21 Chronology of Development of the Mouse Visual System: Comparisons with Human Development

BARBARA L. FINLAY AND BARBARA CLANCY

In this first era of genomic analysis of neural systems, the emphasis falls on what genes code, where particular genes are expressed, and what kinds of disorders appear when genes are mutated, absent, or misapplied. Less emphasis is placed on when and for how long genes are expressed, and less still on the control that coordinates the expression of ensembles of genes that construct developing sensory systems and brains. Control of the timing and duration of gene expression is certainly the major way in which vertebrate eyes differ from each other, because vertebrate eyes are quite conservative in their cell types, neurotransmitters, neuromodulators, and general structure (Rodieck, 1973; Arendt, 2003), with variation in opsins the notable exception (Shyue et al., 1995). The most significant differences in vertebrate eyes are in size, in the ratios of numbers of cell types, and in the arrangement of these cells. These differences suggest that alterations in the control of genes expressed, rather than the nature of the genes expressed, is the principal source of variation in evolution. Understanding the class of variations in developmental timing that can give rise to functional eyes should be a focus of genomic work as well. How the components of the eye are caused to scale gracefully and integrate with each other gives us a different way of approaching the genome than the more static version presented by the study of a single species.

The conservation of the constitutive elements of the eye, and of the visual system in general, is thus good and bad news for the mouse model. Because of the conservation, mechanistic comparability in most domains will be good. On the other hand, permissible and pathological variations in the duration and timing of gene expression are difficult to distinguish or characterize in an animal with such a relatively brief gestation period (ca. 18.5 days). The qualitative trait locus method of correlating variations in parameters such as brain size or gestational length with regions of the genome (e.g., Zhou and Williams, 1999) is a first step toward integrating intra- and interspecies variation with pathological variation. In addition, some natural variations in rapidly and slowing developing mice chimeras could be used to investigate basic questions about overarching control of rates of neurodevelopment (Williams and Goldowitz, 1992).

Understanding the chronology of development has an empirical aspect and a theoretical aspect. In this chapter, we first describe the chronology of development of the mouse visual system in relation to that in humans and monkeys, using a comprehensive model we and our colleagues have developed. This model capitalizes on the essential conservation of developmental timing in mammals for interspecies comparison and for interpolating missing data accurately in those cases where the date have not been or cannot be determined empirically (neurogenesis data, for example, require invasive techniques). This database is intended as a resource for the optimal developmental placement of any observation or experiment, as well as for investigating the control of developmental timing per se. We point out areas of greatest similarity between and among mouse, other experimental animals, and humans that suggest the most reliable prediction back and forth, and also point out areas of difference that would make the mouse model less reliable. Finally, we suggest areas of investigation that would be particularly interesting to pursue in light of mouse and human similarities and differences in chronology.

Timetable of mouse development

Table 21.1 lists the observed and computed times of various visual developmental events in mouse, human, and rhesus macaque, all given in postconception (PC) days, where the day of conception is postnatal day zero. This table is excerpted from a much more extensive database that includes 102 events in early development (principally neurogenesis, tract formation, and structure innervation) from all sensory

TABLE 21.1

Observed and computed (predicted) times of visual developmental events in mouse, human, and rhesus macaque (PC days)

