Developmental Science 4:2 (2001), pp 125–157

ARTICLE WITH PEER COMMENTARIES AND RESPONSE

The cortex in multidimensional space: where do cortical areas come from?

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Abstract

The concept of a cortical 'area' as a discrete phylogenetic, developmental and computational unit is evaluated. Evidence including the comparative organization of the forebrain in vertebrates, the organization of cortex in different mammals, the scaling of the areas of the isocortex in mammals, and the early molecular differentiation of the cortex all suggest a special status for the primary sensory cortical areas, particularly the visual cortex. Furthermore, the overlapping gradients of early molecular expression and the patterning of cortical structure and connectivity by thalamic input suggest a new view of cortical organization that is different from the traditional view of a developmentally mosaic cortex; this view proposes that distinct cortical areas arise combinatorily from the multiple overlapping processes imposed upon the developing cortex.

As a species, we like the idea of species, nations, organs (physical and mental) or any kind of discrete unit that gives organization to our conceptual world. When given any continuum to describe, either single or multi-dimensional, we attempt to describe it in categorical terms (Harnad, 1987). A structure like the isocortex as first described by Brodmann (Brodmann, 1909) comes ready-made for our predispositions, seeming to be a structure of multiple discrete units. Its module-like anatomical differentiation reaches up to the next level of analysis to suggest a corresponding differentiation of cognitive functions – thus, we like to assume that, for each area we identify, a unique data transformation, computation or cognitive function can be defined. The assumption of discrete units also reaches down to genetics and development, to suggest that each region has special and region-typical instructions. However, the existence of discrete boundaries at maturity does not suggest that the developmental mechanisms that produce specific cortical regions are also discrete. Consider two kinds of fabrics, a quilt versus a woven plaid. In both fabrics, we will find a mosaic of local regions with different sizes and internally uniform properties. For a quilt, we might reasonably ask about the history and identity of each square. Knowing how a weaver makes a plaid, however, it would seem a bizarre enterprise, 'missing the point' of the plaid, to analyze it one square at a time, evaluating the unique specification of each region's color and size. We will argue that it may be useful to view the cortex as a sort of hyperdimensional plaid, rather than as a mosaic quilt, developmentally, anatomically and functionally. To distinguish these two kinds of organization, the quilt and the plaid, we must catch them in motion (Bates, Thal, Finlay & Clancy, 2000). Together, evolution and development provide the opportunity to see the pattern under construction.

This kind of multidimensional approach was used insightfully by Van Essen and colleagues (Van Essen & Maunsell, 1985; Van Essen, Anderson & Felleman, 1992) to understand the functional organization of the multiple visual areas in the primate cortex. In this case, the units of two competing levels of analysis had been vying for assignment to each visual area. On one level, there were stimulus attributes – local contrast and spectral cues, the spatial and temporal frequency of the response generated etc. – and at the second, computational outcomes, such as the determination of shape from motion, the location of an object in viewer-centered space or the identity of a particular object. These authors clearly laid out that neither individual

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stimulus attributes nor computations were identical with areas. Rather, both were multiplexed and distributed over a variety of regions, in an architecture that was hierarchical, as well as parallel. We would like to start to understand the developmental literature in the same way, looking for fields larger than individual areas of adult cortex, developmental gradients and external sources of cortical patterning, such as the thalamus, in order to understand how cortical areas with unique local properties might arise from global features of organization.

Two kinds of cortex organization have typically been contrasted. At one extreme, the cortex might be a uniform and equipotential structure from the start (O'Leary, 1989), a highly and uniformly connected neural net that takes its adult local specificity from the information relayed through its major input, the thalamus, and from the negotiations made between the derived cortical areas via their intracortical connectivity. Alternatively, the cortex might be a mosaic from the start (Rakic, 1988), such that each cortical area has individually specified features particularly suitable for the input it will receive or the functions it will perform. For example, somatosensory cortex might have a complement of neurotransmitters and lengths of axonal processes uniquely matched for the temporal and spatial character of haptic information, or inferotemporal cortex might come prewired with the cell assemblies useful for detecting faces in their characteristic orientation and size.

There are alternatives to these two extreme positions. For instance, using the 'plaid' notion introduced above, multiple dimensions of cell structure relevant to stimulus processing could be laid out such that regions arise combinatorily which are uniquely suited for particular computations. For example (hypothetically), cortex regions which receive particular sensory thalamic input might be overlaid by large-scale periodic patterns of neurotransmitter expression, differentially scaled patterns of neuromodulator production and particular patterns of axon extension, such that we might find different areas arising from the unique combination of a subset of these properties during development – for instance, a visual input, high γ-aminobutyric acid A (GABA), high serotonin, short-range connection region or a somatosensory input, low GABA, high serotonin, long-range connection region. Patterning both intrinsic and extrinsic (e.g. the thalamus) to the cortex may be the source of the information that induces these unique features such as particular neurotransmitter complements or rates of axon growth.

We will review the basic specification of the cortex from studies of evolution and development. Most of the evolutionary and developmental literature has approached the cortex from the quilt or mosaic perspective. Our review of this literature will necessarily take on this language, and we will find in some cases good support for a special functional identity of some parts of the isocortex. Further than that, however, our fundamental argument will be that any complex structure like a cortical area will be multidimensional in its attributes, and the job of evolutionary and developmental neuroscientists should be to attempt to identify constellations of developmental processes and attributes that covary in order to best understand the causal structure in cortical architecture. Each cortical area in the adult can be viewed as an intersection of a number of shaping forces; the metaphor of the hyperdimensional plaid will carry throughout this argument.

Candidate organizational schemes for a cortical *Bauplan*: evolutionary perspective

Midway between the notion of a cortex beginning as a mosaic versus a uniform sheet of cells, we might imagine a cortex composed of zones that generally organize cortical input but which are fewer in number than those in the adult mosaic. Are such possibilities suggested in the literature on the comparative organization of the forebrain?

Primary visual cortex (V1) might be unique

Primary visual cortex presents the strongest argument for specialized, area-specific identity from evolutionary information. The area variably called striate cortex, primary visual cortex, V1 or area 17 in mammals gets its major input from the dorsal lateral geniculate nucleus (LGN) of the thalamus, and maps that input into one visuotopic map in isocortex. In birds, the area of the telencephalon that receives input from the dorsal lateral optic nucleus (the avian homologue of the LGN) is called the visual Wulst, which is one part of the 'dorsal cortex' (Butler & Hodos, 1996). The Wulst has a layered organization and response properties very similar to mammalian striate cortex (Pettigrew & Konishi, 1976) and appears to be developmentally, connectionally and functionally homologous to it. Birds and reptiles essentially share the same organization of the visual system, although nomenclature varies (Figure 1; Butler & Hodos, 1996). The Wulst is different in structure from the rest of the telencephalic areas in birds and reptiles thought to be homologous with mammalian isocortex – the remaining telencephalon that receives thalamic input consists of nuclear masses without layered organization

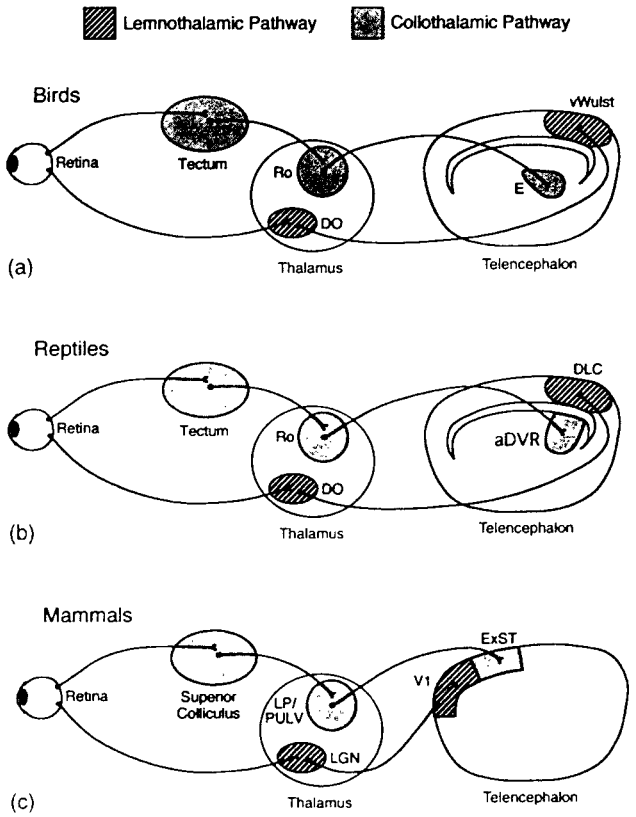

Figure 1 *The dual organization of visual input from the retina to the telencephalon in birds (a), reptiles (b) and mammals (c). All three groups have a similar relay of input via the lemnothalamic and collothalamic pathways. Abbreviations: aDVR, anterior dorsal ventricular ridge; DLC, dorsal lateral cortex; DO, dorsal lateral optic nucleus; E, ectosriatum; ExST, extrastriate cortex; LGN, dorsal lateral geniculate nucleus; LP/PULV, lateral posterior/pulvinar complex; Ro, nucleus rotundus; V1, primary visual cortex; vWulst, visual Wulst. Adapted from* Butler, A.B., & Hodos, W. (1996). *Comparative vertebrate neuroanatomy: Evolution and adaptation* (pp. 390–391). New York: Wiley-Liss.

(Northcutt & Kaas, 1995) (note that part of the dorsal cortex also has a somatosensory representation; it is not only visual). Thus, the avian and reptilian structural homologue of mammalian striate cortex can take on an organization different from the rest of the thalamo-recipient zones in the telencephalon. In addition, striate cortex has a noticeable peculiarity of organization in mammals: while other cortical regions divide into topographically distinct subdivisions when brains enlarge, striate cortex does not. If it is possible for evolution to repeatedly select out and variably elaborate a structure in the forebrain that is homologous to a part of the mammalian isocortex, it suggests that the embryonic precursor of the structure might have some special genetic identity that can make it visible to natural selection.

Two kinds of cortex: Butler's evidence from thalamic connectivity

A second way to divide up the cortex is to look for patterns in the kind of input it receives. In mammals, the visual system has a dual organization, with the retina distributing its input to two major targets, the LGN of the thalamus and the superior colliculus. The LGN then projects to striate cortex, and the superior colliculus projects to the lateral posterior/pulvinar complex of the thalamus, which projects in turn to extrastriate cortex (Figure 1(c)). The dual organization of visual input is even more obvious in birds and reptiles (Figures 1(a) and (b), respectively). This organizational system can be expanded to encompass the somatosensory and auditory pathways as well (Butler, 1994). Part of the thalamus receives its input from sensory nuclei directly (i.e. from the retina or from the dorsal column somatosensory nuclei) and the other part of the thalamus by relay through the midbrain (i.e. the visual superior colliculus, the auditory inferior colliculus or the somatosensory midbrain roof). Butler (1994), who pointed out the possibility of this division, refers to the first set as 'lemnothalamic', for the lemniscal pathways, and the second 'collothalamic', referring to the colliculi of the midbrain. That different vertebrate radiations appear to expand one or the other of these divisions selectively suggests that each pathway has some status as an 'addressable' organizational unit. Since auditory input has only a 'collothalamic' route to the cortex, cortical organization based on collothalamic and lemnothalamic pathways classifies primary auditory cortex (A1) as more similar to extrastriate and secondary sensory cortex than to primary visual (V1) and somatosensory cortices (S1). At this point, however, although there is a reasonably clear, cross-taxa way to divide up the thalamus, the areas of telencephalon across taxa that might correspond to these two thalamic divisions are the subject of much debate (Striedter, 1997).

Islands in the stream: Kaas and Krubitzer

A completely different approach to the question of cortical homologies is to examine the organization of the mature cortex in as diverse a set of mammals as can be generated, looking for commonalities, as Kaas and Krubitzer and their colleagues have done (Kaas, 1987; Kaas & Krubitzer, 1991; Krubitzer, 1995, 1998). This approach finds evidence for the cross-species ubiquity of three primary sensory areas, V1, S1 and A1, in a characteristic topographic relationship to each other in even the smallest isocortices, with secondary and tertiary representations elaborated in the zones between these

areas as brains enlarge. This compartmentalization distinguishes between the isocortex receiving direct input from the primary sensory thalamic nuclei (i.e. from the LGN, the ventrobasal nucleus (VB) and the medial geniculate nucleus) and all other cortical areas. When we discuss development, we will review several features that further support this classification.

