In *Beyond Nature-Nurture: Essays in Honor of Elizabeth Bates*
M. Tomasello and S. Slobin, eds.
Lawrence Earlbaum Publishers pp195-219

**Rethinking Developmental Neurobiology**

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Liz Bates gave a talk at ICIS, the International Conference on Infant Studies in 1996 and the conference organizers offered tapes of it, only $11. A bargain, as I have played it to my Developmental Neuroscience class ever since, and more than I bargained for, as the repetitions of this talk slowly restructured my thinking on developmental neurobiology. In my mind, the talk is titled “Unnecessary Entailments”, though Liz probably titled it something pithier. I have since discovered it touches on virtually all of the major themes that weave through her imposing volume of work. In this talk, she dissected the unnecessary identities that have proliferated in the conceptual structure of cognitive neuroscience. How a complex problem, mapping the structure of the world onto a string of speech, may produce a unique and complicated neural structure but not entail a corresponding structure of complicated innate rules. How the fact that somewhere-localized, physical changes in the brain must accompany any new thought (in this case, her husband George’s shoe size) neither entail biological determinism nor an impenetrable neural center for shoe size. How that the fact we can identify language as a unique human ability does not entail unique corresponding structure in the genome. And most important, this talk supplied the correct response to the “I can’t imagine how…” argument – Liz correctly pointed out that this argument entails only incapacity in the speaker, but nothing about the structure of cognition, the brain, or the genome. Her own imagination has consistently outrun the opposition.

I have since applied this critical approach wholesale to the way people apply the information of developmental neurobiology to cognitive development and the reverse, and I hope here I can literally flesh out some of Liz Bates’ deductions about the nature of
the physical structure of the developing brain. Also, I will spend a little time tracing the tracks of entailments and assumptions back and forth between disciplines. One of my professional roles has come to be interdisciplinary translator, as my research and reading lies principally in developmental neurobiology and biology, while my departmental home and journal work are in psychology and cognitive science. I would hope to explain each group to the other, running the intermediary’s perpetual risk of alienating both.

Biologists and psychologists approach developmental questions in fundamentally different ways, but very often import each other’s terminology without question, using words more often as metaphors than as items with particular definitions. In this paper, I will discuss theory-making in both disciplines first, and then discuss the concepts of modules and cortical areas which do service in both domains, both in their computational and developmental aspects.

Theories of everything. It’s the rare neurobiologist who would make a wholesale claim like “Every neuron in the nervous system is capable of activity-dependent stabilization of its synapses” and then, as a research enterprise, set out to demonstrate the existence of one instance after another. Such broad statements, such as, “Cognition is rule-based” are more typical of cognitive scientists. Neurobiologists more often address a prominent, and promising piece of organization. Hypothesis-generation comes second and concerns how the piece works, or how it got that way. For example, the curiously part-transient, first-generated neurons of the cortex, the subplate, were hypothesized to be a developmental scaffold for the cortex (Shatz, Chun et al. 1988), and the research race was on to confirm or deny the guess. In many cases, the piece of organization is often called a model system which is asked to stand for the actual system
the researcher is interested in, but for reasons or complexity or inaccessibility, cannot. Thus we have the development of bird song motivated as a model system for human language, or long-term potentiation in the hippocampus as a model for learning, more generally. A suitably interesting model system soon takes on its own life and will apply to many more questions than initially motivated its choice, and will generate a set of researchers who will identify themselves with the system, “I work on LTP”, “I’m a bird-song person”.

Investigation of the striped arrangement of ocular dominance columns in primary visual cortex is an interesting case of a self-organizing neurobiological research system using this general approach. Hubel and Wiesel first noted that neurons in primary visual cortex were either sensitive to one eye, or the other, or both, in a columnar organization extending the depth of the cortex. Looking at the cortical surface, these columns were organized in a system of stripes (Hubel and Wiesel 1962; 1968). Further, if one eye were deprived of experience, the stripes belonging to the deprived eye all but disappeared (Wiesel and Hubel 1965; Hubel, Wiesel et al. 1977). The multifarious applications of these observations for understanding the nature of visual perception, activity-dependent learning, the nature of the visual cortex as a learning device, and for various ophthalmologic disorders were immediately apparent. Hundreds of papers have been written on various aspects of ocular dominance columns and stripes, with perhaps the most notable result (of a number of different results) a fairly complete mechanistic explication of how presynaptic axons whose activity are correlated take up and stabilize connections on the same neuron – the mechanism of the basic Hebbian synapse, “fire together, wire together” (for a reasonably recent exemplar, Kirkwood, Lee et al. 1995).
Whether ocular dominance columns themselves have any functional significance is not clear, curiously enough. To be sure, if a deprived eye claims no cortical territory at all, its acuity and capacities are meager (Wiesel 1982). Clearly, correlation and lack of correlation of input from the two eyes serves multiple functions. A difference of location of a single contour in the two eyes signifies depth relative to plane of focus (the use of binocular disparity for stereoscopic depth); a tag about the eye-of-origin of non-matching visual input can be used to segregate object boundaries; duplicate information from the two eyes in low light conditions can be used to confirm a guess about what’s out there. It is the need to segregate eye-specific information into stripes, however, which is not clear. The separation of the two eyes into stripes in their cortical representation can apparently be eliminated with no obvious loss of visual function – old and recent reports of New World monkeys show animals in possession of good binocular vision with nonexistent or variable ocular dominance stripes (Livingstone, Nori et al. 1995; Livingstone 1996; Adams and Horton 2003). Just as any artificial neural net might recover correlated structure coming from two eyes without any corresponding spatial structure of stripes in its “hidden” layer, so can the visual system. So, after years of research, we have some clear answers to “How does it get that way?” and “How does it work?” (in the sense of how receptive fields organize their local input) in this eye-catching piece of morphology but can say little about the functional necessity of stripes per se. In fact, there is every reason to believe that the emergence of stripes is a non-essential epiphenomenon of the combined interaction of a set of neurons and their inputs whose activity-dependent sorting function is trying to satisfy two constraints simultaneously, eye-of-origin, and topographic position within the eye (for example, Swindale 2000). Activity-dependent
sorting parameters or initial conditions may predispose to the stripe solution, but in fact other perfectly functional configurations exist. I have extended this example in order to return to what I will claim is a similar evolution in the understanding of the significance of a “cortical area.”

