

possible to collect many different types of response profile from the same cortical regions. This is what makes it possible to calculate maps of orientation preference, for example, where responses to many different orientations need to be compared. It also is what enables comparisons between ocular dominance and orientation maps from the same regions, allowing them to be related precisely for the first time. By comparing these with maps of retinotopic representation from the same region (see Figs. 2e, 2f) it is possible to obtain unprecedented insights into cortical organizations.

See also: Electroencephalography: Basic Principles and Applications; Functional Brain Imaging; Occipital Lobe (Visual Cortex): Functional Aspects; Visual Perception, Neural Basis of

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G. Blasdel

Cortical Development: Transplantation and Rewiring Studies

The mammalian neocortex, a folded sheet that in humans contains over 10 billion neurons, is the seat of the highest sensory, motor, and cognitive abilities. Cortical development involves the formation of many discrete areas that process different kinds of information uniquely. Individual areas are characterized by specific sets of inputs, processing networks, and outputs. The development of these features involves factors that are intrinsic to the tissue or are regulated by extrinsic or environmental influences. This article examines the relative roles of such influences, employing in particular evidence from experiments that have probed developmental mechanisms by transplanting cortical regions or by rewiring inputs to a part of the cortex.

1. Development of the Cortex

The principal method for studying mechanisms of development is to manipulate developmental processes. In general, it is not possible to separate intrinsic cleanly from extrinsic aspects of developmental programs of an organism: no gene acts independently of an environment, and the environment always acts on a scaffold. A classic paradigm in developmental biology for clarifying the role of the local environment in determining the features of a tissue is to translocate the tissue to a novel environment.

Transplanting one part of the mammalian cortex to another at different stages of development has been a valuable tool for determining whether or not unique features of a cortical area derive from intrinsic properties of the cortex, or are induced by new inputs in the host environment. A powerful recent method that complements transplantation studies is to route sensory inputs that normally drive one part of the cortex to another part. Thus, instead of altering the location of a target and preserving host inputs, the inputs to existing targets are altered. Together, these studies demonstrate that the features that make a cortical area unique are expressed progressively as development proceeds. Importantly, they show that electrical activity can have an instructive role during the development of cortical networks, so that specific spatial and temporal patterns of activity regulate specific patterns of connections between cortical neurons.

2. *Formation of Cortical Layers*

The adult mammalian neocortex consists of six layers. These are generated by a heterogeneous population of precursor cells that lie along the walls of the lateral ventricles very early in development. The time of neurogenesis in the ventricular zone regulates the final disposition of cells in individual layers. Cells which are born earlier form the deeper cortical layers, whereas later-born cells form the progressively more superficial layers. Transplantation experiments have shown that there is a progressive restriction of cell fate in the precursor population: Early progenitors are able to give rise to neurons which come to reside in any cortical layer, whereas later progenitors give rise only to neurons of more superficial layers.

One key set of experiments (McConnell and Kaznowski 1991) demonstrates that transplanting neurons from the ventricular zone of a donor animal at an age when layer 6 is being born, into a host in which layer 2/3 is being born, causes the donor cells to settle into either host-specific layer 2/3 or donor-specific layer 6, depending on the stage of the cell cycle at which donor cells are extracted. If donor cells are extracted prior to or during the phase of DNA synthesis, they are able to switch their fate and migrate to the layer that is being generated in the host (layer 2/3), due presumably to environmental cues in the host. If donor cells are extracted later in the cell cycle, their fate is sealed prior to transplantation and they settle into the layer determined in the donor (layer 6). The precise nature of extrinsic signals that determines or alters the laminar fate of newborn cells during a certain part of the cell cycle is unknown.

Events occurring at the ventricular zone can contribute in other ways to regional differences in cortical architecture. The dynamics of the cell cycle show regional variation. Most notably, the germinal zone of

the primary visual cortex (V1) of primates, a region with twice the neuronal density of other areas, has a notably higher rate of cell production which is associated with changes in the parameters of the cell cycle. Thalamic afferents can exert a mitogenic effect on cortical progenitors, resulting in an increase in the number of cell divisions. Thus, thalamic inputs are one important source of extrinsic influences on cortical development, starting with the cell cycle and lamina formation.

