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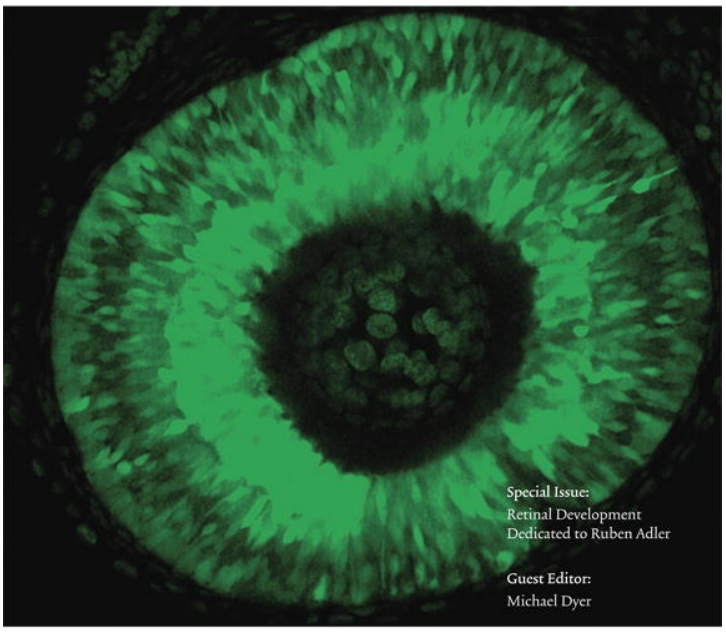

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BRAIN RESEARCH

Review

The developing and evolving retina: Using time to organize form

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ABSTRACT

Evolutionary and other functional accounts of the retina and its normal development highlight different aspects of control of its growth and form than genomic and mechanistic accounts. Discussing examples from opsin expression, developmental regulation of the eye's size and optical quality, regulation of eye size with respect to brain and body size, and the development of the fovea, these different aspects of control are contrasted. Contributions of mouse models, particularly with regard to relative timing of events in different species are reviewed, introducing a Web-based utility for exploration of timing issues (www.translatingtime.net). Variation at the individual level, in early experience, and also across species is an essential source of information to understand normal development and its pathologies.

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1. Introduction

Any collection of titles of articles on retinal development and the genome, or neural development generally will typically show that the word "control" is the most common word elected to describe the relationship between a gene and a process or product. What the word "control" means in research on the genome varies enormously, however, from the direct sense of the activation of a gene that produces a protein immediately involved in function (such as an opsin) to the coordination of genes which regulate the size and placement of whole organ systems. Comparative and evolutionary studies typically consider and describe levels of control at more organismal levels than do mechanistic studies of gene expression in studies of single animals, typically the mouse. Both levels are important, and the issue to be discussed here is their coordination, rather than the choice of one or another.

This review will have two sections. In the first section, three cases will be described in which evolutionary approaches versus genetic–mechanistic approaches contrast relationships between the two types of analysis. Those cases are first, color vision and opsin expression; second, control of retinal and eye size as it relates to optics and visual niche; and finally, control of retinal neuron number with regard to total neuron number in the brain. In the second section, we will consider the particular case of the relative timing and duration of events as a source of order in the developing retina, and how timing might be modified in evolution to produce eyes of different functional classes. The virtues and the limitations of the mouse model for understanding the construction of eyes will be considered in the particular context of developmental timing, from the immediate production of structural proteins, to the coordination of cell specification, to the emerging morphology of the entire organ. Finally, using the concept of "control" we will come back to consider a few ways evolutionary, individual and pathological variation could be linked.

2. Three control problems in retinal development

2.1. *Background: Overall patterns of conservation and variation*

Vertebrate eyes are quite conservative in their cell types, neurotransmitters, neuromodulators and general structure (Rodieck, 1973; Arendt, 2003; Fernald, 2004). It is a remarkable, though rarely noted feature of retinas that the eye of a 20 mm fish may be used quite confidently to explore the fundamental deployment and physiology of the photoreceptor–bipolar–retinal ganglion cell processing unit of the retina, as well as its modulation by horizontal processes, in any other vertebrate, including ourselves (Schmitt and Dowling, 1999). The fundamental cellular morphology and resulting receptive field structure of vertebrate eyes, including both its diurnal and nocturnal variations, apparently represent deep solutions for image analysis for both aquatic and terrestrial life.