Cognitive scientists, both those with developmental interests and not, are more apt to begin from more principled, hypothetical stances about the structure of cognition, often as embodied in a particular intellectual leader – i.e. “Gibsonian”, “Piagetian”, “Vygotskian”. The most salient stances in this context are those who try to understand language by the operation of general-purpose devices, connectionists, and those who in the Chomskian lineage who contend it is rule-based. I do not wish to caricature the members of either group, as various complex interactionist positions have evolved as the evidence evolves. I also acknowledge the cognitive scientists who behave like neurobiologists, those who latch onto juicy-looking phenomena whose explanations promise answers to interesting questions in a number of domains. In general, however, definitions are used quite differently depending what type of theoretical position you start from. A “module” in cognitive psychology has an accepted definition, due to Fodor (1992), history, and the requirements of deductive argumentation. A “module” to a neurobiologist has a fuzzier and inductively derived meaning, often referring to some sort of repeating functional unit, which carries with it no claims of impenetrability or special structure. “Rules” and “laws” have a different status in research areas that are phenomenon- driven versus concept-driven.

Scientists of all descriptions are very interested in importing confirmatory evidence of either the truth of their theory (cognitive scientists, principally) or the
functional importance of the phenomenon they are investigating (neurobiologists).

Neither group is likely to look quite as closely at the evidence supplied by another field as they are to their own, relying, as is quite reasonable, on a mapping of the principal terms used by one field into the other. In the case of the cortical area, cognitive scientists and neurobiologists have unwittingly colluded in their mutual interests in giving special prominence to the “cortical area.” Cortical areas are reasonably prominent pieces of morphology that divide up an anatomical region that appears intractably large and uniform, and which promise a straightforward mechanistic answer to how they come to be; cognitive scientists, for quite some time, were looking for the physiological correlate of the boxes with arrows between them. Cortical areas have been given the status of an important unit in cognition, a location and a module (perhaps impenetrable) where a particular computation is done and shipped out to the next area/module. But increasingly, neither the definitions used nor the evidence evolving in either domain corresponds to reality, nor to each other. I will argue now that cortical areas may well be like the stripes formed by ocular dominance columns, easily-seen morphological divisions that carries information about the process of information segregation and dispersal in the nervous system, but that has little functional interest in its own right. Of course, Liz Bates has been arguing that searching for modules in the nervous system has been a poorly justified enterprise for years. Moreover, one of her very latest articles (Bates, Wilson et al. 2003 “Voxel-based lesion-symptom mapping”) tells us what to do next when deprived of this fundamental piece of grammar/structure in theory-building as the identities of cognitive scientists and neurobiologist finally become entwined in functional brain imaging.
Cortical areas in brain space and developmental time.

**Brodmann’s enduring influence.** The obvious way to begin a talk in any number of areas of cognitive neuroscience or developmental neurobiology (and I do it myself) is to flash a picture of Brodmann’s original delineation of substructure in cortical architecture, showing the divisions of the human cerebral cortex, ca.1900. The whole cerebral cortex (“neocortex” or more properly “isocortex”) has a consistent structure of layering of input and output, the reason it is given a single name. However, local differentiation exists. This local differentiation essentially comes down to thalamic input it attracts (or allows) and eventually receives (though the claim here is not that the cortex is entirely undifferentiated and receives its instructions through the thalamus, to be explained). First, a brief review of relevant cortical structure.

The key to understanding cortical structure, both in development and adulthood, is to understand that the “cortical column” (the fundamental, repeating unit of the cortex) does a stereotyped intake, transformation and distribution of information within a matrix of local and distant influences from the rest of the cortex. The functional contents of any particular column are wildly diverse, depending on their input. The defining input to the cortex (i.e. whether it is called “visual, motor, somatosensory”) comes from the thalamus. The thalamus itself gets its input from 1) the senses including sight, sound, touch and body position 2) from other parts of the brain which give about the body’s state of motion, emotion, homeostasis and arousal state and 3) from the cortex itself. The thalamus might be a kind of transduction device that takes these diverse inputs and transforms it to a common code appropriate to the uniform operations of the cortex, though this characterization remains a guess. The input from the thalamus goes to the
middle layer, Layer IV, and to a lesser extent, to the upper part of Layer VI. This thalamic information in Layer IV is then relayed up and down, to Layers II and III, and to Layers V and VI. The majority of synaptic connections most input cells of the cortex will make are restricted to the column several cells wide that extends perpendicularly from Layer IV to the cortical surface, and down to Layer VI. All the cells in a particular column participate in similar contexts. For a few examples, taken from widely separated parts of the cortex, one column might fire to stimulation of a particular location and type of sensation on the body surface, another before a particular trajectory of arm movement, and another when the individual is anxious in a social context.