Though Kaas and Krubitzer's comparative description of a number of mammalian cortices and Butler's analytical approach to the forebrain across vertebrates are extremely different in method and style, it is interesting how both converge on the distinctive nature of the primary sensory cortices, compared with the rest of the cortical areas.

Scaling of isocortical areas

One intriguing feature of the brain in general, and the isocortex in particular, is how accurately the volume of any part of the brain can be predicted from the volume of any other part of the brain (though the relationship is nonlinear). In primates, the relationship is particularly tight (Hofman, 1989; Finlay & Darlington, 1995), and humans have precisely the size of cortex that would be predicted for a brain of their overall size. Although the cortex enlarges at the highest rate with brain size, relative to other structures, and comes to comprise a majority of brain volume, there is no evidence that it is the object of any differential or unusual selection in humans. Conservation of developmental timing appears to account for this phenomenon. In general we have found that cell groups generated late in development (like the isocortex, or the cerebellum) are the ones that get disproportionately large as brain sizes enlarge in mammals (Finlay & Darlington, 1995; Finlay, Hersman & Darlington, 1998; Darlington, Dunlop & Finlay, 1999; Finlay, Darlington & Nicastro, 2001). Apparently unavoidable tight linkages of volumes is perhaps the major factor driving us to look for organizing principles that make all of the isocortex volume available for use as the brain grows in its rule-like fashion during evolution.

We can also ask how cortical areas scale with the rest of the isocortex to see if any act as independent areas. The 'late makes large' relationship generates a rather simple prediction. If the cortex is just one embryonic unit, cortical areas should scale isometrically with cortical expansion, or perhaps differentially (but systematically) with the isocortex's own internal gradient of generation, rostrolateral to caudomedial (Figure 2(a)). If the cortex has local identity conferred by its input from the thalamus, the size of the cortical areas should scale with the size of the thalamic input fields (Figure 2(b)). Thus, as brains enlarge, the size of the primary sensory cortices should scale less than other cortical areas since the relative size of primary sensory thalamic nuclei increases at a lesser rate than the remaining thalamus (Armstrong, 1979a, 1979b, 1980, 1981). While we are at present in the midst of an extensive analysis of cortical scaling with respect to the thalamus, one feature that has emerged, and in fact was suggested by previous literature (Frahm, Stephan & Baron, 1984), is that primary visual cortex does not scale isometrically with the rest of the cortex, but at a higher slope (Figure 2(c); Snow *et al.*, 1997), even though its input nucleus (LGN) scales at a lesser rate as brains enlarge. This is further evidence for the specialized nature of primary visual cortex.

Summary of the comparative evidence

Overall, the evidence from the comparative literature converges on a few key points. In terms of scaling, connectivity and cross-species commonality, the primary sensory areas emerge as areas differentiable from the rest of the cortex. The strongest evidence for distinction is found for primary visual cortex, the second most for somatosensory cortex, while primary auditory cortex presents a mixed signal. The absence of any robust evidence for more elaborate organization than this is also quite striking. The primary sensory and motor cortices are common to mammals of all sized brains, and it is the region between these areas that undergoes the most expansion as isocortex enlarges separately in the various mammalian radiations. While the pattern by which secondary and tertiary representations emerge in cortical regions outside the sensory areas is fairly rule-like, generating more and more visuo-, somato- and other spatio-topic maps as the cortex enlarges, the pattern is not invariant in the sense of producing obviously identical areas in the various mammalian radiations (Krubitzer, 1995).

In cases of evolutionary data, it is also important to underscore what is not observed. First, large isocortices are not blown-up versions of small ones with just a few large areas (excepting primary visual cortex, which could be characterized this way). Second, small recognizable components of mosaics do not repeatedly emerge. For example, a phenomenon such as a repeatedly emerging area of frontal cortex with the unique characteristics of heavy dopamine innervation and inverted pyramidal cells has not been observed. If the cortex were basically composed of a mosaic of genetically specified areas, we might see various reports of this mosaicism across species.

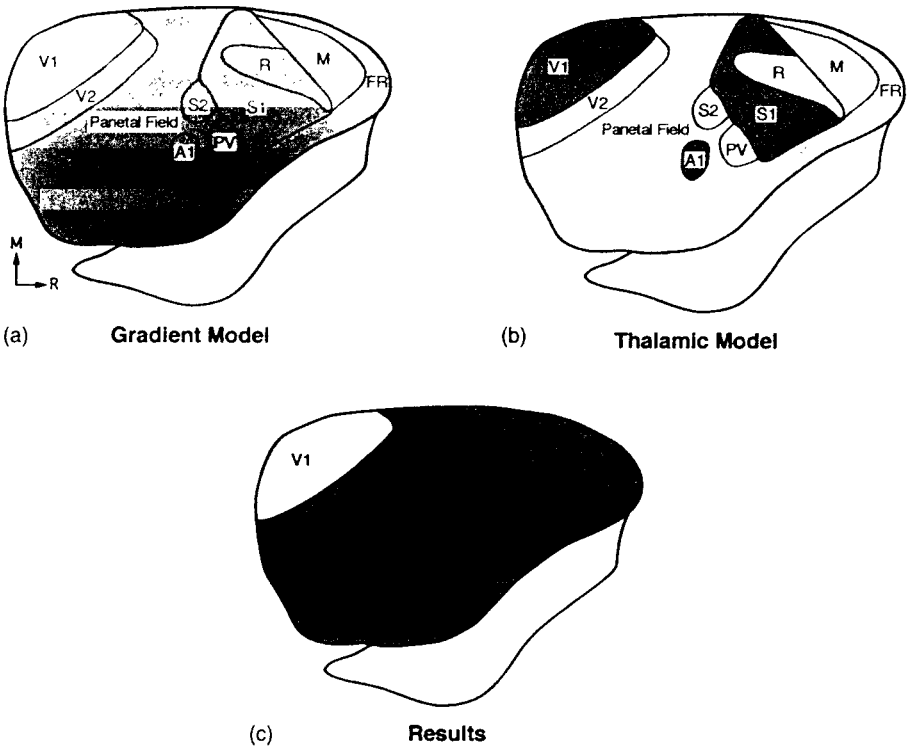

Figure 2 *Scaling of isocortical areas as brains enlarge. In (a)–(c), light gray and dark gray regions represent large and small cortical areas, respectively. (a) Cortical areas may scale according to the isocortex's internal gradient of generation (rostrolateral to caudomedial) where late generated areas (i.e. V1) become larger than earlier generated ones (i.e. PV and A1). (b) Alternatively, cortical areas may scale according to the size of their input from the thalamus. According to this model, the scaling of the primary sensory thalamic nuclei at a lesser rate than the rest of thalamus as brains enlarge would predict that the primary sensory cortices (i.e. V1, S1 and A1) would scale at a lesser rate than the rest of cortex. (c) Our preliminary results show that primary visual cortex scales at a greater rate than the rest of isocortex as brains enlarge, providing evidence for the uniqueness of visual cortex. Note that we do not imply that the entire isocortex but visual scales uniformly; but only that its mean scaling value over all areas is different than visual cortex. Abbreviations: A1, primary auditory cortex; FR, frontral cortex; M, motor cortex; PV, parietal ventral cortex; R, rostral field of somatosensory cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex; V1, primary visual cortex; V2, secondary visual cortex. Adapted from* Kaas, J.H., Krubitzer, L.A., & Johnson, K.L. (1989). *Journal of Comparative Neurology*, **281**, 432.

Comparative neuroanatomy thus far has centered its analysis around homologies of a few discrete areas. With this sort of analysis, some clear signals emerge about the differentiability of a few key areas, the primary sensory regions. But it is even more notable how many areas this leaves out – including most of the volume of the primate isocortex.

Development suggests parallel organizational schemes

Development will be our second source of information for cross-cortical organizational schemes. Two different research approaches characterize this literature. In the first, the isocortex or entire telencephalon is examined wholesale for patterns of interest, such as the expression of molecular markers. In the second, specific cortical areas, typically primary sensory areas, are examined closely for the local details of their development, including cellular positioning, maturation and connectivity. The latter approach often presumes the quilt-like modularity that the first approach does not. We will first review the mechanics of cortical development and nomenclature briefly, and then consider cortical specification during development, examining evidence for both quilt and plaid patterns of organization.

Overview of cortical development

The neurons of the cerebral cortex are generated from progenitor cells formed at the inner surface of the forebrain vesicle (Sauer, 1935; Fujita, 1963; Rakic, 1974). This surface, often referred to as the neuro-

epithelium or proliferative zone, is also called the ventricular zone as it borders the lumen of the ventricles. While early cell division in the ventricular zone serves simply to expand the pool of progenitor cells, later divisions of progenitors give rise to cortical neurons. The first generation of cortical cells migrate from the ventricular zone into overlying tissue to form the preplate, an early scaffold for later-migrating neurons (Marin-Padilla, 1978). The next generation of cortical cells migrate into the preplate and split it into a superficial layer (marginal zone or layer I) and a deep layer (subplate zone or layer VII). Subsequent cortical development is characterized by an inside-out gradient whereby younger neurons occupy more superficial positions in cortex, relative to older neurons (Angevine & Sidman, 1961). Thus, the first neurons to separate the preplate reside in cortical layer VI while later generated neurons sequentially form the overlying cortical layers V, IV and II/III (Figure 3).

Imposed upon this general organizational scheme of isocortical development are differences in the generation and migration of cortical cells from various regions of the neuroepithelium. Cell proliferation along the ventricle follows gradients whereby neurogenesis in rostrolateral regions precedes that in caudomedial regions (Figure 2(a); Bayer & Altman, 1991). Coupled with these differences in the timing of neurogenesis are variations in the migratory paths of cortical neurons. Whereas the majority of cortical neurons travel radially from the ventricular zone to the overlying cortical plate along radial glial fibers (Figure 3; Rakic, 1972), non-radial migration has also been observed (Walsh & Cepko, 1988; O'Rourke, Dailey, Smith & McConnell, 1992). Some cells using non-radial migration traverse great distances. Recent studies demonstrate that cortical neurons generated in the ganglionic eminences (the ventricular zone giving rise to the basal ganglia) migrate tangentially to positions within cortex (Anderson, Eisenstat, Shi & Rubenstein, 1997; Lavdas, Grigoriou, Pachnis & Parnavelas, 1999). Given these variations in the proliferation and migration of cortical cells across different regions of the neuroepithelium, it is remarkable that neurogenesis produces a cortex that is well ordered and multilayered across its extent.

During development, regional differences are imposed upon the fundamental laminar structure of cortex, giving rise to the discrete areas that characterize the adult isocortex. In our discussion of cortical development, we will begin with regional differences that are evident in the ventricular zone and early cortical plate during the generation of the deep cortical layers, and follow with differences that emerge later, during the generation of the superficial layers or shortly thereafter. In conjunction with describing the regional differences, we will discuss how these differences may support particular organizational schemes.

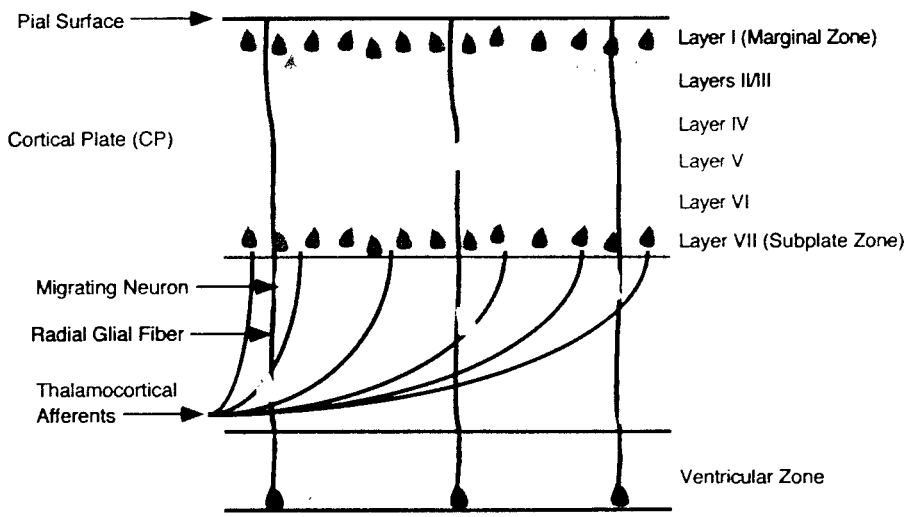

Figure 3 *A schematic illustrating the general development of the isocortex. Cortical neurons are generated in the ventricular zone and migrate into the cortex along radial glial fibers (black cells) or tangential pathways (not shown). The earlier generated cells of the preplate (dark gray cells) are split into a superficial (marginal zone) and deep layer (subplate zone) by the migration of later generated neurons (light gray cells). These younger neurons settle within the developing cortical plate according to an inside-out gradient. Afferents from the sensory thalamic nulcei begin to invade particular isocortical regions during the generation and migration of their primary target neurons, layer IV cells.*

Early regionalization in the ventricular zone

Proliferation rates

Cortical areas can be distinguished from one another on the basis of differences in the rate of cell proliferation. In primates, the rate of neuronal production in the neuroepithelium underlying striate cortex is greater than that underlying extrastriate areas, such that the number of neurons in the primary area of the adult is twice that in surrounding cortex (Dehay, Giroud, Berland, Smart & Kennedy, 1993). While this supports the notion that primate striate cortex is different from other cortex, recent studies in the rat suggest that differences in cell production may also characterize other cortical areas (Polleux, Dehay, Moraillon & Kennedy, 1997).