		Mouse		Human		Monkey	
Structure	Event	Pred.	Obs.	Pred.	Obs.	Pred.	Obs.
Retina	*Ganglion cell—start*	*10*	*10.5*	*38.1*		*30.8*	*30*
Cortex	Subplate—start	10.1	10	48.2		38.7	39.5
SC	Superficial SC—start	10.7	10.5	41.9		33.8	30
LGN	dLGN—start	10.8	10.5	43		34.6	36
Cortex	Subplate—peak	10.9	11	54.5		43.6	43
Cortex	Cortical layer VI—start	11.4	11	57.9		46.3	45
LGN	vLGN—peak	11.7	11.5	47.9		38.4	
Optic nerve	Axons in optic stalk	11.7	12.3	48.2	51	38.7	
Connectivity	Internal capsule appears	11.7		60.8	63	48.5	40
LGN	dLGN—peak	12	12	50		40.1	43
Optic nerve	Optic axons at chiasm	12.2	13	50.9		40.8	36
Retina	*Horizontal cells—peak*	*12.4*		*52.4*		*42*	*40*
SC	SC—peak	12.7	13	53.9		43.1	41
LGN	dLGN—end	12.8	12.5	54.4		43.5	43
Cortex	Cortical layer V—start	12.8	12	68.6		54.6	58.5
Retina	*Ganglion cells—peak*	*12.9*	*13*	*55.6*		*44.4*	*43*
Cortex	Subplate—end	12.9	12	69.8		55.6	48
Cortex	Layer VI—peak	13	12.5	70.3		56	53
Optic nerve	Axons reach dLGN and SC	13.7	14.5	59.8		47.7	
Optic nerve	Axons invade visual centers	14.2	15.5	63.2	60	50.4	
SC	Superficial SC—end	14.2	14	62.8		50.1	56
Cortex	Layer V—peak	14.2	13	79.7		63.3	70
Cortex	Lamina VI—end	14.4	13	80.8		64.2	65
Cortex	Lamina IV—start	14.4	15	81.2		64.5	70
Retina	*Cones—peak*	*14.8*	*14*	*66.3*		*52.8*	*56*
Retina	*Amacrine cells—peak*	*15.3*	*15*	*69.3*		*55.2*	*56*
Cortex	Layer II/III—start	15.2		87.4		69.4	85.5
Cortex	Layer V—end	15.3	14	87.8		69.7	75
Cortex	Layer IV—peak	15.5	17	89.3		70.9	80
Retina	*Ganglion cells—end*	*15.8*	*18.5*	*72.4*		*57.6*	*57*
Connectivity	Corpus callosum appears	15.9	17	92.6	87.5	73.4	
Connectivity	LGN axons in subplate	16.2		94.7		75.1	78
Connectivity	Cortical axons reach dLGN	16.3		95.9		76	67
Cortex	Layer II/III—peak	16.9	15	100.4		79.6	90
Cortex	Layer IV—end	17.1	17	101.7		80.5	85
Optic nerve	Axonal number—peak	17.2		80.9		64.3	69
Cortex	Layer II/III—end	18.3		110.6		87.5	100
Connectivity	Cortical axons in dLGN	18.4		111.5		88.2	81.5
Connectivity	LGN axons in layer IV	21.1		132.3		104.5	91
SC	Superficial—start lamination	21.2		104.7		82.9	86
Retina	*Rods—peak of neurogenesis*	*21.6*	*19*	*106.9*		*84.6*	*85*
Connectivity	Cortical axons in SC	22.5		143.2		113.1	96
Retina	*Onset of retinal waves*	*20.6*		*101.3*		*80.2*	
Retina	*Bipolar cells—peak*	*23*		*115.6*		*91.4*	*85*
Optic nerve	Rapid axonal loss ends	24.3		123.1		97.3	110
LGN/SC	Ipsi-, contralateral segregation	24.5	25.5	124.4	175	98.3	87
Eye opening	Eye opening	29.7	30	155.4	158	122.6	123

Note: Table lists model-derived values (Pred.) versus empirical observations (Obs.) for the postconceptional day of occurrence of various developmental events in the laboratory mouse, human, and rhesus macaque. Retinal events are in italic type for easier identification.

LGN, lateral geniculate nucleus; SC, superior colliculus.

systems and brain regions, and 10 species (also hamster, rat, rabbit, spiny mouse, guinea pig, ferret, and cat). The complete database (www.translatingtime.net) describes the sources in more detail and allows calculation of the desired developmental windows in the species listed; it also gives the confidence intervals for each value calculated (Clancy et al., in press). Predicted developmental times are derived through a general linear model incorporating all the data sources listed on the Web site; a sample calculation on the site is shown in figure 21.1. This model was first derived for a more limited set of developmental events (principally neurogenesis) and a more limited set of species to query about a systematic function to transform the schedule of developmental events of one species into the developmental schedule of another (Finlay and Darlington, 1995; Finlay et al., 1998, 2001). It proved possible to do so with high accuracy, and in subsequent versions the model was expanded to include marsupial mammals and more classes of developmental events (Darlington et al., 1999), to account for the particular deviations of primates in the timing of cortical versus limbic developmental events (Clancy et al., 1999), and finally, to include more species, including humans (Clancy et al., 2001). These citations, as well as the Web site, give the references to the source empirical data; the majority of sources for the mouse data included here come from the laboratories of Angevine, Sidman, Caviness, and their collaborators, and the monkey data come from Rakic and collaborators.