3. *Formation of Cortical Areas*

There is considerable evidence suggesting that at least the initial broad parcellation of the cortex into discrete areas is regulated by molecular determinants that are intrinsic to the proliferative zone of the developing cortex. For example, evidence from transplantation and co-culture studies suggests that the initial expression of region-specific markers or phenotypes is not dependent on specific thalamic innervation. A number of genes are expressed differentially between cortical areas before thalamic afferents are believed to have invaded the cortical plate. Similarly, the expression of several genes can occur normally even in the absence of thalamocortical innervation. Finally, gradients of gene expression in the early cortex can regulate initial cortical parcellation, and such genes can also serve to attract appropriate sets of inputs from the thalamus, or direct appropriate outputs from the cortex (Rubenstein and Rakic 1999).

While the expression of genes and molecules may delineate broad areas of cortex at very early stages of development, subsequently thalamic afferents can influence the size and even the identity of specific areas (O'Leary et al. 1994). Transplants of extremely immature cortex—at embryonic day (E)12 in rats—from the limbic to the somatosensory cortex may take on inputs and express molecules characteristic of the host region rather than the region of origin. This ability is lost if the transplants are derived at a later developmental stage. Transplanting visual cortex into somatosensory cortex in rats causes the graft to accept inputs from the somatosensory thalamus and form 'barrels,' a characteristic of the rodent somatosensory cortex. Other work shows that the transplant needs to occur early, before E16, for the graft to form substantial connections with the somatosensory thalamus, and later grafts are already committed to form connections with the visual thalamus. With respect to output connections, occipital to frontal transplants at E12 can form projections to the spinal cord, a characteristic of the host cortex rather than the donor; however, by E14 that capacity has been lost and projections to the tectum, a characteristic of the region of origin, are formed instead. Interestingly, a similar age-dependent switch between E12 and E14 influences the corticocortical connections made by transplanted

perirhinal cortex into the parietal region. These findings indicate that there is an early time window during which the input and output connections of a cortical area may be sculpted by thalamic and local or regional signals to produce an area-specific phenotype. Thus, cortical areas arise by progressive specification of their region-specific phenotype from a multipotent phenotype (Levitt et al. 1997).

4. Formation of Cortical Networks: Ocular Dominance and Orientation Columns in Visual Cortex

The cortex differentiates progressively into layers, and as layer 4 appears in the cortical plate, thalamic innervation specifies the principal sensory areas. Concurrently, descending projections from the cortex innervate specific thalamic nuclei, primarily by the targeting of axons of layer 5 cells to principal and/or association nuclei, followed by the development of layer 6 projections to principal relay nuclei. Thus, a thalamocortical loop is set up very early in development, 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 follows thalamic innervation; considerable recent evidence, primarily from the visual cortex, demonstrates that a combination of intrinsic and extrinsic factors (such as electrical activity in thalamic inputs) is responsible for the formation and maintenance of specific thalamocortical and intracortical connections.

Ocular dominance columns—regions within layer 4 of V1 in higher mammals that receive input exclusively from one eye or the other via the lateral geniculate nucleus (LGN) of the visual thalamus—are paradigmatic of thalamocortical patterns that specify individual cortical areas. In primates they are present by birth, suggesting that visual experience is not required for their formation. Recent work suggests that they may also be set up before eye opening in ferrets, soon after geniculocortical axons innervate layer 4 (Crowley and Katz 2000), and similarly in cats. Surprisingly, they may not even require the presence of the eyes for their initial establishment. Monocular enucleation does not degrade these early columns immediately, and binocular lid suture does not reduce their development in cats for the first three weeks. 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 rules of development. Thus, if inputs from one eye are correlated with each other and uncorrelated with inputs from the other eye, application of a Hebbian developmental rule for strengthening connections (and of a com-

plementary rule for weakening connections), together with local excitation and long-range inhibition in the cortex, can lead to cortical stripes that resemble ocular dominance columns. Correlated inputs in the form of spontaneous waves of activity exist in the retinae prior to eye opening. In the LGN, the firing of neurons within a given eye-specific layer is well correlated, and uncorrelated with the firing of neurons in an adjacent layer which represents the other eye. Interestingly, ablation of the cortex abolishes these correlations, whereas ablation of inputs from the eyes has little effect. The pattern of electrical activity transferred to the cortex, therefore, appears to be regulated strongly by interactions between the thalamus and the cortex, and activity in the thalamocortical loop may be sufficient for eye-specific patterning. Significant support for the hypothesis that ocular dominance columns can arise, at least in principle, by activity-dependent sorting of inputs comes from the finding that eye-specific stripes form in the optic tectum of 'three-eyed' frogs forced to receive input from two eyes (Law and Constantine-Paton 1981). Whether or not ocular dominance columns in V1 require electrical activity to instruct their formation, there is convincing evidence that electrical activity is required to maintain them (Sherman and Spear 1982).