Expression of molecules

Cortical regions differ in the capacity of progenitor cells to produce neurons expressing a particular molecular phenotype, although the functional significance of many of these molecules is yet unknown. In rats, lateral, but not dorsal, regions of the developing cerebral wall give rise to post-mitotic neurons expressing latexin (Arimatsu & Ishida, 1998). While the importance of this protein in lateral regions of cortex is unclear, it appears to specifically mark a population of excitatory layer VI projection neurons forming corticocortical connections (Arimatsu, Ishida, Sato & Kojima, 1999a). It has also been shown that the cerebral wall generating limbic but not visual or somatosensory cortices produces neurons expressing the limbic-system-associated membrane protein (LAMP; Horton & Levitt, 1988). Limbic cortex includes the perirhinal, cingulate and prefrontal cortices which, together with subcortical structures, are associated with learning, memory and emotion. Cells expressing LAMP selectively promote the growth of limbic axons, suggesting that the protein functions as a recognition molecule for the formation of limbic circuits (Pimenta *et al.*, 1995). The expression of this protein in cortex probably contributes to formation of specific thalamocortical connections by promoting the growth of axons from limbic thalamic nuclei and repelling those from the non-limbic thalamus (Mann, Zhukareva, Pimenta, Levitt & Bolz, 1998). *In vitro* experiments demonstrate that the expression patterns of these two molecules are determined at the level of the ventricular zone. For instance, if progenitor cells from lateral and dorsal or limbic and non-limbic regions of the cerebral wall are removed and placed into culture, the expression of latexin and LAMP is restricted to those cultures comprising cells from the lateral and limbic regions of the dorsal wall, respectively (Arimatsu *et al.*, 1992; Ferri & Levitt, 1993; Arimatsu, Ishida, Takiguchi-Hayashi & Uratani, 1999b). Thus, unique patterns of molecular expression can arise through the differential capacity of progenitor cells. Neither of these two patterns of protein expression serves to define a distinct cortical area, and thus they do not support a quilt organization. Rather, they define a group of areas (i.e. LAMP delineates a number of spatially segregated limbic cortices) or a large region of cortex (i.e. latexin delineates lateral cortical areas).

However, a couple of molecules whose expression is also determined at the level of progenitor cells have been shown to be expressed within a single cortical area. In mice, the postnatal expression of an H-2Z1 transgene precisely delineates a subset of layer IV cells in somatosensory cortex alone (Cohen-Tannoudji, Babinet & Wassef, 1994) while the postnatal expression of the homeobox gene *Otx-2* (a transcription factor, see below) is localized to lower layer IV and/or upper layer V in the visual cortex of rats and mice (Nothias, Fishell & Ruiz i Altaba, 1998). It should be noted that there was no *a priori* reason to expect that these genes would show differential expression in primary visual or somatosensory cortex, although these were the patterns that happened to emerge. Like latexin and LAMP, a cell's fate to express H-2Z1 or *Otx-2* appears to be determined in the ventricular zone. If pieces of tissue (explants) from various regions of the neuroepithelium are removed at the beginning of cortical neurogenesis and cultured in a dish, the subsequent expression of H-2Z1 or *Otx-2* is restricted to those explants taken from cortical regions that normally exhibit expression *in vivo* (Nothias *et al.*, 1998; Gitton, Cohen-Tannoudji & Wassef, 1999a).

Interestingly, although the cell culture experiments tell us that the *commitment* to express each of these genes occurs in the absence of extrinsic factors, the actual expression or maintenance of expression is influenced by thalamic input. Neonatal ablations of the somatosensory thalamus prevent *in vivo* expression of H-2Z1 (Gitton, Cohen-Tannoudji & Wassef, 1999b) and visual cortex cultured with thalamus shows increased cortical *Otx-2* expression relative to visual cortex cultured alone (Nothias *et al.*, 1998).

Early regionalization in the developing cortex

Transcription factors

Molecules known as transcription factors show unique patterns of expression in the developing cortical plate. Transcription factors are proteins produced from regulatory genes which bind to DNA and activate or repress gene expression. Thus, these factors direct a cell's

fate by controlling the expression of particular genes. Most of the transcription factors that have been identified within isocortex thus far (excluding *Otx-2*) are expressed in gradients across the cortex rather than being discretely localized to individual areas (Frantz, Weimann, Levin & McConnell, 1994b; Bulfone *et al.*, 1995; Donoghue & Rakic, 1999; Nakagawa, Johnson & O'Leary, 1999). Moreover, some of these transcription factors show striking localization to discrete cortical layers, rather than specific areas, during early cortex formation (Neuman *et al.*, 1993; Frantz, Bohner, Akers & McConnell, 1994a; Frantz *et al.*, 1994b), supporting an argument for a laminar as opposed to areal division of isocortex. Nevertheless, transcription factors have been identified which show a detectable change in laminar expression at an established isocortical areal boundary (Bulfone *et al.*, 1995; Rubenstein *et al.*, 1999). For instance, the strong expression of transcription factor *Id-2* in cortical layer V ends abruptly at the border of rat somatosensory and motor cortex. Similarly, the expression of transcription factor *Tbr-1* in layer V becomes wider and stronger rostral to this same isocortical boundary. Since the distinct laminar patterns of both proteins mark the same areal boundary, individual cortical areas may be delineated by the combined (or nested) patterns of expression of multiple transcription factors. This notion is further supported by transcription factors *Lhx-2*, *Emx-1* and *SCIP* in the rat, whose combined gradients of expression appear to distinguish putative auditory cortex from putative visual cortex (Nakagawa *et al.*, 1999). While more cortical transcription factors will undoubtedly be discovered, some of which may mark additional boundaries, it is noteworthy that many of the ones currently identified appear to mark boundaries of the sensory cortices.

Ephrins and Eph receptors

Molecules such as cell-surface-bound receptors and their ligands (molecules which bind to and activate the receptors) also demarcate cortical boundaries. Some of the receptors and ligands specifically identified in cortex are the Eph receptor tyrosine kinases and ephrins, respectively (Mori, Wanaka, Taguchi, Kazumasa & Tohyama, 1995; Gao *et al.*, 1998; Donoghue & Rakic, 1999; Mackarehtschian, Lau, Caras & McConnell, 1999; Rubenstein *et al.*, 1999). These molecules are believed to serve as guidance cues for developing axons (reviewed by Flanagan & Vanderhaeghen, 1998). Since the combination of an Eph receptor and its ligand is inhibitory, the expression of one of these molecules in a target may provide negative guidance for axons expressing the other molecule (Cheng, Nakamoto, Bergemann & Flanagan, 1995; Drescher *et al.*, 1995; Gao *et al.*, 1996). In primate cortex, the early nested expression of the *EphA3* and *EphA6* receptors delineates striate and extrastriate areas with *EphA3* expressed in presumptive extrastriate cortex and *EphA6* expressed in both striate and extrastriate areas (Donoghue & Rakic, 1999). The patterns of expression that emerge do not necessarily remain constant throughout cortical development, arguing against a mosaic or quilt organization where each area would have its own individual marker throughout development. For instance, *EphA3* expression changes at later ages so as to extend throughout the occipital lobe, and *Eph7*, initially expressed in posterior cortex, is later expressed anteriorly as well posteriorly (Donoghue & Rakic, 1999). The ligands of the Eph receptors can also show regional expression in the developing cortical plate: *ephrin-A5* is greatest in presumptive somatosensory cortex with diminishing levels in anterior and posterior cortex (Gao *et al.*, 1998; Mackarehtschian *et al.*, 1999).

The combined expression of Eph receptors and ephrins in the cortex and thalamus may contribute to the establishment of area-specific thalamocortical projections. Since the interaction between these receptors and ligands is repulsive, the combined expression of a ligand in a cortex area and a receptor in a thalamic nucleus (or vice versa) may prevent thalamic axons from growing into an inappropriate cortical region. Consistent with this view are studies which show that the high expression of *ephrin-A5* in somatosensory cortex is correlated with (1) a high expression of *EphA5* in medial limbic thalamic nuclei whose axons do not innervate somatosensory cortex (Gao *et al.*, 1998) and (2) a low expression of *EphA5* in the ventrobasal nucleus whose axons do project to somatosensory cortex (Gao *et al.*, 1998; Mackarehtschian *et al.*, 1999).

Cadherins

Cadherins comprise another group of cortical markers that show regional expression. These molecules are proteins located on the surface of cells which function in cell adhesiveness as cells expressing the same cadherin molecule tend to aggregate together, separating themselves from cells expressing other cadherins (reviewed by Redies & Takeichi, 1996). Thus, they provide a means by which cortical cells can preferentially segregate from one another. Like transcription factors, Eph receptors and ephrins, cadherins have graded and varied expression patterns across the developing cortex. Whereas *cadherin-6* is expressed in a high lateral to low medial pattern (Inoue, Tanaka, Suzuki & Takeichi, 1998; Nakagawa *et al.*, 1999), with particularly strong expression in the putative

auditory region (Nakagawa *et al.*, 1999), *cadherin-8* is expressed in a high medial to low lateral gradient with a unique laminar pattern distinguishing motor and visual cortices from the rest of isocortex (Nakagawa *et al.*, 1999).

Molecular regionalization is independent of thalamic input

The *early* regional expression of molecules in cortex is independent of extrinsic cues from the thalamus. In primate cortex where cell-intrinsic factors are more clearly separated from cell-extrinsic factors due to the greater length of neurogenesis, regional differences in the expression of transcription factors and Eph receptors can be observed before thalamic axons have invaded cortex (Donoghue & Rakic, 1999). Moreover, in mutant mice which lack thalamocortical input because of a deficiency in the *Gbx-2* or *Mash-1* gene, emergence of the regionalized expression of molecules is strikingly normal (Miyashita-Lin, Hevner, Wassarman, Martinez & Rubinstein, 1999; Nakagawa *et al.*, 1999). Despite the lack of importance of thalamic input in early cortical regionalization, it is possible that thalamic input is important in sustaining gene expression patterns as has been demonstrated for the postnatal expression of H-2Z1 and *Otx-2*. However, this cannot currently be examined because *Gbx-2* and *Mash-1* mutants die at birth.

Summary of early cortical regionalization

There is considerable regionalization of the ventricular zone and early cortical plate as shown by the expression of various molecules. Most of the molecules that have been identified are expressed in gradients across cortex and show overlapping or nested patterns of expression. Thus, the cortical sheet is likely to be divided into cortical areas by the combined and intricate patterns of molecular expression across cortex, supporting a plaid-like organization. We find little evidence for a quilt-like organization where cortical divisions arise by the discrete expression of a single molecule within each area, although the discrete expression of a single gene has been found within visual and somatosensory cortex. While the functional significance of many of the molecular patterns remains to be determined, some molecules (i.e. LAMP, ephrins and Eph receptors) probably contribute to the establishment of specific thalamocortical projections. These projections are particularly important in producing additional patterning in cortex.

Late regionalization in the developing cortex

During the later stages of cortical neurogenesis (i.e. formation of layers IV and II/III), area-specific differences in cortical cytoarchitecture, receptor expression and connectivity begin to emerge. In S1 of rodents, layer IV cells, initially distributed uniformly, become organized into discrete cell clusters called 'barrels' (Woolsey & Van der Loos, 1970). In addition, primary sensory cortices become clearly distinguishable from secondary association areas due to the development of unique patterns of receptor expression for particular neurotransmitters (Fuchs, 1989; Paysan, Bolz, Mohler & Fritschy, 1994; Broide, Robertson & Leslie, 1996). It is also during this time that area-specific patterns of corticocortical, callosal and subcortical connections begin to emerge (Leergaard, Lakke & Bjaalie, 1995; Prasad, Graf, Kingsbury, Clancy & Finlay, 1999).

