Barbara L. Finlay
Michael N. Hersman
Richard B. Darlington

Department of Psychology,
Cornell University, Ithaca, N.Y., USA

Patterns of Vertebrate Neurogenesis and the Paths of Vertebrate Evolution

Abstract

Any substantial change in brain size requires a change in the number of neurons and their supporting elements in the brain, which in turn requires an alteration in either the rate, or the duration of neurogenesis. The schedule of neurogenesis is surprisingly stable in mammalian brains, and increases in the duration of neurogenesis have predictable outcomes: late-generated structures become disproportionately large. The olfactory bulb and associated limbic structures may deviate in some species from this general brain enlargement: in the rhesus monkey, reduction of limbic system size appears to be produced by an advance in the onset of terminal neurogenesis in limbic system structures. Not only neurogenesis but also many other features of neural maturation such as process extension and retraction, follow the same schedule with the same predictability. Although the underlying order of event onset remains the same for all of the mammals we have yet studied, changes in overall rate of neural maturation distinguish related subclasses, such as marsupial and placental mammals, and changes in duration of neurodevelopment distinguish species within subclasses. A substantial part of the regularity of event sequence in neurogenesis can be related directly to the two dimensions of the neuraxis in a recently proposed prosomeric segmentation of the forebrain [Rubenstein et al., Science, *266:* 578, 1994]. Both the spatial and temporal organization of development have been highly conserved in mammalian brain evolution, showing strong constraint on the types of brain adaptations possible. The neural mechanisms for integrative behaviors may become localized to those locations that have enough plasticity in neuron number to support them.

Organisms may evolve through the types of molecules that the genome may express or in the time and manner of their expression. As cell biologists find more and more deep structure in the fundamental patterning of vertebrates and the kinds of molecular structures that are conserved over diverse functions [Gerhart and Kirschner, 1997], we may also ask what deep structure may be found in the timing of development. This investigation has two parts. First, what alterations in developmental timing occur? Second, what consequences do alterations of development have for the structure of the brain and sensory systems?

In this review we will first describe some observations that we made concerning the stability of timing of events in mammalian neurogenesis and their consequences for brain
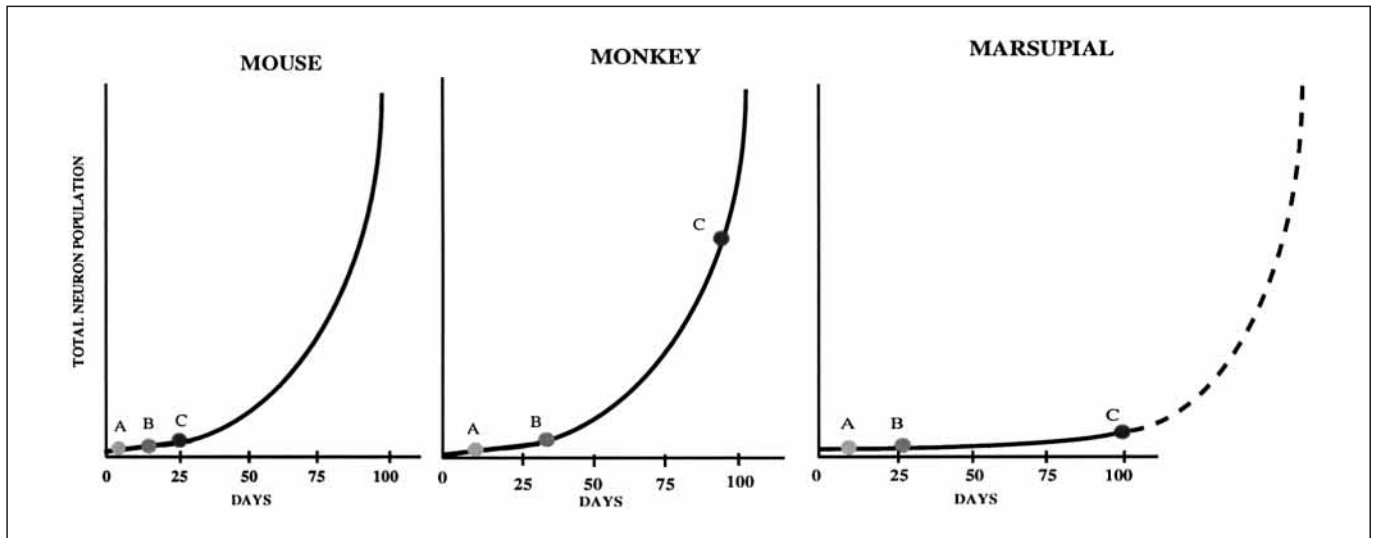
Barbara L. Finlay
Department of Psychology, Cornell University
Ithaca, NY 14853 (USA)
Tel. +1 607 255 6394, Fax +1 607 255 8433
E-Mail blf2@cornell.edu

Fig. 1. Schematic representation of the hypothetical relative timing and the relative amount of neuronal production for three brain structures, A, B and C, for a mouse, a monkey, and a marsupial of comparable body size but smaller brain size than a monkey.

structure as brains of different sizes are constructed. Some interesting qualifications and variations of these observations of neurogenetic stability have emerged. Next, we will describe how the differences in rate and duration of cell deployment have different consequences for brain structure, comparing the contrasting rate of neural development in eutherian and metatherian mammals. Finally, we will show evidence that the dual-axis structure of the prosomeric model of the forebrain [Rubenstein et al., 1994] accounts for much of the stability we see in patterns of neurogenesis.