The model predicts PC dates transformed to the mathematical term Υ as $\Upsilon = \ln(\text{PC days} - 4.34)$. The form of the equation, containing a natural logarithm modified by a constant, is the empirically determined best-fitting function for this data. The biological significance of the constant (4.34) is probably that the function fits best with its zero located after early germinal events (blastulation, differentiation of basic germinal layers) common to all eutherian mammals have occurred, averaging 4.34 days. The biological account of why a logarithmic function best fits the relation between developmental schedules is not so clear (in contrast to, for example, the inaccurate multiplicative rule of thumb that is used to transform dog years to human years). The greater separation, in absolute days, of late events in slow-developing species compared with separation of the same events in more rapidly developing species is the feature of the data reflected in the log function.

Each neural event in the database is assigned an event score (with later events having higher scores), and each species is assigned a species score (with slower-developing species having higher scores) consistent with the general linear model described previously (Darlington, 1990; Finlay and Darlington, 1995). Then Υ is modeled as the sum of three terms: the event score, the species score, and a primate interaction term where appropriate. The primate interaction factor accounts for the fact that limbic and cortical components of rodent and human brains mature at different rates with respect to the rest of the brain (Clancy et al., 1999). This third factor adds 0.248683 to the estimated Υ score of every primate cortical event and subtracts 0.079280 from the estimated Υ score of every primate limbic event. This general linear model has been fitted simultaneously to all cells with data, but it also generates estimates for cells with no empirical data (figure 21.2).

Technical and qualitative evaluation of the model's predictions

Utilizing a regression model to formulate predictions is unusual in developmental neurobiology, and we spend some time here describing considerations at several levels that

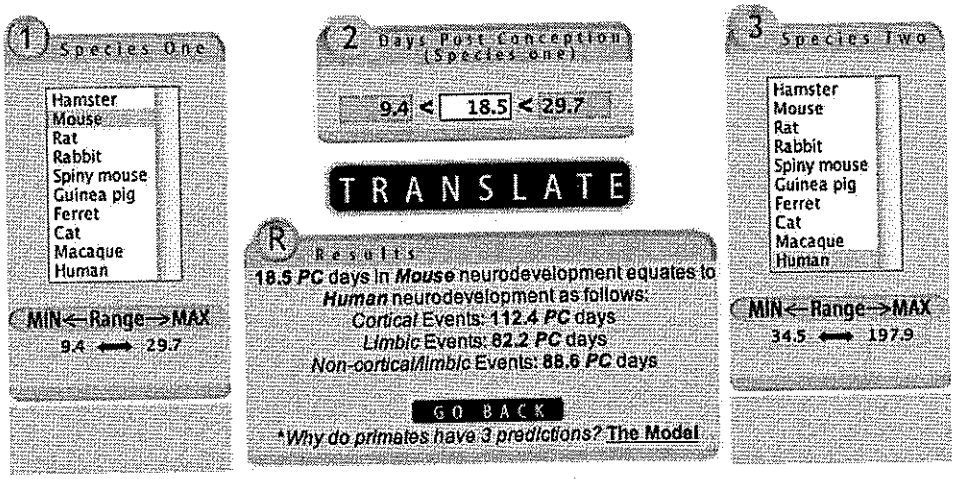

FIGURE 21.1 Representative Web page (www.translatingtime.net) depicting a "translation" from mouse on the day of birth to human neurodevelopmental time. The model predicts that neural events that occur in the mouse brain on the day of birth (14.5 days post conception, PC) translate into PC112 in human cortical development, PC82 in human limbic system development, and PC88 for noncortical, nonlimbic neural events. See color plate ••. 4