Vertebrate eyes vary in the size and arrangement of their basic retinal processing units in typical ways. Eyes can have clearly different rules for scaling with respect to the body and brain, with eye size, photoreceptor number and retinal ganglion cell number scaling differently depending on the animal's niche and taxon (Hughes, 1977). For example, in nocturnal rodents, the number of retinal ganglion cells scales up steeply with brain size, though their eyes are on average relatively small compared to all mammals, while in anthropoid primates (monkeys and great apes), retinal ganglion cell number scales at a very low slope with respect to brain size, while on average their eyes are fairly large (Franco et al., 2000; Heesy and Ross, 2001). Within the eye, vertebrates differ in the conformation of non-neural elements, in the ratio of the numbers of types of cells in the retina and in the "topography" of the arrangement of these cells (Stone, 1983). With the exception of photopigments, the observation that vertebrate eyes appear to be principally "topological" permutations of an essentially conserved structure suggest that timing, duration, or number of genes expressed, rather than the nature of structural proteins produced, are the principal sources of variation in eyes in evolutionary time.

Why should those interested in the mechanistic and medical aspects of retinogenesis, and not evolution per se, have any interest in patterns of evolutionary variability? If your interest is congenital abnormalities, refractive errors, defects of color vision, disorders of cell cycle control leading to cancers, or other disease processes, the unusual features of the color vision of the cichlid fish of Lake Malawi (Kocher, 2004) might at first seem an interesting bit of arcanery at best. The long answer to this question involves a very fundamental change in our understanding of the genome and its control processes that has occurred in biology since the growth of the field of evolution and development, "evo–devo". Callaerts et al. (1997) produced one of the initial observations of conserved developmental sequences across taxa, and Kirschner et al. (2006) offers an accessible and comprehensive account of this enterprise. Essentially, the classes of mechanisms that organize fundamental systems are extremely conserved. Certain classes of genomic variation are permissible and occur very commonly (like gene and partial-gene duplication), while others are not, resulting in highly non-random patterns of individual variation. Finally, multiple and redundant mechanisms cooperate in the construction of adult phenotypes, such that any genetic change will encounter a variety of epigenetic mechanisms in place to assure that the components of any organ scale gracefully, integrated with other organ systems. All of these directly impact the kinds of disorders that can occur. The following examples all illustrate genetic change nested epigenetic mechanisms in various ways.

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2.2. *Case 1: Rapidly varying opsins and "color blindness"*

A major exception to the blanket statement about the conservation of structural–protein encoding gene expression in the retina is the extensive variation in opsins seen both across and within species (Arendt, 2003; Fernald, 2006). In humans, defects in color vision, which are quite common in males, in fact provided one of the first avenues to understanding the central mechanisms of color perception. The opsins, of course, confer differential sensitivity to particular wavelengths, though virtually all opsins are quite broadly tuned (considering vertebrate cone opsins only). The substitution of one or more of a small number of critical amino acids so positioned to change the resting state of the retinol molecule attached to the opsin assemblage changes the best wavelength sensitivity of the retinol–opsin assemblage. Each species expresses only a few of the potentially large number of these broadly tuned opsins, spanning each species' visible spectrum of interest, from ultraviolet to red. For species that possess variant opsins at a single allele (as humans do for their long and middle wavelength opsins, for example, Williams, 1988), only one opsin is typically expressed per cell. Because opsins must simultaneously solve the problems of photon detection with adequate spatial acuity and wavelength discrimination within a spatially constrained receptor sheet, the solution of producing and somehow packing in of a large number of photopigments narrowly tuned to different wavelengths as a solution for wavelength discrimination proves unfeasible. Rather, color discrimination is possible by the neural comparison of the outputs of broadly tuned receptors whose information is separately used in spatial acuity.