The activity in these columns is continually modified by the local, regional and distant context supplied from other cortical areas (Gilbert, Das et al. 1996; Albright and Stoner 2002; see also Merker (in press) for an interesting conceptualization of how to describe this context). Even in primary visual cortex, less than 5% of the excitatory input to a cortical column is estimated to be of thalamic origin, and the rest is intracortical and some external modulatory input (Peters and Payne 1993; Peters, Payne et al. 1994). Intracortical input comes from Layers II and III. Axons from these layers distribute to neighboring cortical areas (for example, from primary to secondary visual cortex); to distant cortical areas (for example, from secondary visual cortex to visuomotor fields in frontal cortex); and across the corpus callosum to the cortex on the other side of the brain. The principal output connection of Layer VI is a reciprocal connection back to the thalamus, which can be massive – even in the case of the lateral geniculate nucleus, the most primary of primary sensory areas in the thalamus, the vast majority of inputs to the nucleus itself are not from the retina, but rather are reciprocal inputs back from primary
visual cortex and modulatory inputs from the brainstem (Erisir, Van Horn et al. 1997). The point of this description is to emphasize that while thalamic input brings new sensory information to the cortex, it might be better to think of the thalamus as installing new information in an immense current and historical context.

The next level of organization past the column, the “cortical area”, has inputs, descending connections and relative specializations of layers that reflect its relative position in this intake and distribution of information. Primary visual cortex, which receives thalamic input of input relayed from the retina, has an unusually large number of cells in Layer IV. In motor cortex, Layer IV is almost absent, and the cells of Layer V, the output layer connecting to downstream motor centers and the spinal cord, are unusually large and prominent. Each cortical area typically contains a topographic representation of a sensory, motor or other computed dimension (any derived ordered array, for example, location in 3-D auditory space, which has no sensory surface like the retina). A large number of these represent egocentric space, in various modalities. The cortical topographic map is often a direct replication of the same topographic array already represented in the thalamus. Each area has unique input and output and a limited repertoire of physiological transformations of its thalamic input, such as the elongated, orientation-selective visual receptive fields of primary visual cortex that are constructed from the symmetrical center-surround visual fields of their visual input.

**Making areas** What is the source of the information that gives cortical areas their distinct input and output connections and other specialized local features? Only recently, the cortex has come to be understood in the same genomic terms that structures like the entire vertebrate body plan, or spinal cord segmentation are understood (Ragsdale
and Grove 2001; Muzio and Mallamaci 2003). These schemes are rather counterintuitive to the amateur human architect, who typically imagines expression of Gene A corresponds to Segment A or Cortical Area A, and Gene B, Segment B and so on. Rather, adult “parts”, like a spinal cord segment or cortical area, correspond to regions in overlapping and nested patterns of regulatory genes. The relative level of expression of these genes controls the expression of other regulatory genes, “transcription factors”, and those in turn, direct the genes that direct the construction of particular molecules like structural proteins of cell bodies and axons, axon-dendrite recognition molecules and all the transmitter production and uptake systems that are the physical components of the cortex (and possibly still more transcription factors). Very rarely would the domain of expression of an early regulatory gene be identical with a recognizable chunk of adult morphology. With the exception of a few genes and other markers that are partially localized to the primary sensory cortices, particularly visual and somatosensory, there is no mosaic organization of gene expression that in any way mirrors the adult mosaic of cortical areas.

A “polarizer” has been discovered at the front of the growing cortical plate that appears to control the orientation of the areas of the cortex with respect to the whole cortical surface– if this region is transplanted to the back, the topographic organization of cortical areas turns around from the normal arrangement such that somatosensory cortex is at the back and visual cortex in the front (Fukuchi-Shimogori and Grove 2001). This polarizer controls the expression of transcription factors, genes that regulate the expression of other genes in the proliferative zone for the cortex and in the developing cortex itself. So far, predominating types of gene expression recognized to be under
control of transcription factors are those that produce different kinds of cell recognition molecules that control axon pathway selection – the mileposts and signals that direct particular thalamic input to particular regions of the cortex (Leingartner, Richards et al. 2003). One of the first things that the developing cortex does, therefore, is specify which input it is to receive.

One clear outcome of this specification is that thalamic input to the cortex is very topographically precise in early development in those primary sensory regions where it has been studied (Crandall and Caviness 1984; Miller, Chou et al. 1993; Molnar, Adams et al. 1998). For example, in the adult, the lateral geniculate nucleus in the thalamus gets a point-to-point projection from the retina and confers this representation directly on the visual cortex. In the embryo, even on first contact, the topology of the projection from the retina to the cortex is nearly as specific as it is in adulthood. Once thalamic input is in place, it can be a source of information for further differentiation. The early arrival and precise placement of thalamic input is well suited to further specify many of the local features of cortical areas. Thalamus-controlled differentiation steps include differences in numbers of cells in the various layers, expression of particular transmitters, and perhaps most important, the effects of the nature and pattern of activity relayed through the thalamus on how cortical neurons wire up (Miller, Windrem et al. 1991; Windrem and Finlay 1991; Kingsbury and Finlay, 2001).

In marked contrast to the thalamic connections, which at least of the primary sensory zones, could be conceptualized as a list independent of who neighbors whom, that is, Nucleus A should connect to Cortical Area Z, Nucleus B to Cortical Area Y, and so on, the early connections of the cortex with itself are dominated by nearest-neighbor
spatial relations. In a study of the development of intracortical connections in the hamster, Barbara Clancy and Marcy Kingsbury described initial projections that covered from one third to one half of the entire cortical area normally distributed from point of origin, quite distinct from an idiosyncratic list of particular projections from one cortical area to various other cortical areas (Prasad, Graf et al. 1999; Kingsbury and Finlay 2001). A similar observation has been made for much larger brains – the colleagues of Scannell and Young (Scannell, Blakemore et al. 1995; Hilgetag, Burns et al. 2000), analyzing the dataset of connectivity compiled for the monkey (Felleman and Van Essen 1991) and the cat, find that 85% of connections within the cortex fall under the rule “nearest neighbor plus one.” Thus, in larger brains, the connections do not normally reach so far when expressed as percent of total area, but are well described by relatively simple rules about connecting to nearest neighbors.