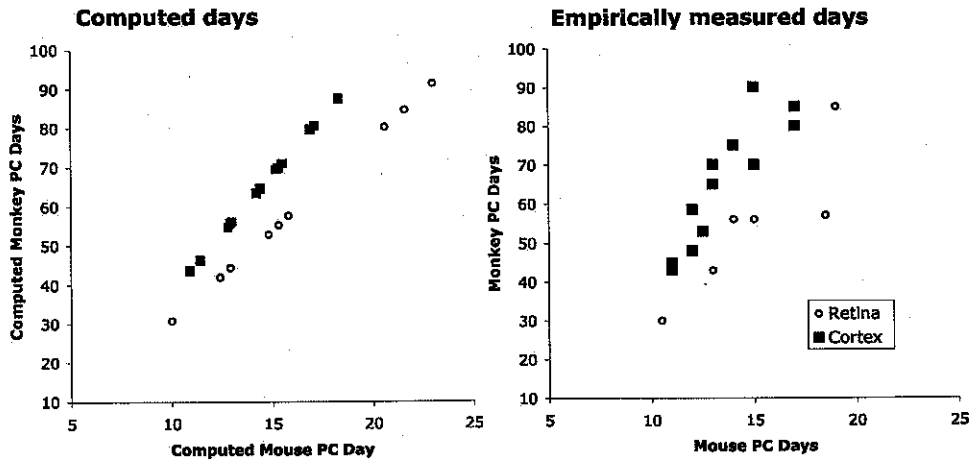

FIGURE 21.2 These graphs contrast the overall function relating the PC day of a number of developmental events in the mouse (*x*-axis) to the monkey (*y*-axis). Plot at *left* shows the generalized relationship determined from a much larger sample of neuroembryological events and species; plot at right shows the empirical measures made for the visual system of mice and monkeys, using data drawn from table 21.1. There are fewer measured than computed events because the generalized function computes a value for all desired events, not just the ones measured empirically for these two species. A further contrast is made in both graphs concerning the different scaling of the cortex (*black squares*) versus the retina (*white circles*) between primates and rodents.

should guide the use of this model in empirical applications. Fitting any mathematical model involves three steps: (1) selecting the variables to include in the model, together with the general way they will be combined (e.g., additively, multiplicatively), (2) estimating the specific numerical values to be used in the model, and (3) testing the fit of data to model. We are convinced that we have the correct overall form for the model based on the high correlation (0.990223) between observed values and the model's predictions, this based on the extended data set (Clancy et al., ~~in press~~). We should also mention that exhaustive investigation of potential additional factors (by species hierarchies, by grouping of functional systems such as visual or auditory, or grouping by location, such as midbrain or spinal cord) produce no further improvements in predictability. Even though the correlations are high, however, the specific numerical values predicted by the model do not exactly match the available empirical data, particularly for the human data (see table 21.1 and Figure 21.2). Based on the assumption just mentioned, how do we understand the model's accuracy?

SAFETY IN NUMBERS Empirical investigators are aware that their observations can be subject to individual variation and observational error, and this is especially true for human developmental data, where specimens are rather rare and often subject to errors in birth dating. For this particular database, intralaboratory differences in the interpretation of such events as "first retinal axons in LGN" are an additional source of concern. However, when numerous error-plagued figures are averaged, the average is likely to be more accurate than the individual figures. The same is true for statistical models of the type described here. Since the estimates generated by the model are each based on all the observations used to build the model, errors can average out, making the model's estimates more accurate than the individual observations on which the model was based.

An illustrative example of the bootstrap effect can be seen in simple regression. Suppose a regression has been derived in a sample of 200 mice, predicting an animal's weight from its age in days, for ages running from one to 100 days. To estimate the average weight of a mouse at 50 days, one could use the regression model (entering age = 50) or one could average the weights of the one or two mice in the sample that happened to be exactly 50 days of age when studied. Assuming a linear relation, the regression model is likely to give a far more accurate estimate of the value of interest than an average of one or two weights. The same argument applies to more complex regression models, such as the one described in this chapter (Clancy et al., 2001). The difference between model predictions and empirical observations for retinal and cortical developmental events in monkey versus mouse are shown in figure 21.2, drawn directly from table 21.1. (It should be noted that the range of empirical observations for this comparison is truncated because there is not a complete matching range of observations).

Because of the difficulty encountered when working with humans, published human data appear to contain about twice as much error as figures for other species, as measured by the fit of human data to the model described here (Clancy et al., 2001). Thus the model is particularly useful for

estimating neural dates in humans, not because the model estimates dates for humans better than for other species (it does not) but because the alternatives may be so much worse. Insofar as each predicted event is based not simply on data available for that particular species but on data available for all species, the model is less restricted than might be expected from the limited—or even inaccurate—data set pertaining to humans. Although we are confident the predictions and comparisons for the neural events that are included in our database are of value, we also caution against overeager interpretations until more data become available.