Orientation selectivity is a major emergent property in visual cortex that is created by aligned thalamic inputs whose activity is amplified by local intracortical connections. Orientation selectivity is present in V1 of primates at birth, and to a degree in cats and ferrets at or before the time of natural eye opening, although selectivity increases with visual experience (Chapman et al. 1999). Orientation-selective cells in visual cortex are linked by long-range horizontal intracortical connections in the superficial layers to form an orientation map. The adult pattern of clustered horizontal connections is present at birth in primates. In cats and ferrets, crude clusters appear just prior to eye opening, and are refined after the onset of vision; binocular deprivation prevents this refinement. The orientation map, revealed by optical imaging of intrinsic signals, develops in parallel with the development of orientation selectivity in single cells.

Monocular lid suture after orientation maps have already formed disrupts the map from the closed eye; reverse lid suture restores the map precisely. In addition, matching orientation maps for the two eyes develop even in cats raised under an alternating-suture paradigm, so that the two eyes never have common visual experience. Together, these studies indicate that the emergence of orientation-selective responses in single cells and the overall layout of the orientation map does not require patterned vision, although visual experience is necessary for orientation selectivity and maps to fully mature. However, blocking electrical activity in V1 reduces both the orientation tuning of single cells and the clustering of horizontal connections. Thus, spontaneous electrical activity in cortex or

in the thalamocortical loop is required for the initial establishment of local and long-range intracortical connections.

5. Patterned Electrical Activity and the Development of Cortical Networks

The vast majority of experiments on the influence of activity on visual cortical networks have involved manipulations such as lid suture or activity blockade that alter the *amount* of activity in the visual pathway. Relatively few experiments have examined the influence of the *pattern* of activity on cortical network development and maintenance; such manipulations include artificial strabismus, specific rearing paradigms, and rewiring of visual projections to the auditory pathway.

Strabismus refers to misalignment of the two eyes' optical axes, so that activity from corresponding retinal loci in the two eyes are no longer temporally correlated. Artificially induced strabismus causes neurons in V1 to become almost exclusively monocular, and ocular dominance columns to be more sharply delineated and have altered spacing compared to 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, in strabismic cats the connections come to link columns with similar eye dominance and orientation preference (Schmidt et al. 1999). Thus, correlations in input activity are used to sharpen and organize ocular dominance columns, and to shape intracortical horizontal connections.

Rearing kittens in a visual environment consisting of alternating black and white stripes at specific orientations restricts pattern vision and appears to shift the orientation preference of cortical cells towards the experienced orientation. While a shift could be caused by a passive loss of responses to nonexperienced orientations, there is an expansion of cortical columns devoted to the experienced orientation (Sengpiel et al. 1999), indicating an instructive effect of patterned visual experience on orientation selectivity and the orientation map.

5.1 Rewiring the Cortex

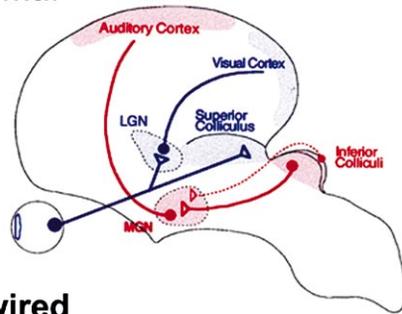
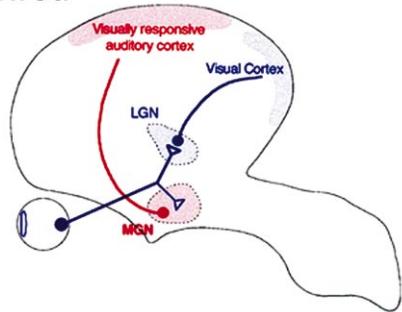
A unique paradigm for investigating the role of patterned afferent activity in the development of cortical circuitry and function is experimentally to redirect afferents carrying information about one sensory modality to central targets and pathways that normally process a different sensory modality (Schneider 1973). Retinal axons can be induced to innervate the auditory thalamus in the ferret (Sur et al.

