomically within V1 to make a visual field map (FIG. 4a, b), whereas MGN projections to A1 are anatomically narrow along the variable frequency axis but highly divergent and convergent along the isofrequency axis to make a sound frequency map[141,142] (FIG. 4c). Such MGN–A1 projection patterns are not altered in rewired ferrets[143,144] (FIG. 4d). The generation of a retinotopic map in rewired A1, despite widely dispersed and overlapping

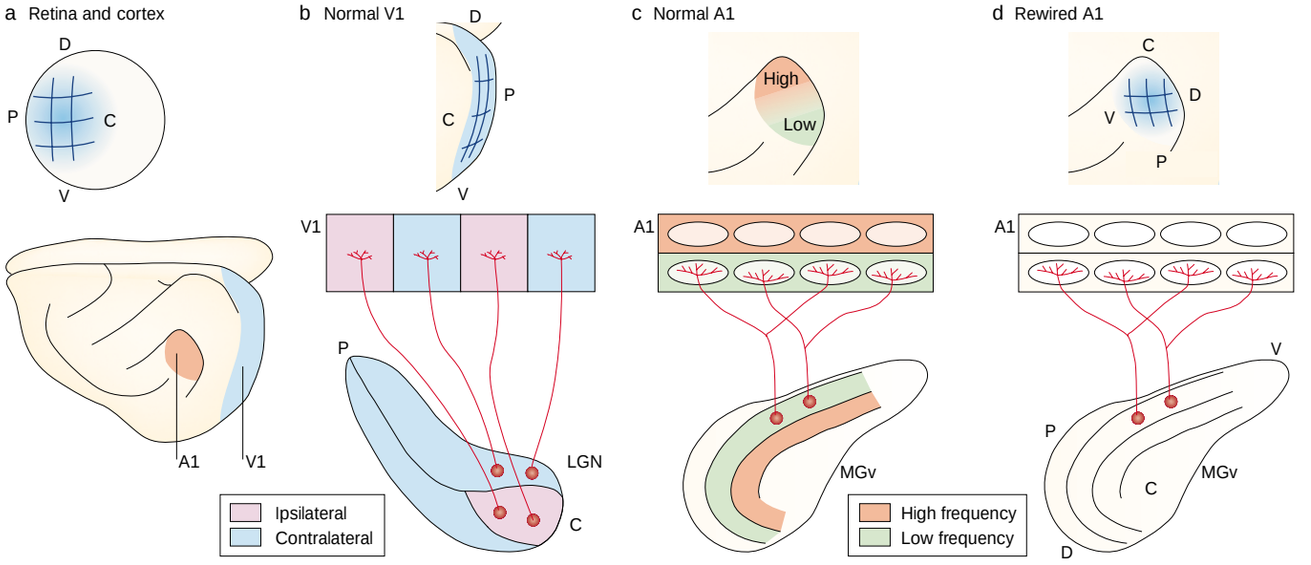


Figure 4 | **Cortical maps and thalamocortical projections in normal and rewired ferrets. a** | Top: Schematic of the right retina, with a grid showing the representation of the right visual field in nasal retina. Retinal locations are marked as C, central; P, peripheral; D, dorsal; V, ventral. Bottom: The left cortex, showing the locations of V1 and A1. **b** | Top: The retinotopic map in normal V1. Note that cortex marked D maps dorsal retinal locations or ventral visual fields, whereas cortex marked V maps ventral retinal locations or dorsal visual fields. Bottom: Schematic diagram of projections from the dorsal lateral geniculate nucleus (LGN) to V1. The LGN is shown in horizontal section (compare with FIG. 3a), so that central retinal locations map medially whereas peripheral locations map laterally; ventral/dorsal retinal locations project to superior/inferior regions of LGN that extend above and below the plane of section shown here. Thalamic axons arising from eye-specific LGN layers terminate in the corresponding ocular dominance column in layer IV of V1. **c** | Top: The representation of the cochlea in normal A1. Low sound frequencies are represented laterally, whereas high sound frequencies are represented medially in cortex. Bottom: Projections from the ventral division of the medial geniculate nucleus (MGv) to A1 in normal ferrets. The MGv is shown in coronal section (compare with FIG. 3b). Thalamic axons arising from a small locus in MGv (see FIG. 3b) form several terminal patches (ovals) that align along anteroposteriorly orientated isofrequency slabs in A1. Thalamocortical axons from individual MGv lamellae project to slabs that represent the same frequency in A1, and different lamellae project to different isofrequency slabs. **d** | Top: The retinotopic map in rewired A1 (from REF. 140). Bottom: Projections from the MGN to A1 in rewired ferrets. Retinotopic projections to the MGv are as shown. The thalamocortical projection pattern in these animals appears similar to that seen in normal animals (**b**), and individual axons show the same degree of convergence and divergence[168]. Thus, a two-dimensional retinotopic map in A1 would require selection of a subset of synapses along the anteroposterior dimension of A1 in order to generate restricted receptive fields and topographic progression along the dorsoventral axis of the retina.