Intracortical connections are also rather easy to rearrange, quite distinct from thalamocortical connections. Intracortical connections are the principal substrate of cortical plasticity of all types that involve reallocation of the cortex to new functions, from gross to fine functional readjustments. Demonstrations of this range from local plasticity that might be caused by producing a gap in the sensory information coming in from the periphery within a particular sensory modality, to experimental “rewiring” of cortex done by inducing retinal axons to innervate auditory centers, which causes the auditory cortex to take on visual properties (Pallas 1990; Pallas 2001) Recent demonstration of multimodal activation of the visual cortex in the early blind, including activation during Braille reading, almost certainly uses intracortical pathways to produce the observed reorganization (Sadato, Pascualleone et al. 1996; Burton 2003).
The significance of embryology for modularity and plasticity

Understanding the cortex in terms of general vertebrate (and invertebrate!) mechanisms that produce the basic body plan opens a wealth of analogies and models. Segmentation of a uniform field into a number of repeating units, and then subsequent differentiation of each unit is the central strategy for creation of the body in embryos, from the segments of an insect body or a worm, to the segments of the vertebrate spinal cord. This “theme and variation” strategy maps in a fairly direct way onto an “easy” evolutionary alteration of the genome that preserves basic function while allowing adaptations (Gerhart and Kirschner 1997; Wilkins 2001). Individual gene or groups of genes are duplicated, followed by modification of the duplicate gene while the functions of the original one are conserved. A typical modification would allow new constellations of genes to come under the control of the regulatory genes in evolving segments of a segmented structure. Consider the spinal cord of a fish, which has a repeating segmental structure that maps onto the relatively uniform (front to back) musculature of the fish trunk for the propagation of the wavelike contraction and relaxation of body-wall musculature in swimming. In animals with limbs, those segments that innervate the limbs must have evolved to acquire new instructions, including some very specific new wiring for complicated limb musculature. Yet, if these limb segments are transplanted into the body trunk region, they are capable of expressing the old trunk pattern and wire up in general accord with their new environment (Lance-Jones and Landmesser 1981). To conscript a Batesian turn of phrase for this phenomenon, old regions may be adapted to new functions, but they don’t give up their day jobs.

The question of whether particular cortical areas, like a “face area” or a “motion area” could have specializations for particular functions or are generic has a very likely answer in this developmental context: all of the above. Because a particular location in cortex is predictable in what information it will receive, that is, it has a very high likelihood of receiving particular thalamic input and standing in predictable neighboring relations to
other cortical areas, regions of cortex could take on novel functions under genetic control.

To hypothesize some possibilities, none of which have been demonstrated, coarse pattern

generating genes like those that produce eye spots in butterfly wings could be sited in a

likely spot in the temporal cortex, the patterns producing factors that induce mutual

connectivity between spots rather than pigments for wings, this producing a crude face
template (Beldade, Brakefield et al. 2002). Regions could express certain

neurotransmitters or change the vigor of axon outgrowth, to name just a few possibilities.

Were the expected thalamic input not available, or perhaps even in the normal case, the

same area of cortex still possesses its generic functions.

**The proliferation of cortical areas in evolution** Finding the right conceptual

framework for understanding cortical evolution is important, since the large area of
cortex of the human brain is its signature feature. As we also know that that number of
cortical areas increases with brain size, it is reasonable to hypothesize that the cortical
area might be the “unit” of cortical evolution – for example, that genes might exist that
could simply duplicate an advantageous cortical region (Kaas 1989). The assumption that
a cortical area has a particular function and is the same as a committed processing
module makes this type of hypothesis particularly attractive. Many alternative

possibilities have been stated – one, for example, Rakic’s “radial unit hypothesis”, that
the developmental unit of a radial glial cells and the neurons that migrate on it that gives
rise to a cortical column is the selectable unit, which can be made more numerous by
increase in the numbers of cell cycles in cortical neurogenesis (Rakic, 1990). For the
moment, however, we will concentrate on the hypothesis that it is the cortical area that is
the important unit of cortical information processing, and of cortical evolution.

If the cortical area is the important feature of cortical evolution, and animals are
selected on the functions that reside in cortical areas, we could make two predictions.

First, that the number of cortical areas animals might have should be variable, as they are
under different selection pressures, and there should be some kind of relationship
between the size or number of cortical areas and the sensory or motor capacities on which an animal most depends. How do the numbers, sizes and arrangements of cortical areas vary in evolution?

At the most general level of allometric scaling, first, it is important to know that the volume of area of the cortex is a highly predictable from brain size (Hofman 1989; Finlay, Darlington et al. 2001). Primates as a group have a high volume of cerebral cortex compared to other mammals (a “grade shift”) and also, the cortex in primates has “positive allometry” -- its volume increases more rapidly than the volume of the whole brain as brain size increases. Yet, the volumetric change is totally predictable – humans have exactly the amount of cortex we should have for an animal of our brain size. So while it is certainly possible that we were selected for behaviors dependent upon the volume of cortex, it is not dissociable from total brain size. Further, cortical regions, like frontal cortex or visual cortex also scale in a predictable manner. Humans do not have an “overdeveloped” frontal lobe, but one that would be expected from scaling relationships with other great apes (Jerison 1997; Semendeferi, Lu et al. 2002).