The development of these area-specific features corresponds with thalamocortical innervation, suggesting that thalamic input may contribute to the cortical differentiation. For instance, the onset of messenger RNA (mRNA) expression for α_7 nicotinic acetycholine (α_7nACh) receptors in the various cortical layers of rat primary somatosensory cortex follows the ingrowth of somatosensory thalamocortical axons by a day (Broide *et al.*, 1996). Moreover, the particularly distinct patterns of α-nACh receptors (as identified by mRNA expression or α-bungarotoxin (α-BTX) binding) and α1-$GABA_A$ receptors that develop in layer IV of the sensory cortices precisely match the pattern of thalamocortical projections (clustered versus unclustered) within these areas (Fuchs, 1989; Broide *et al.*, 1996; Paysan, Kossel, Bolz & Fritschy, 1997). While these observations suggest a role for thalamic input in cortical specification, direct evidence for its importance comes from experiments where the normal relay of thalamocortical information is either changed or reduced.

Thalamic input induces unique cytoarchitecture

Thalamic input is important in the cytoarchitectonic specification of cortical areas. This has been most clearly demonstrated in cortical transplantation experiments in rats, in which the nature of the sensory thalamic input growing into a cortical region was altered (Schlaggar & O'Leary, 1991). Unlike the clustered organization of layer IV cells (barrels) that emerges in S1 of rats, cells in layer IV of V1 normally remain uniformly distributed. If, however, a piece of late fetal visual cortex is transplanted into the somatosensory cortex of a newborn rat, cells in layer IV of the visual transplant cluster to form barrels. Importantly, the emergence of cell

clustering in the transplant is dependent on somatosensory thalamic innervation as barrels fail to form in transplants lacking an ingrowth of ventrobasal thalamic axons. Thus, cues from somatosensory thalamic axons induce the distinct cytoarchitectonic pattern of layer IV cells in rat somatosensory cortex.

Thalamic input also delineates distinct cytoarchitectonic fields in monkeys. Primate striate cortex receives direct thalamic input from the LGN while extrastriate areas receive input from the pulvinar, a neighboring thalamic nucleus. If LGN fibers projecting to primate striate cortex are reduced in embryonic monkeys by bilateral enucleation, the extent of striate cortex (as defined by cytoarchitecture) is also subsequently reduced (Rakic, 1988; Dehay, Horsburgh, Berland, Killackey & Kennedy, 1989; Rakic, Suner & Williams, 1991). The cortex bordering the reduced striate cortex which does not receive its normal thalamic input from the LGN becomes either a hybrid cortex that is cytoarchitectonically distinct from striate and extrastriate areas (Rakic *et al.*, 1991) or simply extrastriate cortex (Dehay, Giroud, Berland, Killackey & Kennedy, 1996). Interestingly, the reduction in striate cortex is not accompanied by a reduction in total isocortex size. Instead, the total amount of cortex devoted to the visual areas remains constant such that the reduction in striate cortex is paralleled by an increase in extrastriate cortex (Dehay *et al.*, 1996). These results suggest that while the broad dimensions of isocortex may be specified earlier in development, afferent input can influence the dimensions and cytoarchitectonics of individual areas, thus contributing to the plaid-like organization of cortex.

Thalamic input regulates neurotransmitter receptors

Thalamic input influences the transient increased expression of neurotransmitter receptors that demarcate the primary sensory areas of the developing cortex. During the first postnatal week in rats, V1, S1 and A1 are distinguished from secondary sensory or association areas by increased α-BTX binding (Fuchs, 1989) that serves as a marker for α_7nACh receptors (Seguela, Wadiche, Dineley-Miller, Dani & Patrick, 1993). In S1, the growth of VB thalamic afferents into cortex slightly precedes the developmental expression of α-BTX binding and α_7nACh receptor mRNA in cortical layers IV and VI (Broide *et al.*, 1996). Unilateral ablation of VB at birth (i.e. when somatosensory thalamocortical axons are just beginning to innervate the cortical plate) results in a significant decrease in the postnatal expression of α_7nACh receptor mRNA and α-BTX in layers IV and VI of the deafferented S1 relative to the intact hemisphere (Broide *et al.*, 1996). Thus, thalamic input regulates the distinct patterns of α_7nACh receptor expression in primary sensory cortex.

Thalamocortical projections also regulate the unique patterns of $GABA_A$ receptor subunits (i.e. α1, α5) that distinguish V1 and S1 from secondary sensory cortices (Paysan *et al.*, 1997). In postnatal rat cortex, cortical layers III–IV of the primary sensory cortices are characterized by a rapid upregulation of α1-$GABA_A$ receptor subunit expression, though the expression in A1 is notably much less distinct than that in V1 and S1. In contrast to the primary areas, layers III–IV of secondary areas show a prominent increase in α5-$GABA_A$ receptor subunit expression. If the thalamic nuclei which project specifically to V1 and S1 (LGN and VB, respectively) are ablated at birth, layers III–IV of V1 and S1 demonstrate a profound decrease in α1 subunit expression and a marked increase in α5 subunit expression at the end of the first postnatal week. As a result of these changes, V1 and S1 are no longer distinguishable from the surrounding secondary areas, suggesting that in the absence of thalamic input primary sensory areas default to the pattern of $GABA_A$ subunit expression in association areas. These findings resemble those of Dehay *et al.* (1996) where primary visual cortex deprived of thalamic input from the LGN acquires cytoarchitecture that is characteristic of surrounding extrastriate cortex.

The transient postnatal increases in α_7nACh receptors and $GABA_A$ receptors following birth correlate with the period of synaptogenesis (Blue & Parnavelas, 1983). Thus, by regulating the expression of distinct receptor subtypes within the primary sensory areas, thalamic afferents may contribute to the emergence of area-specific cortical circuitry. A more direct role for thalamic input in the establishment of cortical circuitry comes from studies which demonstrate an alteration in cortical projections following the manipulation of thalamocortical input.

Thalamic input influences cortical connectivity

Cortical transplantation experiments suggest that thalamocortical afferents may contribute to the patterning of cortical efferent projections. During early postnatal development in rodents, patterns of area-specific connections are established between the isocortex and subcortical targets. For instance, visual cortex forms permanent connections in the tectum but not the spinal cord while sensorimotor cortex forms permanent connections in the spinal cord but not the tectum (O'Leary *et al.*, 1990). If late fetal sensorimotor cortex or visual cortex is transplanted heterotopically into postnatal cortex, the transplanted tissue develops

subcortical connections appropriate for the area into which it is transplanted: visual cortex transplanted to sensorimotor cortex forms a permanent connection to the spinal cord while sensorimotor cortex transplanted to visual cortex projects permanently to the tectum but not the spinal cord (Stanfield & O'Leary, 1985; O'Leary & Stanfield, 1989). Importantly, the transplanted cortex receives thalamocortical afferents appropriate for its new location (Schlaggar & O'Leary, 1991; O'Leary, Schlaggar & Stanfield, 1992). Although some recent experiments suggest that the connectivity of heterotopically transplanted cortex is characteristic of its site of origin (i.e. sensorimotor cortex transplanted to visual cortex develops sensorimotor subcortical connections; Ebrahimi-Gaillard, Guitet, Garnier & Roger, 1994), the subcortical connections of the transplant are nonetheless appropriate for the type of thalamic input it receives (Frappe, Roger & Gaillard, 1999). Taken together, these results suggest that thalamocortical input may influence the patterning of specific cortical connections.

In our laboratory, we have specifically addressed the role of thalamic input in the development of cortical circuitry by examining how connections form in cortical areas that receive reduced thalamic input or no thalamic input at all. In particular, we have studied the adult callosal, corticocortical and corticopontine projections of visual cortex that has been deprived of its normal thalamic input by early visual thalamic ablation. Hamster pups received unilateral thalamic ablations of the visual thalamic nuclei (LGN; lateral nucleus, L; lateral posterior nucleus, LP) on the day of birth before the majority of the thalamic afferents from these nuclei have been shown to invade the developing visual cortex (Miller, Chou & Finlay, 1993). Following this procedure, there is little or no reorganization of the remaining thalamocortical afferents to the denervated cortex (Miller, Windrem & Finlay, 1991).

Using retrograde and anterograde tracers to visualize cortical connections projecting into and out of deafferented visual cortex, we find that early visual thalamic ablations substantially alter adult cortical connectivity. Specifically, ablations result in an increase in the tangential spread and number of retrogradely labeled callosal and corticocortical cells projecting into deafferented visual cortex (compare Figure 4(a) with 4(b); Miller *et al.*, 1991; Kingsbury, Miller & Finlay, 1995). Perhaps most striking is that while most of the corticocortical connections projecting to visual cortex in a normal animal arise from the surrounding visual cortices (V1 and V2; Figure 4(a)), the visual cortex of lesioned animals has a substantial increase in the number of connections from non-visual cortices, particularly from the somatosensory and temporal cortices (S1 and A1; Figure 4(b)).

We also observe a remarkable increase in corticopontine connections arising from the deafferented cortex (Kingsbury, Graf & Finlay, 2000). Whereas efferent projections from visual cortex are normally confined to rostral and caudal patches in the lateral pontine nucleus (Figure 4(c)), projections in lesioned animals spread throughout the lateral pons (Figure 4(d)), as well as into medial pons. Interestingly, the early removal of thalamic input to visual cortex does not arrest visual corticopontine connections in an immature developmental state as projections equivalent to those in the adult animals which received neonatal thalamic ablations are not observed during normal development (Kingsbury *et al.*, 2000).

While it is unclear whether the reorganization in cortical connectivity that we observed following thalamic ablation results from a disruption in the patterned activity relayed by thalamocortical afferents, cross-modal rewiring experiments suggest that the activity in thalamocortical fibers does shape cortical connections. By ablating V1 and the superior (visual) and inferior (auditory) colliculi in neonatal ferrets, retinal input can be diverted into the auditory thalamic nucleus and relayed to primary auditory cortex. Previously, it has been shown that this rewiring results in the development of visual response properties and topography in A1 (Roe, Pallas, Hahm & Sur, 1990; Roe, Pallas, Kwon & Sur, 1992). More recent experiments demonstrate that the functional reorganization in A1 of rewired ferrets is accompanied by an alteration in horizontal and callosal connectivity (Gao & Pallas, 1999; Pallas, Littman & Moore, 1999). The reorganization of connections in A1 following a change in the sensory input to A1, rather than a change in the source of thalamocortical axons, supports the hypothesis that the pattern of activity relayed through the thalamic afferents is responsible for the reorganization.

Summary of late cortical regionalization

The cortex continues to show differentiation during the later stages of neurogenesis, particularly within the primary sensory areas, as discrete patterns of cytoarchitecture, neurotransmitter receptor expression and connectivity begin to emerge. Much of this late cortical patterning is induced, maintained or shaped by the input from specific sensory thalamic nuclei. In experiments in which thalamocortical input is altered or removed, the cortex shows subsequent changes in the organization of these properties.