thalamocortical projections, indicates that well-localized receptive fields and their orderly progression are created by correlation-based mechanisms that operate intracortically to select and strengthen a specific subset of synapses from an anatomically available broader set.

Visual cells in rewired A1 have orientation-tuning, direction-tuning and velocity-tuning indices that are quantitatively indistinguishable from V1 cells[145], suggesting that similar mechanisms operate in the generation of receptive field properties in the two cortices. Optical imaging of intrinsic signals in A1 of rewired ferrets reveals that orientation-tuned neurons are organized into an orientation map[146] (FIG. 5b). Similar to the map in V1 (FIG. 5a), the map in rewired A1 shows a systematic distribution of orientation domains around singularities in a pinwheel-like fashion. In addition, the strength of orientation tuning across the imaged regions is nearly identical in the two cortices (FIG. 5c) and resembles the orientation tuning of single cells. However, there are two differences between the orientation maps between rewired A1 and V1: orientation domains within V1 are smaller in size and show a highly regular, spatially periodic organization[147], whereas the domains in rewired A1 are larger on average and are organized less periodically than in V1. Sharp orientation tuning coupled with a less orderly map in rewired A1 indicate that these two cortical features can develop independently of each other (compare with REF. 125). The differences in the layout of the orientation maps in V1 and rewired A1 reflect differences in the underlying organization of superficial layer long-range horizontal connections in these two cortices[146,148]. In V1, horizontal connections are spatially periodic and ANISOTROPIC, extending along a mediolateral axis parallel to the V1/V2 border (FIG. 5d). By contrast, horizontal connections in normal A1 are more band-like in organization, show little spatial periodicity and have an anisotropic distribution along the isofrequency (anteroposterior) axis of cortex (FIG. 5e). Horizontal connections in rewired A1 (FIG. 5f) resemble connections in V1 more than those in normal A1: the connections in rewired A1 form much smaller and more regular patches than in normal A1, although the patches are larger in size than in V1. So, horizontal connections within cortex are shaped significantly by input activity.

Rewired ferrets also provide a unique opportunity for examining whether the behavioural role of a cortical area is set by intrinsic determinants or by the pattern of afferent activity during development. If the perceptual modality of a cortical area were determined intrinsically and independent of afferents, then ferrets would perceive visual activation of the rewired auditory cortex as

ANISOTROPIC
Medium in which physical properties have different values when measured along axes orientated in different directions.