Within this scaling context, Desmond Cheung in my laboratory undertook an analysis of how the number of cortical areas scale with cortex size (Cheung, Darlington et al. 2002), using the corpus of observations accumulated principally by Kaas, Krubitzer and their associates (see general reviews in Krubitzer 1995; Kaas 1996). He found a very predictable relationship, with $R^2$ ranging from .7’s to .89’s, depending upon the subsets of data considered and the method of analysis. The nature of the logarithmic relationship was such that the number of cortical areas increased very rapidly from the smallest cortices (in shrews) up until about a ferret-sized brain, and thereafter increased slowly. It is at the size of brain that includes ferrets, cats and monkeys where visible substructure of cortical areas becomes prominent, including ocular dominance stripes, cytochrome oxidase blobs and patches of interleaved axonal projections (to give this scaling
relationship a physical referent, the entire cortex of a mouse would fit comfortably in the primary visual cortex of a cat).

In a separate study, Peter Kaskan looked at the scaling of the size of cortical areas, with respect to brain size and niche (Kaskan et al., submitted). He found that very reliable allometric scaling of cortical areas, including the primary sensory and motor areas, as others have shown – V1, S1 and so forth have a predictable relationship to brain size, or cortex area. Most interesting, though, was when the data were divided into primarily nocturnal or primarily diurnal animals, there was no difference whatsoever in the relative sizes of visual, somatosensory and auditory cortices – the data points lay directly on top of each other. Nor was there a difference whether the primary sensory cortices alone were considered, or the primary and secondary sensory regions were added together.

These and other observations suggest a cortical sheet that generates subdivisions in a rather mechanical way with increasing size, rather than by generating novel areas by specifying new connections and new circuitry to produce new and unique regions by adaptation and evolutionary selection. The lack of relationship of niche to cortex area size finds a complement in studies of plasticity, from Lashley to the present. Consider the example already cited, that in individuals blind from birth, the visual cortex becomes activated during Braille reading and other haptic functions (Sadato, Pascualleone et al. 1996). So, while the area defined anatomically by input from the lateral geniculate nucleus of the thalamus remains morphologically identifiable, it acquires new functions. Somewhat less dramatic, but significant remappings were also shown in other individuals with other sensory losses, or those using atypical means of communication (Bavalier, Brozinsky et al., 2001; Elbert, Storr et al, 2002, Newman, Balvalier et al., 2002). This ability of cortical areas to acquire new functions, or at least functions different from the name we have given it (primary “visual” cortex) suggest why the size of anatomically-defined cortical areas is not particularly sensitive to niche -- there appears to be a robust
mechanism already in place, working epigenetically, that assigns cortical regions to new functions on the basis of activity or importance, particularly if the thalamic input is relatively inactive.

Intracortical connections, both their distribution and their plasticity, suggest a different interpretation of the significance of the cortical area. While thalamic input to the cortex is entirely discrete from nucleus to nucleus, topographically ordered in detail, intracortical connections integrate across those areas, in an overlapping tiling pattern. There is an aspect of hierarchy in the laminar distribution of projections as one goes out from primary sensory areas, termed “feedforward” and “feedback” (Felleman and Van Essen 1991; Barone, Batardiere et al. 2000). Projections from primary to secondary areas target preferentially the “input” cortical lamina, Layer IV, while projections in the opposite direction distribute to intracortically-projecting zones, Layers II III and VI. The significance of this pattern of providing cortical context to the operations of individual cortical column is discussed at length Merker in “Cortex, countercurrent context, and the logistics of personal history”. One piece of the anatomical puzzle is missing -- while much is known about subcortical projections, area by area, little is know about whether subcortical projections have an obvious pattern with respect to the whole cortical sheet.

What I will suggest briefly now, and elaborate more after I have also discussed some issues in development of the cortex, is that much like the stripes made by ocular dominance columns in some brains, cortical areas are not particularly important features of cortical organization, and most certainly do not correspond to “modules” – localized regions that do a distinct input-output computation and are functionally isolated. Rather, they are epiphenomena of a particular way of maximally specifying and fanning out information from thalamus to cortex, while allowing intracortical projections to recombine this distributed input quite widely and use prior activity (memory) and other current activity to recognize emerging patterns across this matrix.
Developmental stages in cortex and stages in cognitive abilities: developmental modules?

The most common question asked by developmental psychologists of developmental neurobiologists is if there is a morphological or physiological marker of any sort that accompanies developmental transitions – for example, the development of stereoscopic vision and coordinated visual pursuit in the two eyes at about three months of age; the burst in vocabulary acquisition; the change from the A-not-B area in spatial memory; the emergence of autobiographical memory. Neurobiological candidates for such markers were events like marked synaptogenesis or synaptic loss, establishment or myelination of a connecting pathway, or the “switching on” of an entire cortical area/module. For years, when I was the developmental neurobiologist queried, I had to confess that I did not know of any but hadn’t investigated the matter closely. In 1998, Liz Bates and her colleague Donna Thal asked me and my postdoctoral associate Barbara Clancy if we would be interested in making an update of the article “Early language development and its neural correlates” (Bates, Thal et al. 1992) to investigate specifically the question of the relationship of events in the developing biological system, the cortex, to language development. While the challenge given was more or less the traditional one – find biological markers that accompany behavioral events, Liz Bates and colleagues had already written a great deal about the fact that sharp behavioral accelerations and discontinuities can often be the results of underlying processes that are essentially continuous (Elman, Bates et al. 1996). That paper contains the data we surveyed, written out in detail, and here I will excerpt our principal conclusions that relate to modules, areas, and the general issue of brain/behavior mappings (Bates, Thal et al. 2002).