Late Makes Large

As the brain ranges from less than a gram in the least shrew to the 1300–1500 grams of *Homo sapiens* [Stephan and Frahm, 1988], the component structures enlarge in a very predictable but non-uniform way. Setting aside for the moment some important substructure, some components of the brain (like the medulla) increase in size across species at a slower rate than the whole brain enlarges, some at approximately the same rate as the whole brain (like the diencephalon), and some at a greater rate (like the isocortex – which comes to dominate brain volume) [Finlay and Darlington, 1995]. While the fundamental anatomical unit driving this relationship is the number of cells in each of the brain components, other features like the size of cells and the volume of their processes do scale as well in predictable

ways with brain size [Purves, 1988; Murre and Sturdy, 1995]. Considering potential sources of variability, the predictability of brain enlargement is impressive, given the 20,000 fold range of brain sizes investigated – at any stated brain size, individual structures may differ by a factor of only about 2.5 in size.

Since cell number is the fundamental unit producing brain size (without forgetting the other sources of covariation noted above), we asked what aspects of neurogenesis might be related to both the predictability and the different slopes by which each structure enlarges with brain size. Investigating 'neuronal birthdays' as determined by tritiated thymidine autoradiography in a different sample of seven mammals (one marsupial, four rodents, one carnivore and one primate), we found that the relative order of events in neurogenesis was as predictable as brain size components were and, also, that the order of neurogenesis predicted the slope of the change in size in brain components versus total brain size. Structures like the isocortex, whose precursor pools are generated for a long time (and thus have late 'birthdates'), become disproportionately large as the brain increases in size. This relationship is nonlinear, considering both the transformation of dates of neurogenesis and the eventual size of the brain component (fig. 1A, mouse versus B, monkey). For example, rats have a peak of neurogenesis at 15 days for Purkinje cells of the cerebellum, 16 days for the superficial gray layers of the optic tectum, and 19 days for layers 2–3 of the isocortex on postconceptional days 15,

16 and 19, respectively. The comparable postconceptional days for a monkey are 39, 41 and 90. The overall function predicting the day of peak neurogenesis for any structure in any animal, and which also serves for the transformation of any animal's developmental scale to any other is:

In (Peak neurogenesis day – 7) = (Structure factor) + (Species factor)

At this time, we cannot state the function that links day of peak neurogenesis to total neuron number: the nature of the data sets we are comparing precludes this. In figure 1, however, we do make the limited hypothesis that neuron number will increase with some amount of positive acceleration, as the length of generation is extended, by proliferating the precursor pools for eventual neurons (as in a generic sigmoidal Gompertz curve for growth [Laird et al., 1965], or as has been specifically calculated for neuronal proliferation in the isocortex [Takahashi et al., 1993, 1994]). Eutherian mammals can be imagined proceeding initially along hypothetical uniform curves of brain growth, such as that shown in figure 1A and B for a monkey and a mouse. Imagine that each structure A, B and C has an original set of precursor cells allotted to it that may divide and produce an expanding precursor population. Each structure then exits from the positively accelerating basis curve by sending its cells into terminal differentiation, depleting its precursor population. Thus, nonlinear increase in the size of structures might occur, depending on the ordinal position of the generative events. We are presently investigating the scaling relationships of order of neurogenesis and neuron number in the retina and isocortex where the exact neuron numbers and birthdates of particular cell classes can be obtained in several species.

The graph presented in figure 1A and the argument above has neural events A, B and C independent of each other and noncontingent. Much of the nervous system can be reasonably characterized this way: any division of the neural tube in which neural migration is basically radial is like this. For example, the region that gives rise to the isocortex versus the region giving rise to the anterior horn of the cervical spinal cord region compete only for general organismic resources and not for control of a shared precursor pool. Any separable division of the adult nervous system, however, is not necessarily developmentally independent and noncontingent from every other division. The layers of the retina, for example, arise from a multipotent precursor pool such that an alteration in the number of an early-generated group would necessarily change the number of a late-generated group [Turner et al., 1990]; the isocortex has
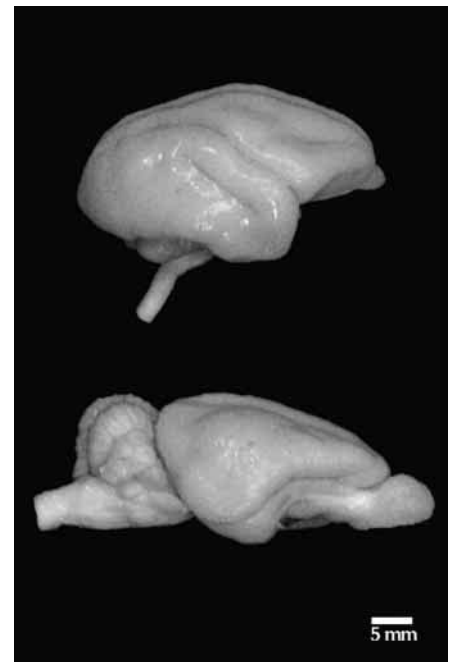
Fig. 2. Photograph of the size and external morphology of the brains of the owl monkey (*Aotus azare:* brain weight, 15 gm; body weight, 500 gm) and the agouti, a hystricomorph 'rodent' (*Dasiprocta agouti:* brain weight, 16 gm; body weight, 2,500 g).