2 *Production of the cortex: Timetable differs in primates*

In figure 21.2, the events associated with corticogenesis and maturation (*black squares*) are contrasted with events associate with the retina (*open circles*), with the timing of mouse events plotted against the same events in rhesus macaque. This figure demonstrates that at any given developmental day, events that occur at the same time in the retina and cortex of the mouse occur at a corresponding time in the retina but later in the cortex in the monkey. This effect is specific to the primates of this database (human and rhesus macaque), not simply any animal with a brain larger than a mouse's. So, for example, the peak of cone generation and the start of generation of pyramidal cells destined for layers II/III of the cortex both happen on PC14 in the mouse but separate in the monkey to occur between PC53 for the retina event and PC69 for the cortical event. All noncortical events (with the exception of the limbic system, not shown here) scale with the retina, which has been selected for illustrative purposes only for figure 21.2. For example, to take another subcortical event that happens at about the same time in the mouse, the end of generation of the superficial layers of the superior colliculus occurs on PC14 in the mouse and PC50 in the monkey. Therefore, to set up appropriate comparisons in experiments, the different scales of the cortex compared to the rest of the brain in primates must be attended to.

This timing difference correlates with an allometric difference in overall brain organization of rodents versus primates, one that has been described in detail numerous times: in rodents and insectivores, relatively more neural mass is allocated to olfactory bulb, olfactory cortex, and entorhinal, subicular, and hippocampal cortices, as well as other basal forebrain structures (the classic limbic system), while in primates relatively more mass is allocated to the neocortex (Jerison, 1973; Gould, 1975; Stephan et al., 1988). We have argued that not only is the difference in developmental timing correlated with the varying size of brain components, it is the direct cause of it, using the shorthand of "late equals large" (Finlay et al., 2001; Reep et al., 2007). In the monkey, the "birthdays" of neurons destined for limbic structures occur comparatively earlier than they would in rodents, which corresponds to precursor cells becoming postmitotic and removing themselves from the precursor pool, thus depleting it. By contrast, the birthdays of cells destined for cortex are comparatively later in primates, allowing their precursor pools to proliferate exponentially for a longer time and thus become disproportionately large.

This timing distinction may have some consequences for the organization of innervation between structures, including guidance molecules and trophic support. A debate existed for some time, for example, about whether there was a "waiting period" for thalamocortical axons in the subplate region or whether thalamocortical fibers directly invaded the cortical plate on arrival (Miller et al., 1990; Catalano et al., 1991; Ghosh and Shatz, 1992). The debate may have been caused directly by this species difference, since the studies that suggested direct innervation were done in rodents, while those suggesting a "waiting period" were done in the cat. Carnivores' cortices scale in the direction of primates' (Reep et al., 2007), and the measured times of cat corticogenesis systematically occur later than their predicted times, though the trend is not distinct enough to justify a "carnivore" factor.

What mice cannot model in human developmental timing

A notable feature of the development of the monkey and human retina that is deliberately absent from table 21.1 is the presence of distinct gradients of neurogenesis and other aspects of maturation within single cell classes, such as retinal ganglion cells (RGCs), or the sublaminae of layer IV of cortex (Rakic, 1974; Rapaport et al., 1992, 1996). In the retina, for example, a distinct gradient of neurogenesis from the center to the periphery of the retina is observed in every mammal studied. Most pronounced in the offset of neurogenesis—the peak of rod neurogenesis in the retina center—in monkey is PC70, but for the very periphery it is PC120 (Rapaport et al., 1996). This allows the extracellular environment of groups of precursor cells to be systematically biased by their spatial location, which is employed to advantage to produce regional differences in the retina. Though the "clock" of cell specification appears to proceed in a rather uniform manner across the retina surface in the well-established order of ganglion cells, cones, amacrine cells, rod, and rod bipolar cells (figure 21.3), the early provision and cessation of precursor cells for specification in the central retina produces an abundance of RGCs and cones and fewer rods, with the opposite the case in the peripheral retina (Cepko et al., 1996; Finlay, Silveira, et al., 2005). The short distances and time available in the mouse retina appear to produce only the shallowest gradients of cell classes across the retinal surface, while in the monkey, the pronounced gradients produce no rods in the central retina (the eventual