To my knowledge, there is no one place where the following is written out specifically, but I believe the following beliefs were (and are) commonly held about the relationship of cortical and behavioral maturation. Humans are quite neurally immature
at birth, with many important functions awaiting simple maturation. Subcortical functions develop first, the cortex later, and functions carried out subcortically are often subsumed by the cortex as development proceeds. Within domains, primary sensory functions appear first, correlated with the coming on line of primary sensory areas, and then new functions are added as subsequent regions mature. Across the cortex, sensory functions develop first, then language and other integrative functions, and finally the executive and organizing functions dependent on the frontal cortex.

It was astonishing to find out how little actual evidence could be found for any single one of those statements, not to mention a rather wide range of contradictory empirical results. First, by precisely and quantitatively comparing the schedule of events in maturation from the nervous system of the monkey to human maturation, we found that contrary to our expectations, humans are born later in development with respect to neural milestones than are macaque monkeys – humans would be born at seven months post-conception, not nine, if we followed the macaque schedule, and lag *in utero* an extra couple months (Clancy, Darlington et al. 1999; Clancy, Darlington et al. 2001). As anthropologists have known, the last couple months in utero for humans is characterized by the acquisition of much body fat (Pawlowski 1998). Relatively little goes on at this time in the way of significant neural events. In fact, virtually all of the neurons and most of the main connectional architecture of the brain are generated and laid down very early in development, in the first three months of life (Clancy, Darlington et al. 1999).

The cortex itself presents a complicated picture. First, there is no evidence that any part of the cortex “switches on” postnatally – in fact, the cortex is electrophysiologically active even at the time it is under basic construction, in the first three months of life (for example, voltage- and ligand-related activity affects even cell migration -- Rakic and Komuro, 1995). There is no single dimension of “maturational state” that any area of the isocortex can be retarded or advanced on (which makes it even less likely there could be a moment when a region “turns on”). Rather, each isocortical area is best viewed an
assembly of different features, including neurogenesis, the maturation of its input, and the maturation of its output, all of those in the context of the maturation of the entire organism (reviewed in Bates et al. 2002; see also Dannemiller, 2001 for a detailed examination of cortical layer, area and regional maturation and their relation to visual function). Because different areas of the brain follow maturational gradients that don’t match in order, interesting mismatches occur — in some areas, intracortical connections will be relatively more mature than thalamic connections (the frontal cortex), and in others, the reverse will hold (primary visual cortex).

The cortical sheet has an intrinsic gradient of maturation. Neurogenesis begins at the front edge of the cortex and proceeds back to primary visual cortex; the limbic cortices on the midline also get an early start. Paradoxically, the frontal cortex, viewed in hierarchical models as the last maturing cortical area, is in fact one of the first to be produced and thus quite “mature” in some features. The order of thalamic development is quite different. In general, the primary sensory nuclei in the thalamus are generated first and establish their axonal connections to the cortex first. Of the various other nuclei, motor and cingulate are intermediate in their timing, and the last to be produced are the thalamic nuclei that innervate the frontal, parietal and part of the inferotemporal cortex (reviewed in Finlay, Darlington et al. 2001; Bates, Thal et al. 2002). The thalamic order of neurogenesis suggested a hierarchical notion of cortical development (primary sensory areas mature early, “association” areas late), but it’s not the whole story. So what might the dual gradients mean for frontal cortex, the area so often described as “maturing late”? The fact that frontal cortex is generated early but receives its input from the thalamus relatively late could predispose it for intracortical processing. In other words, this difference in developmental gradients might mean that frontal cortex is primed for higher-order associative function by the nature of its position and connections, but not because any essential retardation in maturation of its neurons prevents its early function.
Synapses begin to be formed in the cortex from the time that the first neurons move into place and a fair number are in evidence at six months post-conception (Bourgeois and Rakic 1993). The first synapses must account for the many demonstrations of early activity-dependent organization in the cortex, and perhaps for several types of in utero learning, for example, preferences for the language rhythms of the mother (Jusczyk, Friederici et al. 1993). A few months later, though, anticipating birth and all over the cortex, the density and number of excitatory synapses surges ten to a hundredfold (Bourgeois 2001). This observation is quite species-general – synapse numbers surge when the maturing animal anticipates exit from the womb (or burrow) into the environment of real-world experience. It is not caused by the experience of the world (Bourgeois, Jastreboff et al. 1989). Many effects on types and distributions of synapses are caused by experience, but not the time nor amount of the burst of synaptogenesis.

Laying down great numbers of synapses on neurons prior to most experience and learning makes computational sense. The immediate postnatal phase of development is distinguished by axon retraction and synapse elimination, “regressive events”, as well as growth and addition. In the mature nervous systems, synapses are both added and subtracted during learning. Perhaps the developing nervous system is both allowing activity (though initially disorganized) to be easily propagated through itself, and also allowing itself the possibility of subtraction of synapses, as well as additive ones (Quartz and Sejnowski, 1997), by the installation of large numbers of synapses just prior to experience. This initial “overproduction” of synapses may be a way of producing continuity in mechanisms of synaptic stabilization from initial development to adulthood. The impressive statistical learning capabilities of infants in their first year may require this highly elaborated substrate (Saffran, Aslin et al. 1996).