the same laminar structure and the additional complication of some fraction of tangential migration as well as radial migration [Karten, 1997; Kuan et al., 1997]. There are several geometrical and probabilistic features that make 'late makes large' likely to be true for cell groups that are derived from the same precursor population, but it is important to distinguish these two types of populations. Our first analysis of the structural consequences of nervous system timing did not distinguish independent and dependent nervous system components and thus contains several kinds of variability. We will reconsider this in the context of prosomeric organization of the forebrain and how it may be related to the relationships of timing and size we have observed.

Subcomponent Structure in Brain Enlargement: The Limbic System

Shown in figure 2 is an unusual apposition of a rather small monkey (the owl monkey, *Aotus azare,* which has a brain weight of about 15 grams and a body weight of about 500 grams) and a rather larger hystricomorph 'rodent' (the

agouti, *Dasiprocta agouti,* which has a brain weight of 16 grams but a five times bigger body, 2,500 g) both printed at the same scale. The choice of two animals of comparable brain size to compare the relative enlargement of the whole brain versus that of the limbic subcomponent is a useful antidote to the confounding of scaling and structure usually made in the typical textbook comparison of rat and human brains. We, as well as a number of previous investigators, have noted how poorly the main olfactory bulb scales with brain size [Baron et al., 1983; Stephan and Frahm, 1988; Barton et al., 1995]. Shown in figure 3 is the scaling of main olfactory bulb size on brain weight compared to mesencephalon scaling with structure volumes taken from the Stephan data set [Stephan and Frahm, 1988]. Although there is evidence of slight alterations in variability and slope for the different suborders for the mesencephalon, the growth is essentially colinear, while for the olfactory bulb each family and subfamily have distinct slopes and intercepts. However, it is important to note that all the slopes are positive: the olfactory bulb is not entirely decorrelated from brain and body size! Also note we have not taken out the effect of body or brain size in this or any other analysis: we are interested in prediction of absolute brain size, numbers of neurons, and the scaling of subcomponents in this analysis, not the relative brain sizes given by encephalization quotients or regression residuals.

The incomplete separation of the scaling of the olfactory bulb with the rest of the brain extends to other components of the limbic system as well. This component structure of the Stephan data set [Stephan and Frahm, 1988] has been reported by several investigators who have submitted the Stephan data set to different types of factor analysis [Gould, 1975; Jolicoeur et al., 1984; Barton et al., 1995]. In our analysis, whole brain size accounted for 96.29% of the variance in the entire data set, and a factor that strongly loaded on the olfactory bulb but also loaded on a number of limbic system components accounted for another 3.0% [Finlay and Darlington, 1995]. For the simians in the data set, this means that while all structures are increasing with brain size, the limbic structures are increasing at a lesser rate. The particular animals included in the Stephan data set influence the component structure we find. In the Stephan data set, the animals with the largest brains, the primates, have the relatively smallest olfactory bulbs (which need not be the case, as figure 2 demonstrates). Had our sample consisted of a number of animals such as carnivores, with big brains and large olfactory bulbs, the relative magnitude of contribution to variance of the two factors would probably change, as Roger Reep pointed out in discussion of this analysis. The central argument is that
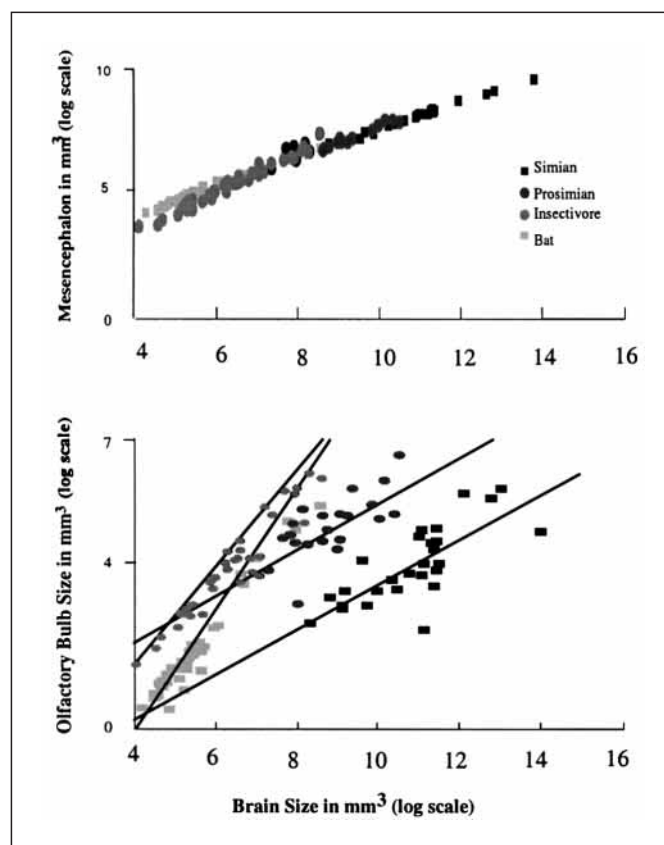
Fig. 3. Comparison of scaling of mesencephalon size versus olfactory bulb size for 131 primates, prosimians, insectivores and bats.

there are two components, which together account for 99% of the variance in brain volume – the brain factor and the limbic factor.