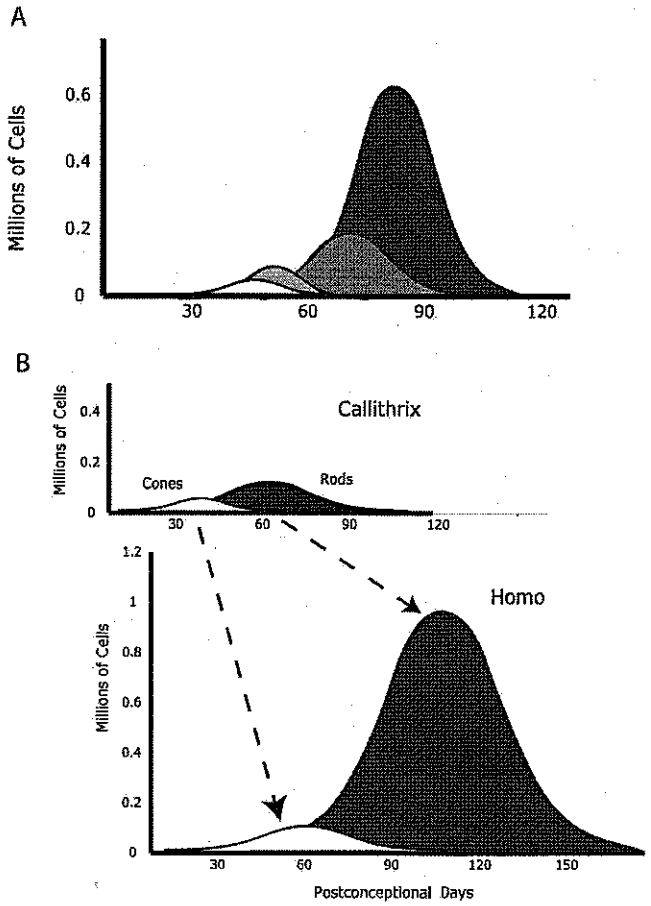

FIGURE 21.3 *A*, Schematized order of production of retinal ganglion cells, cones, bipolar cells, and rods in the retina of rhesus macaque. For the two types of neurons omitted from this map, horizontal cells virtually overlap cones; amacrine cells lead bipolars slightly. The ~~ordinate~~ shows the postconceptional day of terminal cell division, the ~~abscissa~~ the percentage of each cell class produced on that day. *B*, Schematic demonstrating how extension of the period of retina neurogenesis may disproportionately increase the number of later-generated cell groups, in this case rods, by allowing a disproportionate increase in the precursor pool from which later cell groups are drawn.

site of the fovea) and an abundance of rods with virtually no cones in the very periphery. It is possible that the extension of the gradient producing the retina in primates that resulted in a small rod-free region might serve as the initial signaling event to locate the fovea, and that secondary events, such as the compaction of cone outer segments and displacement of cell bodies, might be instigated by this time-based morphological singularity (Finlay, Silveira, et al., 2005). Insofar as these unusual cell complements might be the features permissive of the production of the notable primate specialization of the fovea and whatever new features of genetic specialization that come linked to it, there can be no real mouse homologue, as the fovea is linked to a feature of retinal chronology that mice simply ~~to~~ not have.

The layers of the cortex are a comparable case: every mammal studied exhibits the well-known inside-out gradient of corticogenesis (Rakic, 1974). In mice, however, the overlapping nature of the layer gradients and the small numbers of cells produced would make lamination in cortical layer IV unobservable, though possibly the features that give rise to lamination in a larger structure might be distributed through it (Sidman and Angevine, 1962). In passing, while much has been made of cortical "uniformity" across species (Rockel et al., 1980), it simply isn't so. As the cortex gets larger overall, it also increases in column depth somewhat, and the increase in number is most pronounced in the upper cortical layers, 4, and 2/3. In the animals with the smallest extent of neocortex, layer 4, as distinguished by the presence of spiny stellate cells (Valverde, 1990), may be entirely absent, with thalamocortical axons terminating on the basal dendrites of layer 3 pyramidal cells.