The potential reasons for variation between species in the best frequencies of photopigments are numerous and of varying types, including environmental fit, developmental constraint, genetic covariation, and random drift, but are imperfectly understood. Sometimes, the reason for varying wavelength sensitivity can be found quite easily in the animal's ecology. For example, in fish, photoreceptors positioned to look down into the darker water have a different spectrum of sensitivity than those positioned to look up toward the water surface corresponding to what each looks at (Lythgoe and Partridge, 1989) or an animal which inhabits different environments at different points in its life history may express different opsins at those times (Spady et al., 2006). Quite often, however, given the broad tuning of most photopigments, the precision of the link of between particular photopigments with visual ecology or social communication is weak or altogether mysterious. For example, several mammals, including some species of mice, express one cone type in its dorsal retina, and a different one in its ventral retina, but the absorption spectrum has no obvious relationship to what the dorsal versus ventral retina typically views (Szel et al., 1996). Contrary to original expectations, it has been rather difficult to demonstrate that tuning of best wavelength selectivity directly in the retina (as opposed to computations in the brain) in any way directly reflects the signaling colors a species uses in social communication, as in the brightly colored dewlaps of agonistic lizards. Rather, it appears the signaling animal evolves to have its signal to be maximally contrastive to its environment and perceptible to the receiver (Leal and Fleishman, 2004).

The peculiar evolutionary event in Lake Malawi – the "explosive radiation" that rapidly produced of hundreds of new species with different complements of opsins, niches, and body coloration, as well as various jaw morphologies related to feeding niches has produced a number of explanations integrating various levels of explanation. Considering the visual aspects of the speciation, why such extensive variation? Part of the answer may be "because it can" – although some of the variation serves to match the fish's sensitivity to its environment, in this case, for example, clouded versus open water, much of the variation has no obvious link, and perhaps a general match suffices. The stem cichlid from which all these species are derived is unusual in having a reservoir of diversity in that it expresses up to six opsins at different times in its normal development, and the descendants of this fish have stabilized its developmental diversity into phenotypic diversity (Spady et al., 2006).

One might ask how the central nervous system of the fish succeeds in adapting to varying constellations of inputs with such ease over both developmental and evolutionary time, and in this case, a recent mouse model supplies a clue (Jacobs et al., 2007). Mice, like most mammals but primates, normally have only two cone opsins, and are capable of long versus short-wavelength color discrimination. Most primates add a third long-wavelength centered pigment enabling better discrimination in the red–green–brown zone, and this improvement has evolved three separate times in New and Old World primates, using X-chromosome inactivation which produces a patchy, individually variable mosaic of L- and M-expressing cones (Jacobs, 1998; Jacobs and Deegan, 2001). Using a knock-in paradigm for the mouse X-linked photopigment, Jacobs and colleagues gave a mouse a third opsin, also expressed in the stochastic and patchy manner generally analogous to primates. They showed that some of these mice, presumably those with an advantageous patchy expression of the new gene compared to the convergence patterns of the mouse eye, were able to use this new photopigment successfully for color discriminations, using what can only be general comparator mechanisms in the visual cortex and midbrain (Jacobs et al., 2007).

So what enables primates to be trichromats, when virtually no other mammals are? (Humans often expansively call trichromacy "color vision", though it is only a detail of variation on general mammalian dichromatic color vision.) Perhaps, like the cichlids, it is simply because we can, having in our case morphological preconditions that allow the normal amino acid jitter in opsin composition to become functional, using the generic mechanisms that the mouse model has helped reveal. In most mammals, convergence of cones to single retinal ganglion cells is many-to-one, such that new best frequencies produced by single-amino-acid substitutions described earlier are simply summed onto single ganglion cells, and any possibility of using two separate photopigments for discrimination is lost (the likely reason that some of the knock-in mice described earlier which expressed their new gene with full functionality did not demonstrate perceptual trichromacy). In primates, alone, however, the fovea has separately evolved for fine detail vision, and in the fovea

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alone, convergence from cones to ganglion cells is one-to-one or better (Mollon, 1991). Variation in opsins in the primate fovea thus can make it into the brain reliably in every individual, the signal unaveraged and thus provide a basis for functional trichromacy with no more genetic variation than a single substituted amino acid in the visual periphery. The generic mechanisms for wiring up the visual brain and the epigenetic mechanisms of Hebbian learning appear adequate without further adaptation to allow what would normally be neutral variation in opsin composition to acquire discriminative function (Neitz et al., 2002). A third photopigment, once a foveal morphology has passed its information through, has numerous uses in discrimination of items in forests, with little cost (Lucas et al., 1997; Dominy and Lucas, 2001; Kingdom, 2003). The three extant versions of primate trichromacy, including the peculiar version of the cebid type of New World monkeys where all males are dichromats and most females are functional trichromats, make sense when genetic variation is considered in this epigenetic framework (Jacobs and Deegan, 2001).