Allometric analyses of the relationship of animal behavior and lifestyle have long hoped to find close relationships between lifestyle variables, such as frugivory, method of locomotion or social organization, and constellations of changes in sizes of brain components [Pirlot and Jolicoeur, 1982; Armstrong, 1987; Stephan and Frahm, 1988; Gittleman, 1991, 1994, 1995; Aboitiz, 1996; Barton, 1996]. It is fair to say that these efforts have met with only modest success. While there are a number of factors associated with differences in whole brain/body ratios ('E.Q.'), such as carnivory or other nonfrugivorous diets, attempts to find other correlated structure turn up occasional relationships, with either the olfactory bulb or the nocturnal/diurnal distinction being commonly cited in those studies with positive results. Social system and isocortex size also show several interesting associations.

We attempted to find evidence for functional system co-variation (such as 'visual' or 'motor') in this sample and in our developmental sample in order to explain more variation than the whole brain factor, but we found only the limbic factor. We suggest that the various analyses that have discovered differences in the component structure of the brain may all be looking at different facets of this two-component structure and, essentially, looking at high or low loading on the limbic factor. For example, Barton et al. [1995] found evidence of negative correlation of visual (lateral geniculate nucleus, optic tract, optic nerve and striate cortex) and olfactory structures (main and accessory olfactory bulbs and the pyriform cortex) in primates, bats, and insectivores but positive correlations within functional systems remaining after the effect of whole brain size had been removed. Since the entire limbic component has not been removed from 'whole brain size' by this analysis, remaining correlations between residuals may reflect a limbic contribution to whole brain size rather than independent correlation of sets of the subcomponents.

Developmental Mechanism of the Reduction of Limbic Components in the Rhesus Brain

We reasoned that if for our entire sample 'late makes large', then earlier neurogenesis should be seen in smaller-than-expected brain regions. We therefore examined the onset, peak and offset of neurogenesis of limbic system structures in rats compared to those in monkeys, using the equation described above that relates the developmental schedules of different mammals. Figure 4 shows a number of events in neurogenesis, both limbic and non-limbic, with monkey postconceptional days adjusted to rat developmental period, using expression of the LAMP protein (limbic system-associated membrane protein) as indicative of limbic system membership [Chesselet et al., 1991; Coté et al., 1995, 1996]. Clearly, the onset of terminal neurogenesis is advanced and almost synchronous in LAMP-containing structures in monkeys compared to rats. Neither the peak nor the offset is obviously changed. Everything else equal (which is not known yet), early withdrawal of cells from the precursor pool would reduce the number of cells contributing to the nucleus or cell group of interest. Conversely, isocortical neurogenesis appears to be progressively delayed in monkeys compared to rats, particularly for the upper layers.

The synchronous onset of terminal neurogenesis in limbic structures in monkeys suggests the possibility of some coordinated or systemic signal. The fact that most structures in the limbic system can be labeled by the specific LAMP marker makes it possible that such a distributed cell
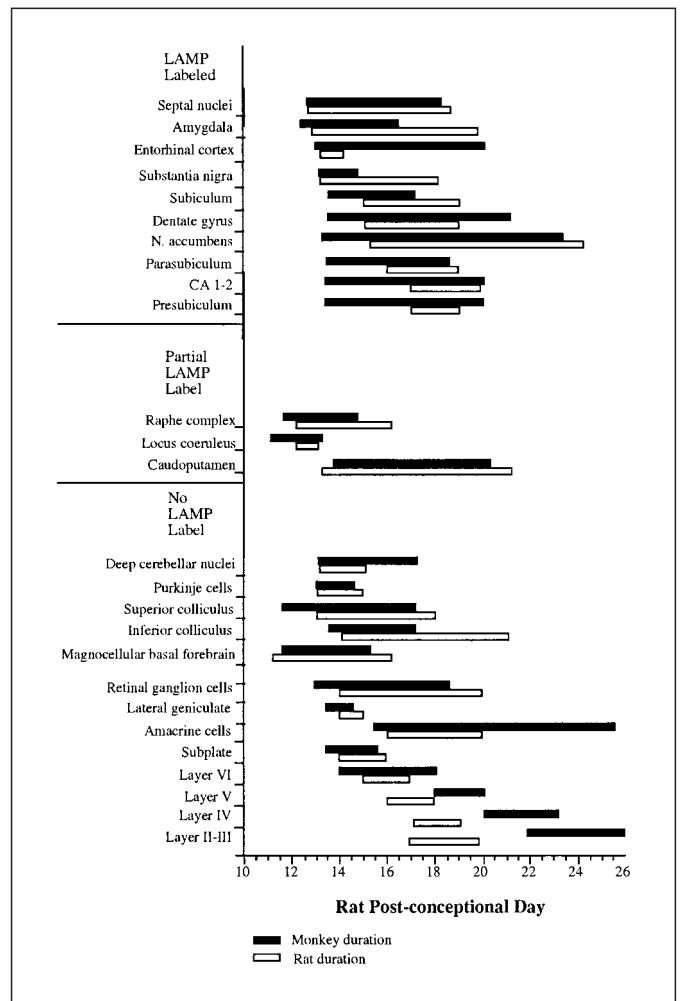
Fig. 4. Comparison of onset and duration of terminal neurogenesis for limbic structures (top), as indicated by the expression of LAMP, versus nonlimbic structures (bottom). The duration of events in monkeys (filled bars) has been adjusted to fit the period of neurogenesis in rats (white bars), using the equations described in the text.

