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

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

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 truly 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

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

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 under-emphasized by Kingsbury and Finlay, namely func-tional 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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