The variability of mouse strains

The often deliberately inbred, "unselected" nature of the various mouse strains raises concern about how representative the mouse is of general mammalian brain organization. And there is some cause for concern: for example, in an allometric study of the relative sizes of subcortical components of the auditory system in a wide range of mammals, the mouse was a notable outlier, along with the little brown bat and the mountain beaver, even though there is no reason to suspect any unusual functionality of the auditory system in the mouse (Glendenning and Masterton, 1998). We have been collecting data on strain variability in the relative sizes of brain parts and comparing examples of individual mouse strains (11 individuals) with individual wild and domesticated pigs (24 individuals) and wild and domesticated minks (12 individuals) (Finlay, Hinz, et al., 2005, analyzing data from Kruska, 1988, and from the Mouse Brain Library, www.mbl.org). When we examined the factorial structure of the size of brain components in this unusual collection of animals, data from four of 49 individuals fell outside the 90% confidence interval, and of those four, three were mice, each of a different strain. Although this study is preliminary, and the majority of the mouse strains used fell into the range of normal variability, it suggests that in planning future studies it would not be a wasted effort to pay close attention to the normality of the structure to be studied in whichever mouse strain is chosen.

What evolutionary variability suggests we should look for in mouse models of the developing visual system

The studies of comparative brain allometry and timing described so far highlight questions of the relative sizes of structures and the problems that arise from scaling animals

over a variety of sizes, and these questions have been addressed in the mouse genome literature. Williams and colleagues have done multiple studies employing natural variation in brain and eye size in mouse strains to highlight regions of the genome involved in control of retinal, visual system, and overall brain size (Williams et al., 1996, 1998; Strom and Williams, 1998; Zhou and Williams, 1999; Airey et al., 2001; Seecharan et al., 2003). Several studies have examined mutations and deletions in mice that have caused the development of abnormally large cortices (Chenn and Walsh, 2002; Kingsbury et al., 2003). Researchers studying the control of cortex size in rodents naturally speculate that the mutations they see might be involved in the production of the "unusually developed" human cortex. Is this a possibility? We are entering an entirely unexplored field when we ask what the relationship is among evolutionary variability, variability between individual species members, "natural" pathology of the kind found in human development that we would like to remediate, and the induced pathologies we might see as a result of mutations and deletions of the mouse genome. We might caricature two types of views of the genome, one in which each feature of the visual system, each cell type in the retina, each connection decision, each instruction for cellular growth, has its own committed and relatively encapsulated genomic machinery. This is in contrast to a second view, in which all features of cell morphology, connectivity, and function are overlapping and contingent, where all the action is in the control genes to set very general parameters of size and timing. We would expect very different relationships among evolutionary variation, individual variation, naturally occurring pathology, and induced pathology, depending on the view of the genome we hold.

We present two pieces of evidence that the emerging features of conserved developmental timing are employed to advantage for the scaling of visual system structures. Both suggest that individual variability and phylogenetic variability are tightly linked at the level of control genes (Finlay, Silveira, et al., 2005), and both are based on the fundamental evolutionary scaling concept that late equals large. In other words, if the schedule of cytogenesis or neurogenesis is extended to make a larger eye, brain, or visual system, those groups of cells exiting cytogenesis last will have a longer time to experience the exponential growth of precursor doubling and will become disproportionately large compared with cell groups exiting early. The most obvious example of this phenomenon is the size of the spinal cord relative to cortex between small- and large-brained mammals. Similarly, if the time of precursor cell differentiation is pushed early or late, as previously described for the cortex and limbic system, the associated structure will become smaller or larger accordingly. The overwhelming evidence in the case of the brains of eutherian mammals is that in order to become larger, brains are made for a longer time, not generated at a faster rate (Darlington et al., 1999).

Scaling the eye and the cortex

The eyes of diurnal primates are large absolutely compared with those of most mammals and scale allometrically with body size (Ross, 2000), ranging from around 10 mm in diameter in the smallest monkeys to around 30 mm in various anthropoid apes and humans (Heesy and Ross, 2001). Scaling an organ (made of cells of constrained size) that has several geometrical features under different constraints is an interesting construction puzzle—not all parts of the eye may scale the same and retain function. The overall conformation of the optics of the eye scale up linearly. For example, the eye of the rat and the eye of the mouse, appropriately scaled, are superimposable (Remtulla and Hallet, 1985). Within the eye, however, retinal thickness may not vary much, owing to the constraints of perfusion and light passage, and stays close to a thickness of approximately 200 μm.