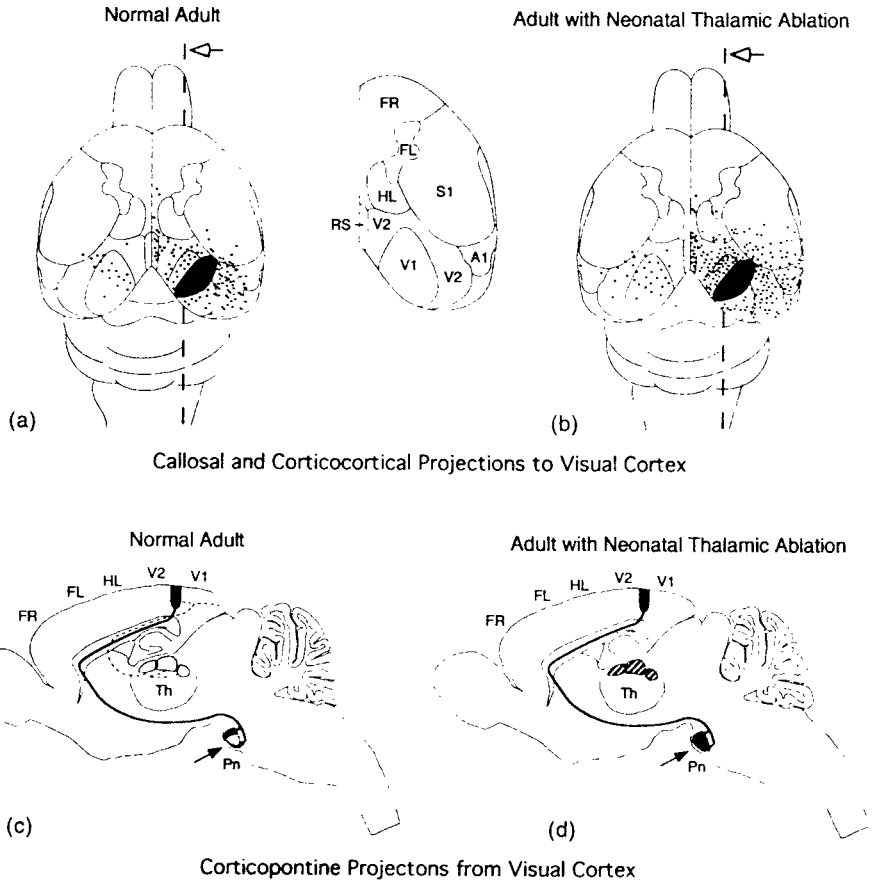

Figure 4 *Comparison of cortical connections in normal adult hamsters and hamsters given neonatal thalamic ablations. (a), (b) Dorsal views of the brain illustrating the distribution of retrogradely labeled callosal (left hemispheres) and corticocortical (right hemispheres) cells projecting into normal visual cortex (a) and visual cortex deafferented of early visual thalamic input (b). The black region represents the injection site in visual cortex; the dots represent labeled cells. The inset between (a) and (b) shows the parcellation of one cortical hemisphere into individual areas. (c), (d) Sagittal views (obtained by partitioning the cortex along the dotted lines in (a) and (b)) illustrating the distribution of corticopontine projections (arrows) from the visual cortex of normal (c) and ablated (d) hamsters. Dotted lines in (c) represent visual thalamic projections to visual cortex. Shaded regions in (d) represent the ablated visual thalamic nuclei. Abbreviations: A1, primary auditory cortex; FL, forelimb cortex; FR, frontal cortex; HL, hindlimb cortex; Pn, pontine nucleus; RS, retrospenial agranular cortex; S1, primary somatosensory cortex; Th, thalamus; V1, primary visual cortex; V2, secondary visual cortex. Rostral is to the top in (a), (b) and to the left in (c), (d).*

When examining the entire period of cortical development (early and late regionalization combined), cortical areas appear to arise from a combination of multiple processes being imposed on the cortex. We have described some of these processes contributing to a differentiated cortex, such as the differential fates of progenitor cells, the graded, overlapping and often changing expression of various molecules, and the incoming sensory thalamic input, although there are likely to be many others factors contributing to cortical patterning (e.g. cell death, cholinergic and serotonergic projections to cortex). Thus, if we return again to the metaphor of the plaid fabric, we find that different processes in cortex are comparable to the threads of the fabric, which, when woven together, generate the plaid organization of cortex. This organization is especially evident when looking at the expression of molecules such as transcription factors and neurotransmitter receptors. We generally do not see each cortical area becoming distinguished from others through the unique expression of a few molecules located solely within that area. Instead, many of the cortical areas share features or molecules with others and it is the unique combination of many of the shared cortical features that defines an area.

Summarizing the evolutionary and developmental literature

Primary visual and somatosensory are candidates for special areal status

Visual cortex

On virtually every dimension that we have described, primary visual cortex stands out as a candidate for special status within the isocortex. The homologue of striate cortex is structurally distinct in birds and reptiles. V1 scales independently of the rest of the cortex and, at least in primates, has a different pattern of cell proliferation. Some early gradients of molecular expression mark striate cortex boundaries and the postnatal expression of one transcription factor, *Otx-2*, precisely delineates visual cortex. Along with other primary sensory cortices, visual cortex shows a distinct pattern of early neurotransmitter complements.

The early differences in gene expression and proliferation suggest the availability of genetic instructions in the visual cortex (and other primary sensory cortices) that could come under the control of other genes, or control other gene expression themselves, such that visual cortex could further differentiate as a unit along lines different from that of neighboring tissue. But, we should recall that visual cortex is in no way entirely separate from other cortical regions – it shares the laminar organization and connectivity sequence of the rest of the cortex, does a transformation of its input that resembles what other cortical areas do, and when transplanted, can take on the characteristics of the cortex into which it is transplanted. To extend our metaphor somewhat, it appears that the visual cortex has aspects of both a quilt and plaid, exhibiting some features which distinguish it as a unique area, and others which integrate it into the hyperdimensional construction of other cortical 'areas'.

Somatosensory cortex

Primary somatosensory cortex has a list of attributes not quite so extensive as primary visual cortex, but enough to also set it aside. Together with visual cortex, somatosensory cortex receives a particular class of thalamic input (lemnothalamic) in mammals. Its borders are marked by gradients of molecular expression, it is precisely delineated by the expression of one gene in a transgenic mouse and it has the feature of organizing the cell assemblies known as 'barrels' for whisker fields, or other species-typical assemblies for hands, or palpating noses. Like other sensory areas, its neurotransmitter complement is distinct, with part of that information conferred by its input from the thalamus. In earlier observations, Purves and colleagues (Purves, Riddle, White, Gutierrezospina & Lamantia, 1994) had pointed out how both primary somatosensory and visual cortex distinguish themselves from the rest of isocortex by their morphological responsiveness to their input – an elaborated layer IV; ocular dominance columns, barrels and so forth.

Auditory cortex

Primary auditory cortex has an interestingly ambiguous status in this discussion. Particularly considering development, it has been the object of far less study than either visual or somatosensory cortex. One of the causes of the concentration on the other two sensory cortices, however, is that they present morphological specializations that can be easily tracked – auditory cortex is not so recognizable. It has a pattern of thalamic innervation distinct from primary visual and somatosensory cortices and a pattern of early transmitter expression that is similar, though not identical, to the other sensory cortices. Furthermore, no molecule has yet been described which precisely delineates auditory cortex, yet the boundaries of auditory cortex are delimited by the graded expression of early molecules, like those of visual and somatosensory cortices.

'Looking where the light is'

It is reasonable to ask whether the number of indices suggesting separability of sensory cortical areas simply reflects the amount of research interest in them, and if the same intense interest was focused on any random region of parietal or frontal cortex we would find evidence for specialization everywhere. To a minor extent, that is true, and as mentioned in the preceding paragraphs, the simple fact that these areas are differentiable causes them to have more research directed at the differentiable features. However, studies that are focusing on organizing gene or transcription factor expression necessarily target the entire cortex, so that this particular class of study is reasonably free from the bias. For those not experts in the field of gene expression in early development, it is worthwhile to point out the current exploratory nature of the work. Researchers are looking wholesale at everything they can make a marker for (and can afford) in hopes of finding spatial and temporal gradients of gene expression that give clues as to how isocortical organization happens. Although this is a fairly unprincipled ap-

proach, it has particular advantages at the early points of a research enterprise.

Other divisions and gradients

'The rest of the cortex' – collothalamic?

An unusual entity that emerges in this discussion is a leftover. Primary visual, somatosensory and perhaps auditory cortex can be distinguished by a number of factors; limbic cortices can be distinguished by LAMP expression. What is 'the rest of the cortex'? It is posterior parietal, inferotemporal and frontal cortex – areas that can be found in some measure in any mammal, but which undergo a marked and differential proliferation in large-brained ones. The input to these regions is from the lateral posterior and pulvinar regions of the thalamus (for parietal and inferotemporal) and the mediodorsal nucleus of the thalamus (for orbitofrontal and other prefrontal regions), and can be loosely related to the Butler collothalamic division. The relative enlargement of the thalamic nuclei supplying input to these areas of cortex parallels the enlargement of these cortical surfaces themselves (Armstrong, 1979a, 1979b, 1980, 1981). Overall these areas are associated with the proliferation of a number of smaller 'areas' typically containing a topographic map of some sensory or computed dimension.

It is in this 'rest of the cortex' where we would argue that our analogy to the pattern making features of plaid construction might have the best use. Can we find evidence for any kind of spatially or temporally modulated expression of transcription factors, neurotransmitters and so forth whose combination would generate a basis of computational diversity in the frontal and parietal cortices?

Plasticity inherent in interactions of thalamus and cortex?

The pattern of coupled and apparently redundantly controlled mechanisms that we have described, such as the independent expression of GABA-ergic receptors by the cortex with required maintenance by the thalamus in the primary sensory cortices, is very characteristic of developing neural systems (Finlay & Niederer, 1999). The multiplicity of developmental mechanisms producing an outcome, when one mechanism would apparently do, can be seen in two ways: (1) as a fail-safe method for insuring a desired developmental outcome, and (2) in evolutionary time, as a way of generating useful cortex when sensory organs change their capacities or when differential scaling of neural elements introduces size disparities between interconnected regions.

One paradoxical feature of the experimental developmental literature to date is that virtually all of the experiments exploring cortical plasticity, such as the transplant experiments of O'Leary and others (Stanfield & O'Leary, 1985; O'Leary & Stanfield, 1989; Schlaggar & O'Leary, 1991; O'Leary *et al.*, 1992; Ebrahimi-Gaillard *et al.*, 1994; Frappe *et al.*, 1999), the reduction of thalamic input (Rakic, 1988; Dehay *et al.*, 1989; Rakic *et al.*, 1991; Kingsbury *et al.*, 1995, 2000) and the introduction of novel input (Roe *et al.*, 1990, 1992; Gao & Pallas, 1999; Pallas *et al.*, 1999) have uniformly chosen precisely those cortical regions, visual, somatosensory and auditory, that give the most evidence for prespecification and differentiability. Yet, in virtually all of these cases, plasticity has been found – transplanted cortex takes on the properties of its new region (within limits), the tangential dimensions of the striate cortex contract with reduced thalamic input, rewired cortex takes on new electrophysiological processes etc. This observation further underlines the fact that the presence of markers distinguishing a cortical area on some dimensions from its neighbors does not prevent that area of cortex from joining its neighbors in functional properties if developmental conditions require.

Future directions

We hope this paper will provide some impetus for researchers to consider cortical organization more generally when they plan investigations, and not to assume that the apparent modularity of the Brodmann maps requires that investigations be restricted to one module or area at a time. Two kinds of studies will be of particular use. The first are experimental alterations of cortical development, but considered in a phylogenetic context. Recent work examining how the entire projection field of the thalamus can come to be represented on a cortical volume substantially reduced in early development (Huffman *et al.*, 1999) is a good example of such an approach; we also view our experimental reductions of thalamic input to the cortex as a model of the increasing size disparity between cortex and thalamus as brains grow large (Kingsbury *et al.*, 1995, 2000).

Second, there is as yet no comparative developmental literature on the cortex, although the first steps are being made (Striedter, 1997; Puelles, Kuwana, Puelles & Rubenstein, 1999). Great strides are being made in the 'evo–devo' movement in understanding basic features of vertebrate and invertebrate body segmentation by seeing the transmutations in the patterns of gene expression control that correspond to subtle and wholesale changes in body organization (Gerhart & Kirschner, 1997). The problem of segmentation and differentiation of isocortical

areas is in many ways formally identical to the problem of the segmentation and differentiation of the entire body and brain. Increasing knowledge about the nested and overlapping expressions of genes that produce the complex structure of the body will certainly give us insight into what produces the complex fabric of isocortical structure.

Acknowledgements

This paper was prepared with support from NIH Grant R01 19245 to B. Finlay, and an NIMH predoctoral research fellowship to M. Kingsbury (T32 MN19389). We thank Barbara Clancy and James Goodson for their helpful comments on the manuscript, and Aaron Nelson and Peter Kaskan for permission to include their work on cortical scaling.