population could be the target of a single signal. LAMP is expressed in the adult nervous system and also in early development, but after cells have differentiated and are in place; it is not expressed in the ventricular zones giving rise to these areas; in fact, cell fate specification to express LAMP can be modified in culture [Eagleson et al., 1997]. However, the fact that all limbic structures express this protein so early in their development implies that there is some other feature of their identity or specification that might allow the probability of early onset of terminal cell division to be increased for the population overall.

In the evolution of mammals, the relative prominence of the limbic versus the visual/isocortical components of the

brain has been argued to be critical at two key points [Jerison, 1973]. The first point is the first divergence of mammals, who invaded the nocturnal niche, differentiating from the diurnal reptiles. It would be intersting to compare the development of the limbic system and olfactory bulb in mammals with that in reptiles to see if there is evidence of coordinated enlargement of these limbic structures and expression of LAMP. The second point of interest is the re-invasion of the diurnal niche by a number of mammals. If a system has been coordinated, resulting in its enlargement at one point in evolutionary time, this could serve as a pre-adaptation for a later coordinated regression.

A Third Component

A third component has also been noted in factor analyses and can be appreciated in the owl monkey/agouti comparison (fig. 2; the agouti's body weight is five times the owl monkey's); this is a factor loading most strongly on spinal cord, medulla and cerebellum and which appears to be related to body size [Fox and Wilczynski, 1986; Aboitiz, 1996]. This component falls within the variation of ± 2.5 noted earlier in our own analysis, and we have been unable as yet to get a clear signal associating it with any difference in neurogenesis. Possibly, this component of brain scaling is related to the systems matching components of cell death and the trophic effects of increased peripheral innervation opportunities on sensory and motor neuron sizes and their processes.

What about Timing May be Altered? Evidence from Marsupials

With Sarah Dunlop, we recently extended our analysis of developmental timing to include a number of metatherian mammals and a variety of new classes of neural events [Darlington et al., 1998]. Through metatherians fall intermediate in rate of body growth, compared to the various families of eutherian mammals, the amount of brain per body mass is less, implying the rate of brain development has been altered [Eisenberg, 1981]. If the 'rate' of neural development is changed, what is the nature of the change? We used information on six marsupial and eight placental mammals taken from tables 1–5 of Robinson and Dreher [1990], table 2 from Finlay and Darlington [1995], tables 1–3 of Ashwell et al. [1996] plus data collected by Dunlop et al. [1997], supplemented by minor additions and corrections. Three of the species examined were three polyprodont marsupials: the fat-tailed dunnart *Sminthopsis crassicaudata*, the short-tailed opossum *Didelphis virginia*,

and the South American opossum *Monodelphis domestica*. Three were diprodont marsupials: the brush-tailed possum *Triturus vulpecula*, the quokka *Setonix brachyurus*, and the tammar wallaby *Macropus eugenii*. The eutherian species include four rodents: the mouse *Mus musculus*, the hamster *Mesocricetus auratus*, the rat *Rattus norvegicus*, and the spiny mouse *Acomys cahirinus*. Other species were the laboratory rabbit *Oryctolagus cuniculus*, the ferret *Mustela putorius furo*, the cat *Felis domestica*, the monkey *Macaca mulatta*, and the human *Homo sapiens*. Eutherian gestation periods in this group range from 15.5 days in hamsters to 270 days in humans; pouch exit times vary from around 60 days to 250 days in the metatherians.

Ninety-three developmental events were used, including all of the neurogenesis information already described plus a number of axon outgrowth and segregation events, as well as eye-opening. Several modelling procedures were explored, and the one described here is a modification of that used by Finlay and Darlington [1995], which was ln(days − a) = species scale + event scale. That is, each species was assigned a score on a species scale, and each developmental event was assigned a score on an event scale, and a constant a was chosen, such that the sum of the two appropriate scale scores would estimate ln(days − a), where days is the number of days since conception that the event occurs in that species. That model is mathematically equivalent to the model

$$\text{days} = \text{species scale} \cdot \text{event scale} + \text{a}.$$

The model for placental mammals by this technique is

$$\text{days} = 7.18 + (\text{species scale}) \cdot (\text{event scale}).$$

The model for marsupials

$$\text{days} = 17.18 + (\text{species scale}) \cdot (\text{event scale})^{1.66}.$$

Thus, compared to placental mammals, the effective 'Day 0' of the marsupial scale occurs about 17 days after conception and is slowed by a power of 1.66. Variability of the marsupial events is about twice as large as for placental events: for placentals, events could be predicted to within 99% confidence within about three days of the predicted time; for marsupials, the figure was six days. In figure 5, the functions showing relative postconceptional days for various developmental events in rabbits versus opossums are graphed. Rabbits have a larger brain weight than opossum but generates their brain in a faster time.