1988), a carnivore with a highly organized visual pathway and which is born at a very early stage in development. The routing of retinal projections to the auditory pathway can be induced at birth, allowing the probing of the role of patterned activity in the *establishment* (and not simply the *maintenance*) of cortical circuitry. Importantly, visual input is relayed from the auditory thalamus to the primary auditory cortex (A1) via thalamocortical projections whose physical identity is unchanged but which provide spatiotemporal patterns of electrical activity to the auditory cortex that are very different from normal (Fig. 1).

Visual driving leads to emergent responses in 'rewired' A1 that demonstrate the role of patterned activity in shaping cortical networks. An orderly two-dimensional retinotopic map develops in A1 of rewired ferrets, in cortex that normally maps a one-dimensional surface, the cochlea. The retinotopic map in rewired A1 arises despite widely dispersed and overlapping thalamocortical projections, suggesting 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 a broader set available anatomically.

Visual cells in rewired A1 have orientation-tuning, direction-tuning, and velocity-tuning properties that are quantitatively indistinguishable from V1 cells, suggesting that similar mechanisms operate in the generation of receptive field properties in the two cortices. Orientation-tuned neurons in A1 are organized into an orientation map that resembles in important respects the map in V1 (Sharma et al. 2000). The differences between orientation maps in V1 and rewired A1 reflect differences in the underlying organization of superficial-layer long-range horizontal connections in these two cortices. In V1, horizontal connections are patchy, spatially periodic, and extend mediolaterally. In contrast, horizontal connections in normal A1 are more band-like in organization, show little spatial periodicity, and are anisotropic antero-posteriorly. Horizontal connections in rewired A1 show features that are intermediate between V1 and normal A1: The connections in rewired A1 form much smaller and more regular patches than in normal A1, though the patches are less tightly clustered and are larger in size than in V1. Thus, horizontal connections within the rewired cortex are significantly altered by visual input, but in a manner that appears to be constrained by intrinsic features of the auditory cortex.

Rewired ferrets also provide an opportunity for examining whether the behavioral role of a cortical area is set by intrinsic determinants or by the pattern of afferent activity during development. Behavioral experiments, supported by several kinds of control experiments, indicate that rewired ferrets interpret visual stimuli which activate the rewired projection as visual rather than as auditory (von Melchner et al.

A. Normal**B. Rewired****Figure 1**

Retinal inputs routed to the auditory thalamus in rewired ferrets drive the auditory cortex with visual activity without altering thalamocortical projections. **A:** Visual and auditory pathways in normal ferrets. The retina projects predominantly to the lateral geniculate nucleus (LGN) and superior colliculus. The LGN projects to the primary visual cortex. The medial geniculate nucleus (MGN) receives most of its subcortical afferents from the ipsilateral inferior colliculus, although afferent projections also arise from the contralateral inferior colliculus. The MGN projects to the primary auditory cortex. **B:** Visual pathways in rewired ferrets. Subcortical inputs to the MGN in one hemisphere are removed in early postnatal ferrets. This induces retinal axons to innervate the deafferented MGN. The MGN still projects to the primary auditory cortex, as in normal ferrets, but in rewired ferrets it relays visual rather than auditory inputs. This change in spatiotemporal patterns of input activity early in development has a profound effect on networks in auditory cortex, and on its function. Adapted from Angelucci et al. (2000)

2000). Thus, the function of a cortical area is dependent fundamentally on the spatiotemporal pattern of activity it receives during development. It is possible that all 'auditory' pathways central to the thalamus in the rewired hemisphere are turned 'visual,' including the cortex and downstream structures, with a concomitant respecification of their perceptual identity.

Cortical development involves a progressive shap-

ing of the fate of the cortical epithelium into discrete cortical areas with specific inputs, outputs, and local networks. Developmental manipulations, which include, importantly, transplantation and rewiring studies, demonstrate a continual interplay of intrinsic and extrinsic factors at all stages of development—at the ventricular zone during the cell cycle, in the cortical plate during the parcellation of cortical areas, and within the cortex during the formation and maintenance of cortical networks. The nature of extrinsic signals varies with developmental time, and likely includes intercellular signals 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, which persist into adulthood as substrates for learning and memory.