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Received: 7 January 2000
Accepted: 13 March 2000

COMMENTARIES

Brain evolution and development: passing through the eye of the needle

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Nobody likes the nature–nurture controversy, and everybody agrees that behavioral development reflects the interaction of genetic and environmental forces. And yet the controversy continues, in part because we lack a coherent and testable theory of gene–environment interactions, including a theory of the mechanisms by which genes build brains to serve as their interface with the environment. Some brave but tentative efforts to build such a theory have been offered (Smith & Thelen, 1993; Thelen & Smith, 1994; Elman *et al.*, 1996; Gottlieb, 1997; Quartz & Sejnowski, 1997), but we are not there yet, and while we wait, heat from the old controversy has grown even more intense. Playing off the public's new romance with molecular biology, evolutionary psychologists and other proponents of the 'new nativism' are fanning the flames, proposing an instinct for language (Pinker, 1994), a gene for grammar (Gopnik & Crago, 1991; Szathmary & Smith, 1995; Wexler, 1996; Newmeyer, 1997), genes for racial differences in intelligence (Herrnstein & Murray, 1994) and 'Darwinian algorithms' for such disparate phenomena as detection of dishonesty in others (Tooby & Cosmides, 1990; Cosmides & Tooby, 1994) and the longing to marry someone rich (Pinker, 1997).

In the midst of this hysteria, Kingsbury and Finlay (K&F) have provided a lucid account of cortical development that offers a potential resolution of the nature–nurture debate, or at least a path that will take us away from the flames (see also Gerhart & Kirschner, 1997). Patiently and dispassionately, they take us through current evidence regarding the emergence of cortical specialization. They show that cortical differentiation begins with a small set of initial cuts that (at least at first) are relatively independent of experience (e.g. patterns of neurogenesis and molecular markers that are evident before there is any thalamic input to the cortex). These starting points are widely shared over species, with minor quantitative variations (although such small variations may have big long-term consequences). After this initial cut, the process of cortical development is highly interactive. To a remarkable degree, regional differentiation emerges from the nature of the information that each cortical region receives. For example, although primary visual cortex differs from other regions of cortex in some of its architectural features from the beginning (with roughly twice as many neurons as any other area), it becomes visual because it gets its information from the eye. We know this because, if we change the information, we end up with a completely different result (i.e. representations that correspond to the unexpected input rather than the 'default input' that would have occurred if we had left the animal alone). However, this plasticity is constrained in both species-general and species-specific ways by waves or gradients of endogenous activity that spread across what will (some day) constitute cortical boundaries.

One of the most striking findings in K&F's review revolves around the strong correlations that are observed in relative size from one brain region to another. We tend to think of species differences in brain organization in terms of a mosaic, with specializations involving the selective enlargement of one region independent of the others. And yet comparative studies across species suggest that this rarely occurs. Instead, adaptations arise through global changes in the length of neurogenesis that affect the entire brain, or apply across the few broad cuts that evolution can 'see' (because they are governed by a small set of selectable genes). In other words, species differences in brain organization (with implications for species differences in behavior) reflect quantitative variations across a highly conservative

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vertebrate brain plan with interlocking parts. This is the basis of K&F's central metaphor: cortical differentiation may look like a quilt, but it is built like a plaid.

The evidence summarized by K&F led this reader to a surprising realization: evolutionary psychologists and their behaviorist opponents are wrong for the same reason. Although they lie at opposite extremes in the nature–nurture controversy, each is invested in a radical form of environmentalism: reinforcement for behaviorists, natural selection for evolutionary psychologists. Such overwhelming faith in the power of the environment (in ontogeny, or in phylogeny) ignores the powerful contribution of developmental constraints.

In the eyes of many critics, behaviorism failed as an intellectual program because it failed to take into account the organization of mental life, including species-specific constraints on learning. Reinforcement and frequency do play a role in learning, but they are always superimposed on highly biased and exquisitely organized bodies and brains with a long history, both phylogenetic and ontogenetic. Simply put, one cannot reinforce an elephant to fly, and no amount of operant conditioning will produce a talking flea.

If K&F are right, then evolutionary psychology can be viewed as a form of 'nativist behaviorism', subject to the same kind of criticism. Evolutionary psychologists have based their entire program on principles that are the evolutionary equivalent of reinforcement and frequency: if a behavioral outcome is well established in the species, then it must have been selected (reinforced), and frequent selections (reinforcements) lead to deeper entrenchment in the genome. Underlying these two principles is the crucial assumption that we can get anything we want: (1) if an outcome is desirable, it will be selected; (2) if an outcome occurs, it must have been selected; (3) if an outcome was selected, it must have been desirable. What K&F (and Gerhart & Kirschner) have shown us is that natural selection is important, but it does not work alone, and it cannot have whatever it wants. It must operate within the highly conservative and heavily constrained framework of development, including constraints that are widely shared over species. Out of the vast set of behavioral outcomes that might be desirable, the set that are 'evolvable' is very small (Gerhart & Kirschner, 1997). Furthermore, because of the dynamic and interactive nature of brain development, selection in one domain often brings about unselected consequences in another. Evolution has to pass through the eye of the needle. Development is the eye of the needle, and the key to evolution.

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Multidimensional gene expression in cortical space

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Overlapping and nested gradients? Or discrete regions of gene expression? Plaid? Or quilt? In their paper Kingsbury and Finlay discuss the possible factors leading to specification of cortical tissue in discrete computational units, addressing the topic from both evolutionary and developmental perspectives. I found the work informative, and thought provoking. The authors nicely outlined the current state and future goals of an emerging field. The question they addressed primarily gets to the heart of whether isocortex exists as developmentally and evolutionarily uniform and equipotential tissue, or whether it is patched together in a mosaic fashion. For the most part, it would seem, the answer is a little of both. They urge us to 'look for fields larger than individual areas of adult cortex, developmental gradients and external sources of the cortical patterning, ... in order to understand how cortical areas with unique local properties might arise from global features of organization', but they also give us good reason to make exceptions for primary sensory cortices, particularly visual cortex. Based on current observations, then, I agree with this larger view. On considering what may turn up in a very few years upon more detailed molecular analyses, however, I feel that this view is subject to change pending new discoveries.

It may be all plaid

Kingsbury and Finlay present some very powerful evidence for a 'special status' for primary visual cortex including its likely homologues in birds and reptiles, its molecular profile, its cell density indicative of differences during the proliferative stage of development, and its scaling with respect to the thalamus. Consider though its early development: the genes necessary for making and scaling a visual cortex distinct from other cortex were probably also the result of complex, nested gradients of some gene expression at some stage of development. Regarding scaling: it was recently reported that the area of V1 is contracted into the extreme caudal portion of cortex in mice lacking a transcription factor that is normally expressed in a caudal to rostral gradient, *Emx2* (Bishop, Goudreau & O'Leary, 2000). I would be very interested to know whether a gene similar to *Emx2* exists in birds and reptiles, and whether it impacts development of visual Wulst and dorsal lateral cortex. Or is this gene entirely unrelated to the development of these structures? The issue may be better thought of not as *whether* any area of cortex has special status, but *when* did the final key genes making it a distinct area appear. Key functional changes made prior to the evolution of an isocortex may not be a good enough reason to exempt primary sensory cortices from the plaid. Kingsbury and Finlay's plaid is an attractive metaphor precisely because it is so common a rule of patterning in embryonic development to have particular expression patterns of genes resulting from combinatorial influences of nested expressions of other genes. Every level, then, of brain development is likely to be the result of a hyperdimensional plaid-like process. The special status of V1, or other primary sensory areas, would probably be conferred by the earlier timing of the occurrence of key genes with respect to other cortical areas either evolutionarily or developmentally. Conversely, a late developing expression of the unique features (genes) may well correlate with a later-evolved, possibly later-developing expression (related to Finlay's previous ideas on scaling (Finlay & Darlington, 1995)).

It may be all quilt

Our predispositions for discrete conceptual units aside, consider the following.

If a distinctive anatomy exists in an area of cortex, a distinct gene might be there. Perhaps it will be a glial gene regulating density of myelin, or a cytoskeletal gene regulating dendritic branching. Perhaps it will be there during only one stage of development.

If a distinctive cellular physiology exists, a distinct gene might be there. Perhaps it will be a channel with a

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unique gating feature, or a G-protein linked receptor capable of regulating bursting. Perhaps it will be in only one layer.

If a distinctive type of synaptic plasticity is observed, a distinct gene might be there, though maybe it is only expressed under certain circumstances of thalamic input. Perhaps it will be a particular enzyme, or a transcription factor. Or a gene for sensitivity to thalamic input? And the upregulation or downregulation of the genes regulating plasticity durations (critical periods) – surely these are regulated by genes, subject to selection, and dependent on proper exposure to external influences and gradients of other genes. All can be very area-specific.

Kingsbury and Finlay state that they find little evidence for a quilt-like organization where cortical divisions arise by the discrete expression of a single molecule within each area. They do acknowledge that expressions of single genes have been found delineating visual and somatosensory cortex. They also agree that nested expressions of some genes representing specific areas very probably have resulted in the specific expression of those genes in the induction of area-specific genes and therefore area-specific transmitters, receptors or anatomy etc. My point is that many genes will be found to be area-specific, and the cortex will begin to look very quilt-like as these genes are discovered.

Do single genes confer specific anatomy/physiology/development to particular cortical areas? In fact, it is unlikely to be so. The plasticity of the system speaks volumes (Schlaggar & O'Leary, 1991). But I find it equally unlikely that genes specific for each and every cortical area described will not be found, and at least one will be traced through at least some stage of development. When genes identifying specific regions of cortex are found (and I think that they will be found in abundance), an examination of their expression patterns (across phylogeny and during development) will give a more complete picture of just when and how that area of cortex arose. On this point, I differ from the views expressed by Kingsbury and Finlay in that I simply believe it is unwise to form a conclusion on what is not found, particularly as we stand on the brink of sequencing the entire human genome. No doubt, though, the specific genes to which I am referring will be found in specific areas precisely for the reasons outlined by Kingsbury and Finlay – by nested patterns of genes regulating expression of others in a hyperdimensional fashion.

We don't know – yet

I am acknowledging that there is much to do and much to understand before conclusions are to be drawn (though I do not mean to imply that Kingsbury and Finlay will disagree with this statement). Positive results are compelling, and we should continue to look out for these. Negative results or lack of results, however, will have to wait before they are to be interpreted as proof of the unspecified cortex. We have an incomplete data set at present, and I may be waiting for a very long time before all the genes in cortex are mapped with respect to development, evolution, connectional influence and sensory influence. But I do look forward to the possibility of seeing some obvious evolutionary relationships that had not been previously identified as evolutionary precursors for cortical areas, revealed only by their molecular profile.

I predict that a unique gene will be found for each and every distinct cortical area (an apparent quilt, constructed as a plaid). With the genes in hand, the developmental rules governing their expression and their comparative relationships can be determined. Then, and I think only then, will the 'quilt, plaid or a little of both' question be answered for each area (even layer) of cortex. We may find that the complexity of the 'hyperdimensional plaid' is more than we are prepared to handle. Will the pattern we hope to see end up being overwhelmed and obscured by the complexity of expression patterns? Perhaps. But oh, the misfortune of having too much data to think about!

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Gradients and boundaries: limits of modularity and its influence on the isocortex

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The dominant paradigm in biology at the dawn of the millennium is without doubt reductionist. The impact of the genetic code on biology as a whole and theories of development in particular is truely overwhelming, particularly since the demonstration of the conservation of homeobox genes going from fruitflies to elephants. This approach, however, ignores a basic feature of biological systems, which is the demonstration of huge varieties of adaptive mechanisms. Whereas comparative anatomy and physiology was a main-line feature of biological studies up to 10 or 20 years ago, molecular biology and the promises of the molecular blueprint has become the dominant theme. In neuroscience, because knock-out and knock-in technology has been implemented largely in rodents, we have a blooming understanding of rodent physiology and development (although in passing we need to remember the large number of absent phenotypes in knock-out experiments).

The question of the universality of the rodent model becomes particularly acute when one comes to consider the function and development of the cortex. The question of what the cortex does and how this function is put together during development is a dual challenge. It requires the specification of significant processes and their study during development. This combined approach has been highly significant in the visual system where Hubel and Wiesel pioneered investigations of function–structure relationships which were later investigated during development.

A cornerstone of this work was the physiological role of the multiple representations of the visual field in the cortex. This raised the question, what is a cortical area and what does it do? One of the triumphs of neuroscience is that this question has been so clearly articulated in work at first in cats and more recently and more extensively in monkeys. One of the pitfalls of developmental investigations of the cortex is that a response to this question has been largely confined to investigations of the rodent. A minimal assumption of the latter approach is that cortical areas in mouse are equivalent to cortical areas in primates. Given the psychophysical and behavioural differences in rodents and primates this alone would seem difficult to defend. However, more pragmatically the connectivity of mouse cortex exhibits radically different structural principles from that found in monkey cortex. This suggests a higher degree of equipotentiality in the rodent whereas modularity is characteristic of the primate (Murre & Sturdy, 1995).