Stability of the Order of Events in Vertebrate Brain
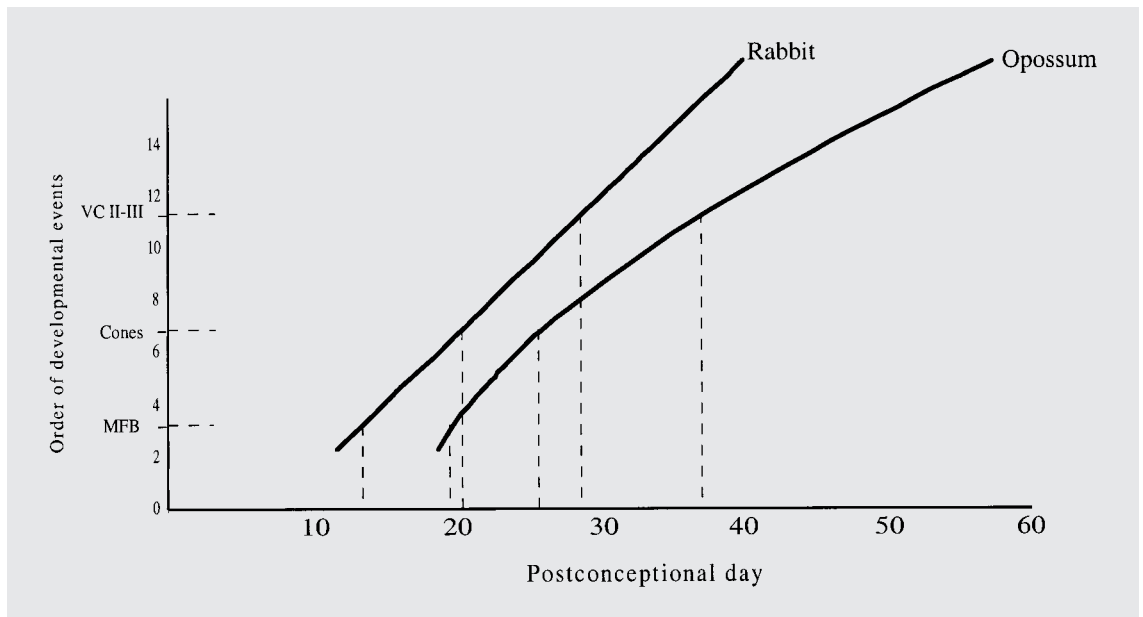
Fig. 5. Comparison of the times at which three sample developmental events (appearance of the medial forebrain bundle, MFB; peak generation of cones; and generation of layers II–III in primary visual cortex) occur in rabbits *(Oryctolagus cuniculus)* versus opossums *(Monodelphis domestica).* Although rabbit brains are about one third larger than opossum brains, the duration of neuronal production is shorter.

Development; Variability in Rate and Duration

In our first study of temporal ordering of neurogenesis in a sample consisting primarily of placental mammals [Finlay and Darlington, 1995], we showed a high degree of conservation of order and interval of developmental events, even though the duration of neurogenesis varied nearly tenfold. Greater durations of neurogenesis were correlated with a proportional increase in overall brain size and differential effects on the size of brain components, depending on their order: late-generated structures get disproportionately large, as described here. The second analysis of a sample that included a number of marsupials shows that the rate of neurogenesis can also be variable in mammals, with the procession of events slowed in real time. This results in lesser encephalization in the metatherians as a group.

Overall, returning to figure 1, we find that closely related species may vary considerably in the duration of neurogenesis, spacing developmental events along a standardized temporal curve. Our comparison of two distantly related groups showed that they differed collectively in rate of neurogenesis (fig. 1C, marsupials), moving along an event curve of differing acceleration, producing brain mass at a lower rate. There is simply not enough data at this point to know whether one may speak generally of the rates of neural development in differing mammalian radiations: the

data we have available are in no way the systematic cross-radiation assessment such a claim would require. Particularly, we make no claim from this limited data set that within eutherian mammals the rate of neural maturation is the same. In fact, eutherian mammal groups do differ systematically in their rates of somatic growth [German et al., 1994; Gaillard et al., 1997] and neural growth: primates produce brain mass more quickly than do other mammals [Sacher, 1982].