**Experience-induced maturation** One of the longest- and best-studied features of perinatal development from both behavioral and neural perspectives is the development of binocular vision, and its relationship to binocular interactions in the visual cortex, both
anatomically and physiologically defined (Movshon and Van Sluyters 1981; Teller and Movshon 1986; Dannemiller 2001). Several observations of interest about structure-function links arise from this work. First, in normally developing individuals with normal experience and reasonable optics, there is a critical period for the establishment of a balance of influence from the two eyes on perceptual decisions, for sorting information by eye-of-origin, and for the development of stereoscopic depth perception which happens in the first several years of life. Absence of activity in either eye or incoordination of the eyes can permanently derail the development of normal visual function during this period. If all visual experience is denied, however, and both eyes are closed, what occurs is delay of the critical period -- the representation of the two eyes does not begin its segregation that results in the physical marker of ocular dominance column in those animals that possess them. The special neurotransmitters and receptors that are responsible for this structural change are held at their initial state (Kirkwood, Lee et al. 1995). When experience is reinstated, anatomical, pharmacological and physiological events then progress, as they would have independent of the animal’s age (to a point). A similar phenomenon has been observed in birds that learn their songs from tutors – for the unfortunate nestlings born too late in the season to hear any of the spring songs that establish territories, the “critical period” is held over until the next spring, when singing begins again (Doupe and Kuhl 1999).

Presumably this allocation of neurons to particular functions on the basis of activity occurs everywhere in the cortex. Assignment of initial function to structure is often called “maturation” and the property of “maturity” is ascribed to the tissue, but the example above shows this need not be so. Returning to the frontal cortex, the “immaturity” of frontal cortex on which many executive and self-monitoring skills depend could reflect an absence of events likely to activate frontal cortex in early childhood, not a maturational deficit of the tissue itself.
Continuous brain, discontinuous behavior. One instructive structure-function relationship that appeared in the binocular interaction research was a mismatch between the gradual spatial segregation of the neurons responsive to either the right or left eye in the cortex and a stepwise change in an aspect of visual behavior likely to be dependent on it, the development of binocular rivalry. Infants presented with horizontal stripes to one eye and vertical stripes to the other indicate by their pattern of habituation that their experience is a checkerboard, and not the alternating rivalry between the horizontal and vertical stripes that an adult experiences. In longitudinal studies, the infants switched in a matter of days from the immature checkerboard to the mature rivalrous state, at about 3 months of age, while no such instant of sharp segregation has ever been observed in the presumably corresponding anatomy -- from single neurons to stripes, ocular dominance columns in the cortex move slowly to their mature organization (Held 1991; Movshon and Van Sluyters 1981). A different discontinuity with a similar lesson was described in the development of infant walking by Esther Thelen. At birth, all infants will show an alternating stepping movement when supported over a surface, which disappears around 2-3 months, with “real” walking appearing at about a year. This progression was first described as a “spinal reflex” becoming supplanted by cortical control as the cortex matured. In fact, the spinal reflex never disappears, is the basis of adult walking, and can be elicited at any time if the infant is appropriately weighted and balanced (Thelen, Fisher et al. 1984). In this case, spinal circuitry can produce many different rhythmic patterns at any age, dependent on the particular pattern of peripheral load, and “maturation” lies in the changing periphery.

Mapping complex changing functions onto complex, changing tissue. The point of the prior section on maturation is to discount as much as possible the notion of cortical areas maturing as single functional modules blossoming one at a time, but rather to emphasize the continuous activity of the cortex from the time of its generation, with a single point of punctuation in the surge of synapse production at the time of birth. What
then is known about the postnatal maturation of the cortex and its relationship to behavior? Until quite recently, very little. Attempts had been made to locate discontinuities or inflections in graphs of changes in the volume or structure of brain tissue, synapses and processes and correlate them with discontinuities in behavior (for example, the period of very rapid vocabulary addition in learning), although, as we have discussed, the assumption that anatomical and physiological discontinuities should correspond in any case is questionable. Myelination, the growth of the insulating glial sheaths that increase the speed of axon conduction of impulses, is something that occurs postnatally and can be correlated with behavioral abnormalities, but has never produced any great insight unto the physical correlate of normal behavioral stages (Sampaio and Truwit 2001). Measurements of spontaneous electrical activity in the cortex and evoked activity (ERP’s) could be compared from infant to adolescent to adult, with the typical result showing that the frontal cortex, and sometimes the parietal cortex showed the mature pattern later than sensory cortices, but the anatomical correlate of these physiological changes remained obscure.

With new structural and functional imaging techniques including new versions of ERP’s, some striking results have already emerged that integrate well with the picture of the developing brain presented here, consistent across both brain damage and imaging studies (Nelson and Monk 2001; Casey, Thomas et al. 2001; Stiles, Bates et al. 1998). What is presented here are a few examples, with no attempt at review. Although the cortical areas involved in early and adult performance of the same tasks are rarely disjunct, they are never identical. The structures important for learning language are quite different to those required for mature language performance, both in laterality and in anterior-posterior position, as determined in longitudinal studies of children with early brain damage (Bates and Roe 2001). A different constellation of areas is activated for facial and spatial judgments in children, though general adult divisions are employed. Overall, there is an interesting tendency for the right hemisphere to be preferentially
involved in initial stages of learning (both in children and adults). The frontal cortex was found to be more active in children engaged in response inhibition tasks than adults, though its activity was not related to success in the task (Casey, Thomas et al. 2001). Identification and understanding of neural structures that are preferentially engaged in the acquisition of new knowledge, rather than the performance of practiced abilities will probably be one of the first outcomes of this research enterprise.

**Distribution of functions in space and time**

Following any of a number of interviews with the media, Liz Bates has bemoaned the lack of a simple, graspable result to convey the interest and the nature of the emergence of complicated distributed system. It seems to be news to say that the emergence of past tense in language depends on a spurt of synaptogenesis in Brodmann’s area 41-b, the syntax module/area, which in turn reflects the activation of the FOX-PX gene on chromosome 18. To fully elaborate the interactionist position that production of the same ability requires virtually all the cortical areas, most of the genes, and a highly elaborated language experience does not make much of a sound bite, and there won’t be one here. Yet, the picture that the cortex gives us about how information is deployed in both in development and in the mature functioning of the cortex does converge on a single story.