See also: Brain Implants and Transplants; Cerebral Cortex: Organization and Function; Cognitive Development in Infancy: Neural Mechanisms; Neural Development: Mechanisms and Models; Prefrontal Cortex Development and Development of Cognitive Function; Topographic Maps in the Brain; Visual Development: Infant

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M. Sur

Cosmopolitanism

Cosmopolitanism is a western notion that epitomizes the need social agents have to conceive of a political and cultural entity, larger than their own homeland, that would encompass all human beings on a global scale. Cosmopolite in Ancient Greece meant citizen of the world. Cosmopolitanism presupposes a positive attitude towards difference, a desire to construct broad allegiances and equal and peaceful global communities of citizens who should be able to communicate across cultural and social boundaries forming a universalist solidarity. Its inclusive drive is most evident in moments of crisis of other modes of representing and ascribing membership to existing sociopolitical and cultural units. Much of the malaise and misunderstanding cosmopolitanism may provoke are related to its ambiguity, that is, its unique way of uniting difference and equality, an apparent paradox of wishing to reconcile universal values with a diversity of culturally and historically constructed subject positions.

The composition of the Greek term, *cosmopolis*, already indicates this unsolved tension: *cosmos*, a natural universal order, is related to *polis*, society's variable order. As a consequence, from the Greek democratic city-state to the global village, the idea of a cosmopolite has been haunted by questions such as *whose* world this is. Can homogeneous external expansionist forces coexist with heterogeneous localized ones? A truly cosmopolitan answer would imply a permanent interest in difference and the recognition that globals and locals depend on each other to exist.

Since its inception, cosmopolitanism has been a category marked by a need to negotiate with 'others' and has reflected tensions between local and supralocal realities, ethnocentric and relativist perspectives, and particularism and universalism. Historically, cosmopolitanism has mirrored the ideologies of different periods and modes of integration to larger, imperial or global, political entities. As a category mostly held by elites, it often means the sophistication that results from familiarity with what is different. It has become

a metaphor for mobility, migrancy, sensitivity, and tolerance to otherness, independence from specific authorities, and transcultural and transnational realities and claims. Its opposing concepts have often indicated xenophobia, fixity, parochialism, restricted sovereignty, and allegiance to a motherland, or a nation-state.

1. A Brief History

The history of the relationships between local and supralocal conceptions is probably as old as humankind. A strong trend towards local reality, particularism, diversity, and context may oscillate, such as at the end of the Renaissance or during the Enlightenment, towards an emphasis on general formal timeless statements that pretend to be universal. Having its roots in Ancient Greece, cosmopolitanism has been variably present in western philosophical or political discussions.

The military conquests of Alexander the Great (356–323 BC) opened up the conditions for the existence of a 'world empire' that allegedly aimed at uniting East and West into an enlightened commonwealth. Greek became the *lingua franca* of the Hellenistic age (fourth to first century BC), a period that lasted until the establishment of Roman hegemony. Although cosmopolitanism was an issue for Greek philosophers before Stoicism, this school of philosophy established in Athens by 300 BC systematized cosmopolitan theories advancing visions such as that of a world city, an ideal state where everyone would be a citizen. Stoics were instrumental in criticizing Greek ethnocentrism towards barbarians and fostered a sense of brotherhood, a vision of humankind that was transmitted to Romans and predated Christianity's claims to universalism. From the Roman Empire through Medieval Europe cosmopolitanism passed on to different political and intellectual elites. The Christian church played a major role in the reproduction of cosmopolitan ideals and apparatuses by forming transcultural sacred imagined communities and diffusing Latin as the language of a transnational European power.

Some of the fundamental historical processes of long duration that strengthened cosmopolitanism were related to the establishment of modernity, itself a civilizatory cosmopolitan notion and force. The printed book, a new technology of communication developed in mid-fifteenth century, put into question parochialisms in time and space, performing a typical cosmopolitan operation: the enhancement of the consciousness of diversity and the construction of larger imagined communities. Sixteenth-century European expansion gave impulse to the world capitalist system through the incorporation of new territories and populations, and established global colonialism,