This comparative frame makes color vision "defects" in humans seem a little less of a problem on the one hand: it is a disorder that is often unnoticed, in fact, until formal testing, as color discrimination and naming is not much impaired over most of the spectrum. Conversely, the natural experiments of the cichlids and primates along with the laboratory trichromatic mouse suggest we would do well to examine more closely the range of natural variability in all structural proteins, not only opsins, but also neurotransmitters and neuromodulators and other functional components in the retina, with attention to how the brain may automatically either preserve or engulf new aspects of peripheral function when they are produced by variation in the direct products of gene expression. When chance couplings of independent kinds of variation occur that expose each other, such as foveal acuity and natural variation in photopigment composition, it seems likely that the typical outcome may not be so fortunate as primate trichromacy.

2.3. *Case 2: Myopia, eye size and nocturnality*

Myopia, which is typically emerges a developmental disorder in which the power of the eye's optics become mismatched to its length, often a consequence of a great deal of close work or reading early in life (see Wallman and Winawer, 2004, for a comprehensive review), acquires an additional explanatory framework in an evolutionary context (Finlay et al., 2005). First, the major features of early eye development are as follows. After birth in primates, much retinal maturation is still to occur, though all cells have been generated, all central connections stabilized in gross numbers, and lamination is adult-like. The eye will grow substantially in size from birth to adulthood accompanied by non-uniform expansion of the retina, principally by stretching rather than adding elements. The fovea begins its development somewhat before birth, and will continue in the first year of life (Hendrickson, 1994). In early development, the growth of the eye is in part under the control of experience. "Deprivation myopia" was first described in primates (Wiesel and Raviola, 1977), noting the unusual growth of the eye after early eye suture in infant macaques; and early "runaway myopia" is a well-known clinical syndrome. Recently, induced addition of neural elements in the retinal periphery in this kind of induced eye enlargement has been documented, a very unusual event in primates (Tkatchenko et al., 2006).

"Emmetropization" refers to the process of matching of the power of the optics of the eye (principally contributed by lens and cornea) to the length of the eye. While most primates are born with a general match achieved, early acuity is very poor compared to the adult (Howland and Sayles, 1985). During the first year of life, the optics undergo much modification, under the control of eye activity. Defocus can be measured directly by the retina and alter eye growth directly without the brain, even if the optic nerve is severed (Troilo et al., 1987). A simple correlate of "defocus" is available as the relative amount of cone photoreceptor activity (or any neuron linked to it), since a blurred image is a poor stimulus to photoreceptors. Alternatively or additionally, other optical features of blur or image movement might be used, as the direction of defocus can often be detected. A high-contrast image signals that the length of eye and optics match, and growth of the eye is checked. A blurred image is taken as evidence (evolutionarily) that the eye is too small, and the eye continues to grow, which can result in the positive feedback condition of "runaway myopia" if the eye has made the wrong guess about the direction of defocus and the eye is already too long. Initial focus and blur must be initially transduced by cones, though the signal that modulates eye growth and elasticity probably involves secondary cell groups and messengers, and numerous candidates have been proposed. We will discuss the particular case of the dopaminergic amacrine cell in the next paragraph. Several candidate mechanisms are in play, including scleral tracking of changes in choroidal thickness (Wallman and Winawer, 2004), glucagon amacrine cells (Feldkaemper and Schaeffel, 2002), or ionically driven fluid movement in the immediate ocular media (Crewther et al., 2006). Recently, a mouse model for deprivation myopia is being considered (Schaeffel et al., 2004), and two quantitative trait loci in mice, one related to eye and retinal ganglion cell size together and the other eye size alone, have been described (Zhou and Williams, 1999). As will be argued, however, nocturnal eyes might be under entirely different control regimes.