*Establishment of Connections Moves on the
Same Timetable*

We limited our first study of developmental timing to neurogenesis for the theoretical reason that neurogenesis was most closely related to brain size and the practical reason that the peak of neurogenesis was an easily measured event, comparable between laboratories. It also seemed reasonable that axon extension and projection segregation events might be controlled by more variable and local factors than neurogenesis, though considerable stability had already been noted in a sample that included several kinds of developmental events [Robinson and Dreher, 1990]. We were able to compare the variability of a fairly large sample of generation events to events related to establishment of early connectivity in the brain. Both classes of events were

equally predictable. It should be emphasized that this is not a simple case of clocklike maturation of individual neurons expressed repeatedly throughout the nervous system – i.e., each neuron undergoes terminal division, migrates, differentiates, sends out axons, elaborates dendrites, and segregates connections in a standard pattern. To take the case of axonogenesis in the isocortex alone, some neurons extend axons while migrating, some only in situ, and different subpopulations extend axons at grossly different rates [Kagayama and Robertson, 1993; Miller et al., 1993]. The observation of stability of the basic timing of connectional development over millions of years of mammalian evolution suggests that these apparently locally idiosyncratic events are conserved along with basic neurogenesis. For the most part, this observation is born out in the bulk of the developmental literature, such that investigators feel properly comfortable proposing any mammal as a 'model' for generic mammalian neurodevelopment [for examples of this in metatherians: Reynolds et al., 1985; Harman and Beazley, 1986; Krause and Saunders, 1994]. Many interesting deviations do occur: for example, thalamocortical axons in metatherians do not appear to undergo a waiting period in the subplate as they do in eutherians [Harman et al., 1995]. Most notably, metatherians do not possess a corpus callosum. It is not our intent to argue that there is no variability in development but to quantify that variability so that deviations may show in best relief.

How do two brains of the same size, but generated at different rates, differ in their adult organization? Not all events are slowed: the basic physiology of action potentials and the structure of events in the environment, to name only two things, are independent of maturational rate. If a car manufacturer were to take twice the amount of time to build one car as another of similar proportions, everything else equal, we might presume that the more slowly built car was the better car. For example, marsupial brains might have more time to assimilate the statistical structure in activity-dependent correlations, correct developmental errors, match populations of cells, and segregate dissimilar inputs to structures. Such a claim has been made, with substantial empirical evidence in support, for greater specificity in the initial and the terminal structure of visual system segregation for primates versus smaller brained eutherian mammals [Chalupa and Dreher, 1991]. Primates have both more brain and more time to build it; a careful comparison of eutherian and metatherian brains would allow dissociation of brain size from duration of neurogenesis.

Spatial Structure in Temporal Order:

The Prosomeric Model

Is the stability of developmental structure we observe across mammals due to chance stabilization of the chronology of development at the time early mammals diverged, or is there a deeper structure to developmental chronology? Such a deeper structure has been hypothesized in the prosomeric model of brain organization [Rubenstein et al., 1994; Puelles, 1995; Rubenstein and Shimamura, 1997]. To quote

> … studies of the molecular and cellular mechanisms that pattern the prosencephalon need to establish how the primary D/V and A/P organization is set up… it is likely that organizers also modulate cellular proliferation, which secondarily regulates morphogenesis of brain regions.
[Rubenstein and Shimamura, 1997, p. 17]

Since we had on hand a compendium of data on cell proliferation, we organized the structures on which we had data on neurogenesis into the anterior-posterior and alar-to-basal axes as outlined in the prosomeric model. It should be noted that this analysis differs substantially from the nucleus-based analysis we described previously [Finlay and Darlington, 1995]. The prosomeric model is concerned with segmentation with respect to the initial neural tube – it is a development model of segmentation. Therefore, everything that arises from a single location on the neural tube is a single point in an analysis of prosomere-based patterns of neurogenesis. Therefore, for example, for any tangential location in the isocortex, events of interest extend from the first generation of the subplate to layers 2–3 and for the retina from the first retinal ganglion cells to the rods. For some areas of the neural tube, most notably the nuclear regions of the neuraxis, we are somewhat less likely to know all the neural progeny of a single neural tube region, but we included what was available, with the resulting caveat that total duration of neurogenesis is likely to be underestimated due to missing data for parts of the neuraxis giving rise to diverse nuclei, as in the diencephalon. We could consider onset of neurogenesis, total duration of terminal neurogenesis, or offset; this information was available in adequate depth for two species only, a rat and a monkey, gathered by the laboratories of Altman and Bayer and Rakic, respectively (citation list in Finlay and Darlington [1995]). Plotted in figure 6 is a schematic of the total duration of terminal neurogenesis plotted onto the anterior-posterior and basal-alar axes of the prosomeric model. The rat and monkey data are combined by normalizing them to a single time frame, as we did earlier for the limbic system analysis. As is clear,

there is a strong relationship between position on the prosomeric axes and duration of neurogenesis: the more alar and anterior, the more protracted neurogenesis is. This bivariate regression accounts for approximately 50% of the total variance. The same charaterization can be made for the end of neurogenesis but not for the beginning: overall, most positions in the neuraxis begin generating neurons at about the same time, but anterior and alar positions contribute neurons much longer. Rephrasing in terms of the cell cycle, the 'Q' or quiescent fraction of the cycling population stays lower longer in alar and anterior positions. This allows the precursor pool in these regions to proliferate at a higher rate, producing larger structures as the duration of embryogenesis is extended.