These considerations suggest to us that it is necessary to exercise caution when lumping together considerations of rodent and primate development as in the review of Kingsbury and Finlay. While it may be true that similar developmental mechanisms may underlie very early stages of development, the fact that there are widely different operational principles in the adult state suggests that there must be important differences, possibly of a qualitative nature, operating at later stages.

Nested gene expression has provided a powerful description of early segmentation of the hindbrain and it is perhaps too early to say that similarly satisfying descriptions will not be available for the forebrain. Kingsbury and Finlay provide an overview of the numerous examples of gene expression in the cortex, which suggests gradients of expression, but at first sight this does not appear to fit easily with the highly modular organization of the primate cortex. A striking feature of histogenesis of the cortex is that there are important variations of the cell cycle in the ventricular zone generating different cortical areas (Dehay, Giroud, Berland, Smart & Kennedy, 1993; Polleux, Dehay, Moraillon & Kennedy, 1997). We have provided evidence that these regional differences in rates of proliferation transcribe into local differences in neuron number which in turn determine areal differences in cytoarchitecture.

The finding of gradients during cortical development is not restricted to extrastriate areas. In the case of monkey area 17 we found that there was a relatively shallow

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gradient going from very high rates of proliferation in the core region of area 17 to much lower rates of proliferation in area 18 (Kennedy & Dehay, 1993). Part of this gradient is thought to be in response to thalamic release of mitogenic factors (Dehay, Savatier, Cortay & Kennedy, 2001). These findings contrast with the adult where the change in neuron number occurs in a stepwise fashion at the 17–18 border. The mystery is how to go from the developmental gradient to the adult areal pattern. The solution is almost certainly to be found in late stages of development. One possibility is that there are differential rates of migration which could also come under control of the thalamus (Kennedy & Dehay, 1997).

Boundaries and discontinuities have a special significance and in physical systems are based on some sort of gradient. They underline modularity which may be largely developed in the primate. Understanding how gradients are sharpened in development to generate boundaries will be an important step in corticogenesis and the review of Kingsbury and Finlay has the merit of focusing on this important issue.

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Specification of mammalian neocortex: the power of the evo–devo approach in resolving the nature–nurture dichotomy

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Kingsbury and Finlay have put together an illuminating and much-needed review of our current knowledge on the phylogenetic origin and development of primary sensory neocortex. They cleanly lay out the evidence in support of or in refutation of each of the issues to be considered, and propose a unique way of thinking through the remaining questions. The 'evo–devo' approach of combining evolutionary and developmental studies (Goodman & Coughlin, 2000) is extremely powerful. The cortical development field has been mired in controversy for some time, and hopefully with the direction provided by their review Kingsbury and Finlay will give us all a nudge toward a cooperative resolution of the issues.

The authors present some intriguing evidence from their own work and the work of others that certain cortical areas, such as primary visual cortex, represent units that have a uniquely coherent genetic identity, and therefore do not follow the same rules for evolutionary changes such as scaling and connectivity as other cortical areas. Why should the primary sensory cortical areas have a unique visibility to natural selection? It would seem more likely that higher order areas such as inferotemporal cortex would be subject to extreme selection pressures. Perhaps it is the proximity of primary sensory cortex to the outside world, and thus its immediate exposure to natural selection, that causes

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it to be so uniquely specified. In contrast, the influence of the environment on subsequent cortical levels is highly filtered, reducing the impact of extrinsic information. Alternatively, is sensory cortex especially plastic because sensory thalamus is special? Are primary sensory cortices uniquely susceptible to extrinsic (thalamic) influence simply because they receive a lot of it? These are some interesting questions which arise from the information presented in the review.

As the authors point out, there has been a nature–nurture-type dichotomy of views on the developmental control of cortical specification. Such dichotomous views have definite heuristic value, but they always tend to outlive their usefulness. I think we have come to that point with the protomap–protocortex dichotomy, and it is time to move toward a synthesis of what both approaches have yielded and failed to yield. Kingsbury and Finlay stress the likelihood that intrinsic and extrinsic patterning information could act synergistically to specify an area. Early events, prior to connections between the brain and the sensory organs, are necessarily controlled by intrinsic factors, while later events may be directed by extrinsic factors, intrinsic factors, or both. Furthermore, specification events that are under intrinsic control initially may be reversible at later stages by extrinsic information such as patterned sensory activity (see below), and intrinsic and extrinsic factors are likely to interact in as yet unknown ways.

Intrinsic specification of cortical areas might seem to require markers that are unique to each cortical area, or that mark the boundaries of the areas, but in fact this is not necessary. How can the more typical graded pattern of markers be consistent with the need for specification of distinct areas? Kingsbury and Finlay develop the inventive notion of a plaid-like arrangement, in which multiple morphogens are interwoven, producing boundaries between cortical regions by virtue of their combined action at each point in the ventricular zone epithelium. Such boundaries could be produced through differential, threshold-type responses of the tissue to a gradient of a morphogenetic factor, or to several nested factors, as occurs in the hindbrain (Puelles & Rubenstein, 1993). A recent paper by O'Leary and colleagues (Bishop, Goudreau & O'Leary, 2000) supports this notion strongly. They show that knock-out of the regulatory genes *Emx2* or *Pax6* results in the prenatal loss of caudal or rostral portions of the cortical epithelium, respectively, where these genes are normally highly expressed, and a disproportionate expansion of more rostral areas of cortex. The results suggest that the gene is conferring regional identity on portions of cortex. Whether such a regional identity translates into an identity for discrete cortical areas remains an open question.

Given that molecular markers are capable of establishing at least some aspects of cortical regional identity on their own (Miyashita-Lin, Hevner, Wasserman, Martinez & Rubenstein, 1999), what is the role of experience-dependent factors in areal specification? There is substantial evidence that certain areal features can be altered by sensory information. But it is not clear whether this means that an initial intrinsically specified identity is altered by manipulations of thalamic input. For example, sensory deprivation can markedly affect the cytoarchitecture of visual cortex (Dehay, Horsburgh, Berland, Killackey & Kennedy, 1991; Rakic, Suner & Williams, 1991), and heterotopic transplantation of one embryonic cortical region into the place of another can cause the donor tissue to develop host-specific cytoarchitecture and subcortical connectivity patterns (O'Leary & Stanfield, 1989; Schlaggar & O'Leary, 1991). Although the authors propose that thalamic afferents may be the causal factor in the respecification, there are alternative interpretations. The bilateral enucleation paradigm employed by Rakic, Kennedy and colleagues causes massively increased cell death in striate cortex (Rakic, 1988), and this alone would cause marked changes in cytoarchitecture, especially that of layer IV. The cortical transplantation results are also difficult to interpret; although the switch from donor to host characteristics could well result from the change in thalamic input, there are many other potential organizing factors that change with a change in location, such as corticocortical inputs, developmental timing and distribution of morphogens, to name a few. Any or all of these could contribute to the altered appearance of the donor tissue, and thus all that can be rigorously concluded is that the presence of different thalamocortical afferents is coincident with the appearance of host-specific features in the donor tissue. Whether there remain some donor-specific characteristics in the tissue has not been thoroughly investigated. Experience may alter only later-developing characteristics of cortex, but then at what point do we consider that cortical 'identity' has been respecified by extrinsic factors? At some point the argument becomes a semantic one, although one could argue sensibly that early choices made by molecular markers bias later ones made by extrinsic factors.

The importance of extrinsic factors in cortical areal specification would be strongly supported by a demonstration that extrinsic factors could actually respecify cortex that had previously been specified by intrinsic factors. Our work involving the cross-modal 'rewiring' of retinal axons into the auditory thalamus provides visually patterned activity to primary auditory cortex at birth, prior to thalamocortical ingrowth, and without

manipulating the thalamocortical projection pathway (most recently reviewed in Pallas, in press; see also Swindale, 2000). Our results show that primary auditory cortex provided with early visual input resembles visual cortex topographically (Roe, Pallas, Hahm & Sur, 1990), physiologically (Roe, Pallas, Kwon & Sur, 1992) and perceptually (von Melchner, Pallas & Sur, 2000). This surprising situation does not result from coopting existing auditory circuits by the visual activity. Rather, our recent work suggests that patterned visual inputs arriving via auditory thalamus induce and orchestrate physical changes in cortical circuitry that are then responsible for the change in function (Gao & Pallas, 1999; Pallas, Littman & Moore, 1999; Gao, Power, Misra & Pallas, in press). Does this mean that we have created a new cortical area, as might have occurred during evolution? Before it is possible to answer that question, the field must come to a consensus on what 'area' means and what feature(s) mark its origin in both developmental and evolutionary terms. Only by addressing both intrinsic and extrinsic factors involved in cortical specification will this be possible.

What will be interesting in the future is to investigate the interactions between intrinsic and extrinsic factors influencing cortical parcellation. If, as several studies suggest, a change in the periphery can direct differentiation of cortex for the new purpose, then what are the constraints imposed on this plasticity by the intrinsic specification of gradients in polarity, the 'scaffolding' of the cortex? Are there limits to plasticity that can explain some of the evolutionary variation, or lack of variation, that we see? The provocative review by Kingsbury and Finlay will hopefully provoke some study in this direction on the part of all parties to the debate.

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Embryonic stage of commitment of neocortical cells to develop area-specific connections

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Kingsbury and Finlay provide an excellent review on some principles of formation of cortical areas. The authors examine the concept of cortical area from two different aspects: phylogenetic and developmental. They argue that the cortex should be considered as a 'hyperdimensional plaid' rather than a 'patchwork quilt'. Following examination of evolutionary data, they provide evidence that mosaicism is not the rule across species. The most convincing evidence that cortical areas arise from combination of overlapping processes comes from their presentation of developmental data. Most studies indicate that early expression of various molecules shows overlapping gradients of distribution across areas (nested patterns). Only exceptionally are molecule expressions restricted to a single, distinct cortical area. One interesting observation is that molecular regionalization is independent of thalamic axon ingrowth and probably contributes to the subsequent establishment of appropriate thalamocortical connections which, in turn, control area-specific cytoarchitecture organization, receptor expression, connection patterns etc.

In support of this assumption we found that at a certain point in development cortical cells become regionally specified as to their pattern of subcortical connections. Indeed, we found that cells that were taken from the presumptive frontal cortex of embryonic day 16 (E16) rat fetuses and grafted into the occipital cortex of newborn recipients developed and maintained a spinal cord projection (Ebrahimi-Gaillard & Roger, 1996). In contrast, E16 occipital cells grafted into the frontal cortex failed to develop and maintain a spinal projection. In a subsequent series of experiments, we showed that the thalamic connectivity of cortical cells is also specified at the same embryonic age. Cells from the parietal cortex of E16 fetuses grafted into the parietal cortex of newborns systematically developed and maintained connections with the thalamic ventrobasal (VB) complex (Gaillard & Roger, 2000). In marked contrast, E16 cells from the occipital cortex grafted into the parietal cortex of newborns failed to develop and maintain connections with the VB complex but established connections with the dorsal lateral geniculate nucleus. Specifically, our tract-tracing studies clearly showed that VB axons developed normally within the host parietal cortex adjacent to the graft of occipital cells but were incapable of invading it. It is likely, therefore, that these cells had acquired a specific phenotype that no longer allowed VB axon ingrowth. Interestingly, our results also showed that occipital-to-parietal grafts lacking VB input were unable to develop and maintain the specific barrel cytoarchitecture of normal parietal cortex. These findings lend further support to the assumption that thalamocortical afferents from the VB complex provide the immature parietal cortex with barrel-patterning information (Schlaggar & O'Leary, 1994). Taken together, these results indicate that the pattern of connectivity developed by at least some cortical cells is committed by E16 and is not modified following subsequent modification in their environment (heterotopic transplantation). By this embryonic age, therefore, the developing cortical plate can no longer be considered a *tabula rasa*.