Since all ophthalmologists are diurnal, however, our human niche–centrism may have caused us to somewhat mischaracterize the nature of the mechanisms underlying myopia. While not all nocturnal animals have large eyes, many do, and specifically, nocturnal primates do (Heesy and Ross, 2001). A nocturnal primate will want a different control regime for its eye than the emmetropization model described – although it is always useful for the image to be focused properly on the retina, linking retinal activity to growth inhibition of the eye is a poor strategy for a nocturnal animal, as a much larger eye will allow a much greater photon capture. For example, the owl monkey, compared to other New World monkeys of similar body size, has an eye three times larger than expected. We hypothesize that primate eyes may have available two competing control regimes, a rod-dominated regime for optimal nocturnal vision, and the cone-dominated mechanism already described, which may account for the

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often confusing and contradictory outcomes of experiments in this research area.

Dopaminergic amacrine cells first attracted attention as the possible signaling cell in the emmetropization process, as pharmacological manipulations of dopamine affect the normal refractive development (Schaeffel et al., 1995). However, it would appear that these cells are more likely acting as gates between the nocturnal and diurnal states than as devices coding retinal activity. The "emmetropization" signal is gated by circadian rhythms, and the transition between nocturnal and diurnal processing in the retina is controlled by dopamine. Why should control of eye size by defocus be affected by what part of the day the animal believes itself to be in? In a diurnal animal, the absence of retinal activity at night, cone or rod, should not be taken as evidence of poor focus, but rather, closed eyes. However, if there is a great deal of rod activity at night, or an absence of cone activity during the day, this could be interpreted as a signal that a nocturnal eye is required. The primate with evidence of more night than day activity should perhaps produce the optimally large nocturnal eye, which would be an adaptation, not a "failure of emmetropization". In humans, there is tantalizing evidence of this possibility. An increased population incidence of myopia in children who use night-lights was found (Quinn et al., 1999), then denied (Guggenheim et al., 2003) the results consistent with a small effect or poorly controlled "manipulation". Further evidence for some instability in control of retinal topography related to nocturnality is primate-wide, showing up as unusually large prevalence of single individuals with atypical foveas (Franco et al., 2000).

While the last argument is speculative, it at minimum argues for extreme caution in employing the "mouse model" as a sort of generic animal to investigate pathological mechanisms involved in myopia – in this case, the mouse is most certainly not a generic small primate. Not only are mice nocturnal, but also, unlike primates, the size of their eyes has an entirely different relationship to niche: in fact, many diurnal rodents, such as squirrels and gerbils, have unusually large eyes compared to the nocturnal one. Niche, evolutionary history, and typical developmental patterns will all be key in understanding development of the eye's refractive power and the role of the retina in controlling it.

2.4. *Case 3: How many cells should the retina have?*

This question is first best illustrated by leaving the retina altogether and considering a very popular topic, the evolution of the cortex in hominids. Quite rightly, the notable relative growth of brain is highlighted in hominid evolution, and beyond that, the particular prominence of the cortex, and beyond that still, the frontal cortex. Researchers comparing the genomes of other great apes to the human genome have been particularly interested in exploring genes whose expression concentrates in the cortex (Enard et al., 2002a,b; Caceres et al., 2003; Pollard et al., 2006). Researchers working with genetically varying mouse models have been particularly excited when they find genetic deviants that produce mice with an unusually large cortex (Chenn and Walsh, 2002; Kingsbury et al., 2003). But, is there anything we need to account for about our "unusually" large cortex?

For context, we need first to consider what we expect to be the case in scaling overall. Misunderstanding of what the "expected" size of a brain part should be has been a continual source of unnecessary controversy. In fact, considering volume, the human cortex is just the size it should be for a primate of our brain size (Hofman, 1989; Finlay and Darlington, 1995), as is the area of our frontal cortex with respect to the rest of the cortex (Jerison, 1997; Semendeferi et al., 2002) – neither are "unusually well-developed" in humans, it is simply that our whole brain is unusually large. Considering neuron number rather than volume, which scales differently, the same predictability appears to hold (Herculano-Houzel et al., 2006, 2007). Neocortex volume scales with positive allometry compared to the rest of the brain, which means that as the brain becomes large, the cortex becomes proportionately greater than the fraction of the entire brain, and the frontal cortex a proportionately greater fraction of the cortex, but predictably so. The few brains absolutely larger than human brains – elephants and some cetaceans – continue the same function (Hofman, 1989). Thus, there is no evidence for differential selection for cortex size in humans, only brain size overall.