Numbers of rods and cones must scale at different slopes with eye size in order to hold constant their particular functions. If an eye becomes twice as large in diameter, no change in the number of cones is necessary to retain the same visual acuity: since the retina is flooded with photons in diurnal vision, a single cone will have no difficulty encountering a photon in the visual angle it represents, regardless of the angle the cone itself subtends. More cones could be added, to improve acuity, but we are discussing here what is required to maintain equivalent, not improved, function over different eye sizes.

The same solution will not work for rods. At low light levels and low photon numbers, a single rod located in a larger absolute retinal angle will fail to detect most photons, even allowing for biologically plausible increases in the size of a single rod. Rods must tile the surface of the retina to maintain sensitivity, increasing in number approximately as the square of change in retinal diameter. The observed scaling of rods and cones in diurnal primates conforms closely to this functional necessity: where cones increase in number by less than a factor of 2 between marmosets (*Callithrix jacchus*) and humans, rods increase by more than a factor of 10 (Finlay, Silveira, et al., 2005).

How is this consistent, within- and across-species scaling executed in the schedule of neurogenesis of the retina? Although the precise kinetics remain to be worked out, the schedule of neurogenesis in the retina is arranged such that extension of the period of embryogenesis automatically produces the desired differential scaling. Such is the case for the relative timing of cone and rod neurogenesis in the retina, as modeled for marmoset versus human (see figure 21.3). Those cell types that must change in number exponentially with eye diameter, rods and their attendant bipolar cells are

differentiated last, and those that need not change are produced first. Those potential ancestors with the opposite order of neurogenesis in the retina that might have had a selective advantage at a larger body size but that unfortunately became blind in the dark as a result presumably would enjoy less reproductive success.

This obligatory, coordinated scaling of retinal cell classes to match functional requirements has direct consequences for the kind of genetic control we might look for. For example, a researcher noticing the markedly large number of rods in the human retina might be tempted to look for the genetic specification events that produce the greater number. We argue that there is no such effect, except for the genetic event that causes the overall extension of neurogenesis for the entire brain, because the change in the relative numbers of rods and cones in larger eyes comes directly out of the kinetics of cell division and the longer period of neurogenesis required for larger retinas.

The enlarged size of the human cortex has a similar explanation. It has been shown repeatedly that the size of the cortex and the size of is subcomponents, such as primary visual cortex, or frontal cortex in humans, are precisely the size they should be with respect to overall brain size (visual cortex: Frahm et al., 1984; Kaskan et al., 2005; frontal cortex: Hofman, 1989; Jerison, 1997; Semendeferi et al., 2002). We argue that this phenomenon has exactly the same late-equals-large explanation given for the rods and cones in the retina, and the the apparently disproportionate size of the human cortex similarly falls directly out of cell cycle kinetics and an extended period of neurogenesis, given first a larger allocation of precursor cells to the cortex in all primates. Therefore, mutations in mice that cause unusual proliferation of the cortex through alterations in the rate of proliferation, or changes in the amount of early cell death, though very interesting, would be unlikely to have anything to do with the particular size of the human cortex. Mutations in genes that alter cortex size may well be involved in the normal regulation of cortex size in mice and humans, but they would be unlikely to be essentially different in their regulation.

Future directions

Change in the duration of embryogenesis is one of the principal ways that animals differ from each other: it simply takes more cell divisions, and thus more time, to make a larger brain or body. Given the notable of size differences both within species and between species, the filter of evolution appears to have positioned the orders of cytogenesis with respect to nonlinearity of the kinetics of cytogenesis. This permits graceful scaling, as we have discussed for rods and cones in the retina, and for the cortex, and probably for any number of other functional systems. But what sets the overall duration of neurogenesis, and the developmental clock overall? Are there chronology mutants in mice that complete cytogenesis in abnormally short or long times? If so, what covaries with this property, and what controls it? These aspects of cell cycle regulation, yet to be identified, are fundamental to our understanding of both development and evolution.

ACKNOWLEDGMENTS Work was supported by grants nos. IBN-0138113, P20 RR-16460, and P20 RR-16460 (the IDeA Networks of Biomedical Research Excellence Program of the National Center for Research Resources), National Institutes of Health. We thank Richard Darlington for his central role in the original studies on which this chapter depends.

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