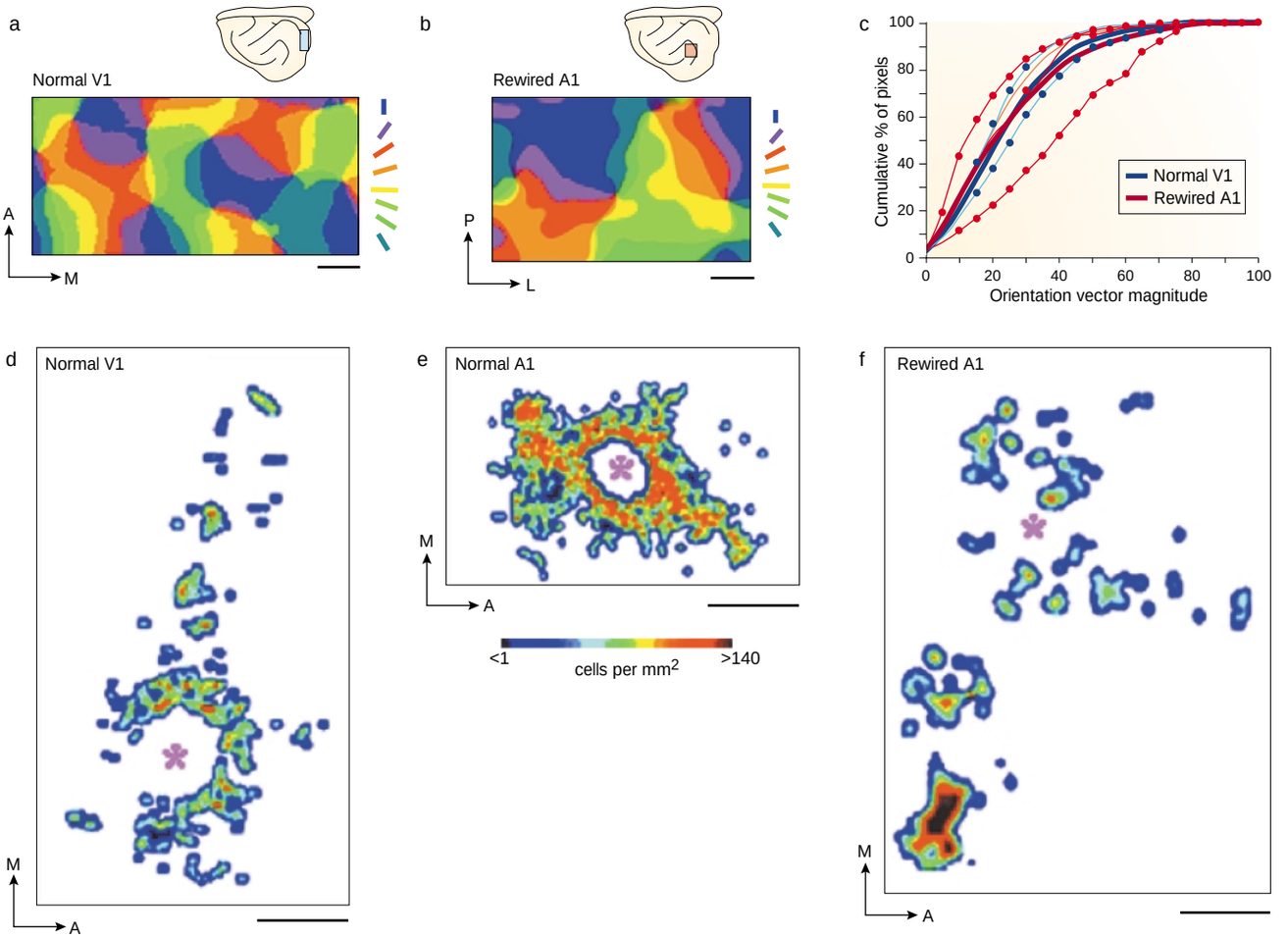


Figure 5 | **Orientation maps and horizontal connections in V1 of normal ferrets and in A1 of rewired ferrets. a** | Orientation map in normal V1. Top: Lateral view of the ferret brain showing the location of the imaged region (blue). Optical imaging of intrinsic signals[133] was carried out by illuminating the cortex with light of 610 nm and obtaining images of the cortex while stimuli (gratings of different orientations) were shown to the animal. Neurons that respond selectively to a particular grating orientation cluster in iso-orientation domains, and the use of oxygen in these domains causes them to appear as dark spots in the single orientation images[106]. Images obtained in response to a range of equally spaced stimulus orientations (typically eight) are used to compute a vector average at each pixel of the responses and yield a composite map of the angle of orientation preference. Bottom: The orientation map in V1. Colour bar: key used for representing different orientations. Scale bar: 0.5 mm. **b** | Orientation map in rewired A1. Top: Location of the imaged region (red). Bottom: Orientation map obtained in similar fashion as the map shown in (**a**). Single orientation domains are organized quasi-periodically, and different domains are arranged in pinwheel-like fashion around singularities. Scale bar: 0.5 mm. **c** | Cumulative distributions of the magnitude of the orientation vector of pixels in normal V1 (blue; *n*= 3) and rewired A1 (red; *n*= 4) maps. Light thin traces indicate individual cases, thick traces indicate means. The orientation vector magnitude represents the strength of orientation tuning at each pixel in the cortex and is a measure of the degree of orientation selectivity. **d–f** | Distribution of retrogradely labelled cells in the superficial layers of cortex following injection of tracer in normal V1, normal A1 and rewired A1. Asterisks indicate injection site centres. Colour bar underneath **e** shows cell density, ranging from <1 cell per mm^2 to >140 cells per mm^2, and applies to **d** and **f** as well. Scale bars: 500 µm. (A, anterior; L, lateral; M, medial; P, posterior.) (Adapted with permission from REF. 146 © (2000) Macmillan Magazines Ltd.)