In general, structures with positive allometry that become, by definition, "disproportionately" large in large brains differ systematically in the timing of their development. Structures or cell groups with positive allometry (like the cortex or cerebellum) have an envelope of cytogenesis that extends later in development than structures with negative allometry, like the spinal cord. When neural development is extended to produce a larger brain, a large cortex falls directly out of the basic kinetics of cell division, after division of the embryonic brain into the embryonic divisions of rhombomeres and prosomeres that give rise to all neurons. So, unless researchers have a particular hypothesis about some new kind of organization *within the cortex* special to humans, for which there is very little evidence, there is no reason at all to imagine that the ventricular zone giving rise to the cortex has any unusual properties of proliferation, faster or more extended, certainly not between chimpanzees and humans.

Returning to the retina, we find that the human retina more or less fits into expected patterns of size across vertebrates (Finlay et al., 2001; Finlay et al., 2005). Retinal ganglion cells are one of the earliest cell groups to stop production in the developing nervous system, and therefore have a pronounced negative allometry compared to the whole brain. Comparing the mouse to human, we find that while humans have about 20 times as many ganglion cells as the mouse, humans have more than 1000 times as many cortical neurons (Herculano-Houzel et al., 2006, 2007). Compared to what might be expected for other primates, human retinal ganglion cell numbers are low, staying relatively constant in humans, chimps, and the rhesus monkey at about one million cells per eye. This may be due to the constraining effects of total foveal size, which retains approximately the same absolute dimensions from marmosets to humans (Franco et al., 2000).

Considering evolution, therefore, if we consider the "control" of retinal ganglion cell number, its lack of independence from total brain size suggests that it is simply a subcategory of total brain size. If we consider eye size, we must further consider an epigenetic envelope that matches the length of the eye to the power of the lens and cornea through both

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cellular elasticity and cellular proliferation. This is a much different sense than the use of "control" that is employed for the now extensive and elegant studies of control of retinogenesis (Neumann, 2001; Locker et al., 2006; Wang et al., 2006; Ingham and McMahon, 2007), and the control of the cell cycle, and the progressive specification of cell type (Dyer and Cepko, 2001a,b; Dyer et al., 2003). Review of this extensive literature is not possible here, but to point out that these studies address the level of how cells are instructed to leave the precursor pool in general, the specific details of exit and entry into the cell cycle and regulation of its length, and how the microenvironment is managed to progressively restrict cell fate in terms of location of the cell and the type of properties it will have. "Control" of retinal ganglion cell at the comparative and evolutionary level must derive from the basic regionalization of the embryo, since retinal ganglion cell number is so closely related to brain size. Features of retinal organization which are true species differences, such as the different complements of cells in nocturnal and diurnal retinas, the differing topographies of cell distribution across the eyes depending upon predator/predated niche and so forth would all have to find their mechanisms within the control parameters of the cell biology literature. In this case, the interesting observation is that understanding "control" simply comes down to an empirical description of what is predictable and what is variable between individuals and species.