Until recently, little information was available on the embryonic age at which the hodological phenotype developed by cortical cells becomes specified. We addressed this issue by examining the spinal or tectal projections developed by grafted cells of varying embryonic ages. The grafts were dissected out of the presumptive frontal or occipital neocortex and placed into the frontal or occipital neocortex of newborn hosts (Pinaudeau, Gaillard & Roger, 2000). We found that grafts of E13, E14 and E16 cells of the frontal cortex that were transplanted into the occipital cortex of newborns were capable of developing and maintaining in adulthood a spinal cord axon. Practically no cells in E12 grafts sent projections to the spinal cord. At E12, therefore, all the instructions necessary for the ultimate

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differentiation of pyramidal neurons with spinal axons are not yet available within the neuroepithelium of the rostral part of the telencephalic vesicle. Indeed, when E12 progenitor cells are removed from the frontal part of the telencephalic vesicle and allowed to complete their evolution in the occipital cortex of newborn hosts. practically no daughter cells differentiate the phenotype of layer V neurons of the frontal cortex.

In addition, we found that E12 frontal cortical cells that were transplanted into the occipital cortex of newborns sent fibers to the superficial layers of the tectum. Our findings therefore provide evidence that regionalizing signals are still present at birth within the occipital cortex so that E12 progenitors from the rostral neuroepithelium subsequently differentiate into neurons with an occipital hodological phenotype. These conclusions are further substantiated by the findings derived from occipital-to-frontal grafts. Indeed, following transplantation into the frontal cortex, early embryonic (E12–E13) cells from the presumptive occipital cortex were capable of differentiating into neurons with spinal cord projections. Our findings indicate that, up to a certain point in development, some precursor cells of the occipital cortex are competent to subsequently differentiate into neurons with phenotypic traits of frontal pyramidal cells. Our results further indicate that, after E13, transplants of presumptive occipital origin fail to respond to signals still available in the frontal cortical region and become practically unable to develop and maintain a spinal projection. Interestingly, these occipital cells that lose the capacity to project to the spinal cord then become able to send fibers to the tectum. Taken together, these findings indicate that young (E12) embryonic frontal and occipital cortical cells are competent to subsequently differentiate into neurons projecting to the spinal cord or tectum according to instructive signals available in the cortical territory where they complete their development. By E13/E14, some cortical cells are specified and their capacity to contact targets that are not appropriate to their embryonic origin is much reduced.

In conclusion, our findings do indicate that transplant cells are capable of developing connections appropriate for the cortical area into which they are grafted. This holds true, however, only up to E13. From E14 onwards, some cortical progenitors become specified. Accordingly, these cells retain the capacity to generate neurons with a hodological phenotype related to their site of origin along the cerebral wall even though appropriate regionalizing signals are lacking. Also, their capacity to develop the hodological phenotype corresponding to the cortical site into which they are grafted is much reduced, even though appropriate regionalizing signals are present.

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Activity-dependent processes in regional cortical specialization

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Most of adult neuropsychology is concerned with attributing functions to particular regions of the cerebral cortex. Few researchers, however, address the more fundamental question of how such specializations develop in the first place. Kingsbury and Finlay are to be congratulated on addressing this critical question head on. Like many issues in biology, the answer to the question of how the cortex differentiates into areas and regions is far from simple. These authors suggest that for most, but not all, regions of cortex differentiation is a result of multiple interacting molecular gradients in interaction with thalamic input. In their words, it is a 'plaid' of interacting threads rather than a 'quilt' of separate panels. In this commentary we expand upon these conclusions in two directions: first, we draw out some of the implications of these views for developmental psychologists, and second we draw attention to the likely importance of functional neural activity in cortical differentiation.

One current thrust in infancy research is based on the assumption that, early in life, the infant's brain is composed of a number of domain-specific modules. These modules are often assumed to have a genetic basis, and one type of explanation of some developmental disorders of genetic origin is that one or other of these modules is 'lesioned'. The data reviewed by Kingsbury and Finlay, however, suggest that, primary sensory cortices apart, it is unlikely that there are cortical regions defined by region-specific gene expression. The implication of this is that cortical specialization for cognitive function is better described in terms of an interacting factors framework (Johnson, 2000). Thus, we believe that the evidence reviewed by Kingsbury and Finlay is more consistent with cognitive models that attempt to explain the gradual emergence of functions (e.g. Munakata, McClelland, Johnson & Siegler, 1997).

The second point we wish to make in our commentary concerns an additional factor involved in cortical differentiation that we believe was somewhat underemphasized by Kingsbury and Finlay, namely functional activity. There is now considerable evidence for the importance of neuronal activity in shaping subsequent neural circuitry (Greenough, Black & Wallace, 1993; Katz & Shatz, 1996). Some of the mechanisms underlying this activity-dependent shaping have been studied in detail through artificial neural network modelling (Jacobs, 1999). These models show that an initially homogeneous neural architecture can be differentiated into functionally specialized structures through the application of simple activity-dependent learning rules. Critical factors for such models are the refinement of synaptic weights in response to structured afferent input and competition between elements. The formation of both small-scale and large-scale structures has been modelled using similar mechanisms. In the former class are those models which simulate the functional specialization of neurons and cortical columns using competition between neuronal elements, e.g. the many models of ocular dominance and orientation column formation in V1 (Swindale, 1996). In the latter class are models of the functional specialization of cortical regions, in which there is competition between separate neural networks resulting in each network learning a different task (Dailey & Cottrell, 1999; Jacobs, 1999). Competition between elements (either neurons or networks) is essential for differentiation. An element which has a small initial bias for a particular function will be likely to win the competition for that function and hence learn to be even better suited to it. Competitive mechanisms thus tend to enhance any initial differences that may exist between elements. These models thus show that small, gradual, innate differences across the cortex could give rise to large, sharply bounded structures in adults with a high degree of uniformity across individuals despite the plasticity of the cortex. The same outcome could result whether the initial bias was due to a genetic predetermination to generate specific cortical regions or resulted from arbitrary variations. In contrast, the origin of the functional activity is crucial to determining the resulting structure, and is thus at least as important as molecular factors.

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We conclude that the structural and functional development of the cortex are inextricably intertwined, and a full account of structural differentiation within the cortex will need to take account of activity-dependent processes. Computational modelling provides a valuable tool for evaluating and refining such theories and is likely to play an important role in helping to understand the regional specialization of the cortex.

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RESPONSE

An evo–devo tapestry: quilts, plaids and needles

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While we have no particular desire to encourage the further proliferation of textile metaphors in developmental neurobiology, we are pleased that most of the commentators found the idea of the areas of cortex arising from the type of process that makes a plaid a useful one. The collection of evidence that shows nested and graded patterns of gene expression that appeared capable of producing new cortical areas in large brains in combinatorial fashion was viewed as an accurate understanding of our knowledge this far. Dudek and Pallas point out a new paper of importance to this perspective which we would also like to underline: the observation of Bishop, Goudreau and O'Leary (2000) that alteration of the expression of early, graded, gene expression caused a shifting of the boundaries of cortical areas across the cortical surface in a wholesale manner.

Epigenesis of areas: what's a commitment?

Important semantic and interpretative issues in cortical epigenesis were brought up by a number of the commentators. Pallas brings up the essential problem of what we mean by 'commitment': both cortical neurons and cortical areas have multiple dimensions on which their fate is progressively restricted. On which continua and on what basis do we decide (or should we decide) that a neuron or area has been 'committed' to its adult fate, separate from an exhaustive list of its properties? Are there clusters of properties that covary, as if in response to the same specification event? As Dudek points out, one common criterion of the unique status of an area has been the expression of any gene that spatially delineates it, but this type of marker could certainly arise from 'plaid' mechanisms, or even activity-dependent environmental interactions. One persistent semantic problem of the developmental literature is that the word 'specify' is used interchangeably in the senses of both 'delineate' and also 'determine the properties of'. This semantic problem goes straight to a recurring interpretative problem, in that we are predisposed to assume that any single dimension that identifies an area should covary with many other attributes, as it would for an object or an individual in the world. Developmental neurobiology needs to come to terms with its limited version of the descriptive problem produced by wave/quantum entities that physics has dealt with for many decades.

Several empirical issues in epigenesis were also pointed out. Roger underlined new data on the progressive restriction of cortical cell fate across time, citing his most recent results from transplant experiments. These results demonstrate that thalamocortical and subcortical connections of cortical cells are specified as early as embryonic day 13 (Gaillard & Roger, 2000; Pinaudeau, Gaillard & Roger, 2000). While these experiments show the initiation of a trajectory that in a context determines a particular cell fate, it is important to remember that it does not disclose all the potential or natural further determinants of that fate, or every aspect of cell fate, as above. For example, the fate of cells in somatosensory cortex to express a molecular marker is determined at E11.5 (Gitton, Cohen-Tannoudji & Wassef, 1999a), yet the maintenance of this molecular expression after birth is dependent on intact somatosensory thalamic afferents (Gitton, Cohen-Tannoudji & Wassef, 1999b). Our experiments (Kingsbury, Graf & Finlay, 2000) and those of Pallas and her colleagues (Gao & Pallas, 1999; Pallas, Littman & Moore, 1999) show that cortical connectivity can be changed during development by removing thalamic input or altering the nature of thalamic input to cortex. We believe that the search for multiple processes acting on cortical cells at numerous development time points (and the interactions between processes) will provide a richer view of cortical development, as well as a better grasp of plasticity at the

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various ages. With regard to the transplant experiments, it would be interesting to know if the commitment to express particular molecular markers can be correlated with the commitment to develop particular patterns of connectivity. If so, what happens to the molecular and connectional phenotype of transplanted cortical cells if they are denied any thalamocortical input during development or if molecular markers are misexpressed in a cortical region?

Spratling and Johnson point out that the important role of functional activity in shaping cortical structure was underemphasized in our review, which is certainly the case, given our focus on early gene expression. The central importance of functional activity has been eloquently demonstrated in rewiring experiments where ferrets have visual input directed to auditory cortex during early development. As Pallas mentions in her commentary, auditory cortex receiving peripheral input from retinal afferents resembles visual cortex in topography, physiology, connectivity and perceptual processing (Roe, Pallas, Hahm & Sur, 1990; Roe, Pallas, Kwon & Sur, 1992; Gao & Pallas, 1999; Pallas *et al.*, 1999; von Melchner, Pallas & Sur, 2000).

Kennedy and Dehay stress caution when considering similar developmental mechanisms for rodents and primates since they claim that important differences must exist at some stage to generate the functional and behavioral differences characterizing each species. The cortices in larger mammals are certainly not multiplicatively enlarged versions of those in smaller mammals, but we stress the importance of systematic search for rules of extrapolation. For example, the analysis of Murre and Sturdy (1995) that Kennedy and Dehay cite as evidence of the fundamental difference of small and large cortices does not posit two types of cortex with different connection rules. Rather, they argue that, as interconnected structures progressively enlarge, interconnectivity must be systematically reduced to counteract the combinatorial explosion of connectivity that would otherwise result. Given the ubiquitous nature of the primary sensory cortices (without discounting the unique specializations within these cortices, e.g. barrels, blobs etc.), perhaps examination of the developmental organization of cortices that are greatly expanded in primates (i.e. posterior parietal, inferotemporal and frontal cortices) can provide meaningful insight into how functional differences arise between rodents and primates.

What can change, and how?

Pallas pointed out the interesting and somewhat counterintuitive nature of the observation that it is the most ancient cortical areas that show the most evidence of specialization in terms of gene expression, while areas that might seem most likely to be the targets of special selection, e.g. face-recognition areas in inferotemporal cortex, have not popped out in terms of localized gene expression. In another sense, this observation is quite logical, in that the most ancient and stable areas have had the most time to accrue specific adaptations. An interesting entailment of this observation is that the most recent, apparently idiosyncratic and species-specific behavioral adaptations may at their core be required to use the most generic neural mechanisms for their production. For example, perhaps recognition of objects over variation in retinal size, a species-general ability, might have a genetically specified, visual-domain-specific, 'wired-in' solution, while the recognition of other types of relational invariants that only primates and humans show (Tomasello, 1998) would use domain-general architecture.

Finally, Bates finds a very interesting parallel of behaviorism and current evolutionary psychology in that both assume the environment has extreme power to produce new behavior and associated neural structure in developmental time on the one hand and evolutionary time on the other. Both schools downplay the constraints of existing neural and genetic architecture, allowing unlimited behavioral plasticity on the one hand or panselectionism on the other. But how are we to understand the role of existing architecture? In combination with Pallas's observation, we might explore a new taxonomy of perceptual and cognitive capacities – those that are the 'most ancient' or most common to all species would be the most likely to have committed or unusual processing mechanisms, while newer ones might have more generality. A rigorous evolutionary and developmental approach to cognition, in the explicit context of our rapidly expanding knowledge of brain evolution and development, is an inviting possibility.

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