an auditory stimulus. Conversely, if the modality were determined by afferent activity, visual inputs would be perceived as such. Ferrets were rewired in one hemisphere and were trained in a forced-choice task to associate one reward location with a visual stimulus presented to their normal hemisphere and a different location with an auditory stimulus[149]. Subsequently, visual stimuli were presented only to the rewired hemisphere under three successive conditions. With both the normal retina–LGN and rewired retina– MGN pathways intact, animals associated visual stimuli with a response at the visual reward location. With the visual thalamus, including the LGN and adjacent thalamic nuclei, lesioned but the retina–MGN pathway intact, animals still associated visual stimuli with the visual (and not the auditory) reward location. Finally, animals with the rewired auditory cortex also lesioned were functionally blind in the rewired hemisphere and responded at chance levels at either location. Several control experiments supported the conclusion that rewired ferrets interpret visual stimuli that activate the rewired projection as visual rather than as auditory. Similarly, rewired hamsters are able to use ectopic pathways from the retina through the thalamus to mediate visual discriminations[150]. Rewired ferrets can distinguish different spatial frequencies of visual gratings with the rewired projec-

tion, although the acuity of the projection is less than that of the normal visual pathway[149].

Everything the cortex knows about the external world is contained in the spatiotemporal activity of its afferents. These experiments show that the perceptual modality of a cortical area can be instructed by the pattern of activity in thalamocortical projections without altering the connections themselves[151]. One way in which the rewired auditory cortex could mediate a visual response is through the development of new connections between the rewired A1 and subcortical brain regions. It is also possible that all 'auditory' pathways central to the thalamus in the rewired hemisphere are made 'visual', including the cortex and downstream structures, with a concomitant respecification of their perceptual identity.

Conclusions

Experiments in ferrets with visual projections directed to the auditory pathway have addressed whether the pattern of activity has an instructive role in the establishment of cortical networks. Many experiments on the influence of activity on cortical development have involved reductions in activity (by lid suture or activity blockade) and hence cannot address the issue of instruction by patterned activity. Other studies have used manipulations that start late in development, after properties such as orientation selectivity or even ocular dominance are already in place, and hence address the role of activity in the maintenance of networks rather than in their establishment.

Rewired ferrets and 'three-eyed' frogs demonstrate that correlated activity can create eye-specific stripes, orientation selectivity and orientation maps. That is, each of these features of V1 can, in principle, be constructed by activity-dependent mechanisms alone. In the normal brain, of course, activity acts alongside intrinsic cues that guide development.

Cortical development involves shaping the fate of the cortical epithelium into discrete cortical areas with specific inputs, outputs and networks. This involves a continuous interplay of intrinsic and extrinsic factors at all stages of development — at the ventricular zone during neurogenesis, in the cortical plate during parcellation of cortical areas and within the cortex during formation and maintenance of cortical networks. Specifically, we suggest that there are continual interactions between the thalamus and cortex in shaping these features. The nature of extrinsic signals would vary with developmental time. These signals probably include diffusible factors in the ventricular zone that influence the formation of layers, trophic or permissive electrical signals in early area formation, and instructive electrical signals in late network development that persist into adulthood as substrates for learning and memory.

Links

DATABASE LINKS bFGF | *Latexin* | *Tbr-1* | *Cad6* | *Cad11* | *COUP-TF1* | *CHL1* | *Gbx2* | *Mash1* | *Pax6* | *Emx2* | ephrin-A2 | ephrin-A5 | BDNF | NR2B | NR2A

ENCYCLOPEDIA OF LIFE SCIENCES Cerebral cortex development | Cortex plasticity: use-dependent remodelling

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