Brodmann pointed out discontinuities in the cortex, modules were proposed for behavior, cortical areas were proposed to be the biological analogue of those modules, and a list of those cortical areas is for the most part is what is produced in any current imaging study of the cortex when individuals are engaged in any cognitive task. Increasingly, however, it is clear that any particular cortical area makes a very poor one-to-one map with any perceptual or cognitive skill, even in those domains where perceptual decisions can be reasonably precisely defined, as in color or aspects of form-from-motion in vision. Rather, the thalamus lays out dimensions of sensory and motor
experience on the cortical surface, losing little hard-won topographic detail in the projection. At least in primary visual cortex, and perhaps more generally, redundancy in this topographic projection is reduced within the processing class known as “sparse coding” (Field 1994). Information is relayed forward and back, recombining new information with processed information, or with other modalities (Shimojo and Shams, 2001). The scope of intracortical projections exceeds that of a cortical area, and we could view the concert of thalamocortical and intracortical projections as permuting and recombining relationships between the structure of new and incoming information, information recently perceived, remembered structure, and action. In this view, while presumably useful assemblies could arise in any one cortical area, it seems likely that perceptual or motor decisions of any complexity would involve many.

Cortical areas within general processing domains have had a disconcerting tendency to be just slightly different from each other, and rarely reflect what we would imagine to be processing “stages”. I will take a few examples from visual processing. In posterior parietal cortex, there are several areas that participate in the coordinate transformation of visual space from a retinally-based code, to a eye-in-head based one, to a body-centered one, and perhaps, in concert with information about self-motion, to a body-independent allocentric code. Conceptually, this would appear to be successive additions of information to the retinal signal, but the neurons representing these coordinate additions do not appear in a stage-like manner in successive areas, but are distributed among the areas (Andersen 1997). Single neurons responsive to faces can be found in numerous locations over the ventral aspect of the orbitofrontal cortex, not confined to a single area, and responses to objects and faces can be discriminated even if the maximally-responsive area is eliminated from the analysis (Haxby, Gobbini et al. 2001). An area in visual cortex was described as “unusually responsive” to motion, particularly area MT, (but this is a statistical statement, as most of the visual cortex areas will respond to image motion), or unusually responsive to color (Area V4), and these two areas were perhaps
the best candidates for special modules (Zeki, Watson et al. 1991). Complete ablation of either or both of these areas in macaque produces only mild and transient deficits in abilities in motion, color detection and stereopsis that these areas might be expected to be entirely responsible for, were the brain modular (Schiller 1993).

No claim is being made here that cortical areas do not differ from each other, or that they might not be genetically different, perhaps containing some area-specific computations, or that the process they represent is not critical to cognitive function. The claim is rather that the cortical areas we can see morphologically are the basic foundations of an information dispersal and recombination system, and as such, are extremely unlikely to correspond to any higher-order perceptual and cognitive functions, or even lower-order ones, if color and motion decisions should be construed that way.

The story of cortical development amplifies these same themes. In terms of maturation of its elements, each cortical area arises in time in a different place in converging maturational streams. There is no evidence that any part of cortex wholesale “switches on” as a module might be expected to, but rather, can be seen to be active from the very beginning of development, and changes function, contributing to different capacities and no doubt changing its own capacities as development proceeds.

Navigating the functioning cortex

He had bought a large map representing the sea  
Without the least vestige of land  
And the crew were much pleased when they found it to be  
A map they could all understand

Lewis Carroll (1876) (Carroll 1876)

Without cortical areas as anchor to a functional description of the cortex, how are we to proceed? While it is certainly the case that the distribution of information that
characterizes the thalamocortical projection may be of help discriminating cognitive 
operations from each other, it may also mislead, much like word-frequency counts might 
discriminate various writers from each other, but miss the most important components of 
meaning and message that writers optimally should be contrasted on. It was hard to 
imagine how to understand the cortex without the fundamental unit of the “cortical area”, 
but as we know, this statement entails only incapacity in the speaker, not impossibility of 
the task.

Fortunately, Liz Bates and her team of colleagues have imagined it for us. The 
spatial layout of the cortex persists, whether or not we assign areas to it. A taxonomy of 
cortex wholly based on function, either function lost by the loss of cortical tissue, as in 
(Bates, Wilson et al. 2003) or by activation of cortex can replace an outmoded modular 
view of cortical function. The challenge then is to get the description of behavior right, 
and it is appreciating this necessity in future studies that makes yet another aspect of Liz 
Bates’ work fall in place. She has laid out for us the complex and generative theoretical 
position minimally sketched at the outset of this chapter, perhaps best described in 
Rethinking Innateness. Consistent with this theoretical perspective, she outlines a better 
way to see the information that the cortex presents us in “voxel-based mapping”. Finally, 
she tells us how to get the cortex to give us information we can use, producing the 
fundamental, basic descriptive, and grindingly difficult studies of language operations – 
the “MacArthur Communicative Development Inventories,” cross-language picture- 
naming norming studies and gigantic longitudinal studies of the changing deficit patterns 
in language and cognition after early brain damage. These encyclopedic studies seem 
almost out of place in what would otherwise appear to be a very theory driven-corpus. 
But if we understand that our understanding of cortical function must arise from a good 
taxonomy of real-world cognition, and not from misapplied anatomy, this is the critical 
and essential step. She has given us latitude, longitude, a ship to sail with, and firm 
ground to sail from.
Citations


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