A substantial proportion of the conservation of timing we see in mammalian development may therefore be referred to the spatial organization of the two neuraxes, an organization that certainly precedes mammals and, in part, precedes vertebrates. We argue that the significance of the observation is large for understanding how brains evolve when evolution is characterized in behavioral and adaptive terms rather than cellular and genetic ones. Recent work has shown that both available variability and adaptation channel evolutionary change in morphology [Schluter, 1997; 'Adaptive radiation along genetic lines of least resistance']. There are two general kinds of models of the brain we might consider when animals are selected on brain traits such as sensory processing and motor capabilities and learning and other cognitive capabilities. The first model makes specific function of the brain tissue primary and localized: for example, visual information comes in through the eyes and is processed in the visual centers of the brain; olfactory information enters through the nose; spatial information is processed in the hippocampal areas specialized for this purpose. To select on a behavioral function is to select on a brain location, specialized for the purpose, that will become larger or more efficient as required. In part, this model is certainly true: for example, in no case has a vertebrate going from a nocturnal to a diurnal niche converted its olfactory epithelium to photoreceptors, even given the tantalizing similarity in their structure [Eisthen, 1997].

It is not clear, however, that this is the best model for all integrative functions. The second model might posit that all neural tissue ever described shows evidence of possessing powerful and generic learning structures – minimally adaptation and quite often mechanisms sensitive to temporal correlation like Hebbian learning. Potentially, neural tissue might easily produce many of the more powerful neural net architectures. In this case, adaptive pressure for better inte-
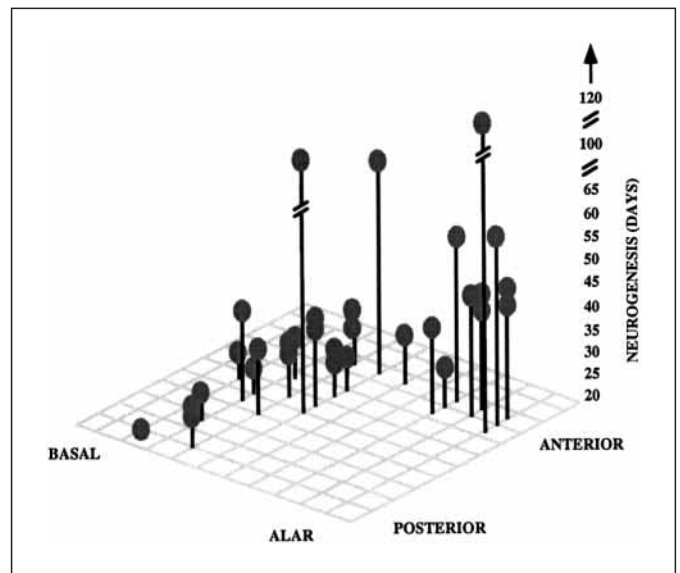
Fig. 6. Termination of neurogenesis by location, anterior to posterior and alar to basal, in the neural tube, organized according to the prosomeric model, combining data from rats and monkeys. Structures are plotted posterior to anterior, basal to alar: Row 1, Cranial motor nuclei, cranial sensory nuclei, vestibular nuclei; Row 2, Inferior olivary nuclei; Row 3, Cochlear nuclei; Row 4, Pontine nuclei; Row 5, Locus coeruleus, deep cerebellar nuclei, Purkinje cells, granule cells; Row 6, Red nucleus, substantia nigra, raphe complex, inferior colliculus, superior colliculus; Row 7, Lateral geniculate nucleus, medial geniculate nucleus; Row 8, Ventrolateral geniculate nucleus, reticular nuclei; Row 9, Amygdala, dentate gyrus, granule cells, CA-1–2; Row 10, Globus pallidus, caudoputamen, subplate and cortical layers 2–6; Row 11, Anteroventral, anteromedial, and anterodorsal nuclei, suprachiasmatic nucleus, ventroposterolateral and ventrobasal nuclei, retinal structures, magnocellular basal forebrain, preoptic nucleus, nucleus accumbens, subicular structures, septal nuclei, olfactory structures, entorhinal cortex.

grative function, such as spatial memory, temporal contingencies in foraging, complex perceptual decisions or communication might push these functions to places (if the information can get there) where brain space is being made and learning mechanisms are available. This is not an unfamiliar argument – the migration of function termed 'encephalization' has been noted by comparative biologists and psychologists for some time. Functions have been posited to migrate from brainstem and midbrain to cortex many times; if a reason is stated, it is imagined that there might be some structural superiority to isocortex (laminar organization or map segregation, for example) over the brainstem. The argument presented here is simpler still: functions 'migrate' to the isocortex because there is more of it as brain gets big, due to the privileged position of the

isocortex on the anterior-alar axes. Perhaps all neural tissue can produce powerful learning configurations.

Gould has discussed the problems of conceptual separation of an 'adaptation' from a developmental constraint. Since a developmental constraint must be at least marginally adaptive, demonstration of such constraints has often focused on structures with peculiar organization such as the panda's thumb, adequate to its purpose but of clumsy construction due to its lineage [Gould, 1980]. Current developmental biology has continued to turn up such extreme conservation of basic patterning mechanisms and physiological functions that interest has turned to understanding how there has come to be an identity of developmental constraint and adaptation in so many cases. As Gerhart and Kirschner say in their marvelously comprehensive book *Cells, Embryos and Evolution* [1997].

'Rampant diversification gives further emphasis to the view that its (an early embryonic stage) conservation is not merely an inalterability due to inadvertent constraints built up at that stage, but is a selected conservation of flexible robust properties.' (p. 440)

The evidence of constraint in the ways brain enlargement can occur should now direct our attention to the flexible, robust properties of neural tissue that make such morphological constraint possible.

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