3. The chronology of development of the retina as a source of structure, and the uses and limitations of the mouse model

3.1. *Comparing developmental timetables*

Over the past several years, a comprehensive model of stability and variation in developmental timing across mammals using various multivariate methods has been developed, which is available as a Web-based utility, www.translatingtime.net, registered through the Neuroscience Database link as "TNAMS" at http://ndg.sfn.org/eavData.aspx?db=10&cl=81&o=29212. The model is based primarily on assessments of neurogenesis as well as gross and fine morphological assessments, for example, the first appearance of axons in a tract. Timing of gene expression in various structures is presently being added. The model capitalizes on the essential conservation of developmental timing in mammals for interspecies comparison for interpolating missing data accurately in those cases where it has not been or cannot be determined empirically, as in humans or rare species. It is intended as a resource for the optimal developmental placement of any observation or experiment, as well as for investigation of the control of developmental timing per se. Considering the visual system and retina, one interesting observation is that, of all the "systems" in the brain, one might propose or imagine – for example, the motor system, vocal–auditory communication systems, the limbic system and so on – that the visual system is the most predictable and conserved of all we have investigated as measured by the fit of data to model (Fig. 1). This may reflect the relative stability of the basic tasks of vision across species, providing information for postural stability and navigation in the external world, detection of novel events, object and locations of interest, compared to the auditory system, for example, which is much more variable in the extent to which it is specialized for intraspecies communication, or the somatosensory system, where marked morphological specializations like hands or trunks often occur.

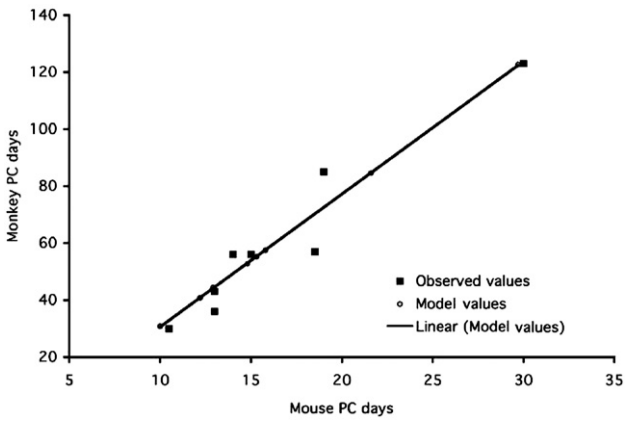

Fig. 1 – Empirical versus modeled values for retinal events, comparing mouse to monkey. PC=postconceptional day.

Table 1 – Observed and predicted retinal developmental events in mice, rhesus macaques and humans

	Event	Mouse		Human		Monkey	
		Pred	Obs	Pred	Obs	Pred	Obs
Retina	Ganglion cell – start	10	10.5	38.1		30.8	30
Optic nerve	Axons in optic stalk	11.7	12.3	48.2	51	38.7	
Optic nerve	Optic axons at chiasm	12.2	13	50.9		40.8	36
Retina	Horizontal cells – peak	12.4		52.4		42	40
Retina	Ganglion cells – peak	12.9	13	55.6		44.4	43
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	
Retina	Cones – peak	14.8	14	66.3		52.8	56
Retina	Amacrine cells – peak	15.3	15	69.3		55.2	56
Retina	Ganglion cells – end	15.8	18.5	72.4		57.6	57
Optic nerve	Axon number – peak	17.2		80.9		64.3	69
Retina	Rods – peak of neurogenesis	21.6	19	106.9		84.6	85
Retina	Onset of retinal waves	20.6		101.3		80.2	
Retina	Bipolar cells – peak	23		115.6		91.4	85
Optic nerve	Rapid axon loss ends	24.3		123.1		97.3	110
Eye opening	Eye opening	29.7	30	155.4	158	122.6	123

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3.2. *The timetable of mouse development*

We reproduce the observed and computed times of various visual developmental events for mouse, human and rhesus macaque, all given as postconception (PC) day, where the day of conception is postnatal day 0 in Table 1; this table taken from a much more extensive database that includes 102 events in early development (principally neurogenesis, tract formation and structure innervation) from all sensory systems and brain regions, and ten species (also hamster, rat, rabbit, spiny mouse, guinea pig, ferret and cat). The complete database lists the empirical sources in more detail and will calculate desired developmental windows in the species listed; it also gives the confidence intervals for each value calculated here (Clancy et al., 2007). Predicted developmental times are derived through a general linear model incorporating all the data sources listed on the website. This model was first derived for a more limited set of developmental events (principally neurogenesis) and a more limited set of species to ask if there was a systematic function to transform the schedule of developmental events of one species into the developmental schedule of another, as well as locate deviations in timing of developmental events in particular species (Finlay and Darlington, 1995; Finlay et al., 1998, 2001). It proved possible to do so with high accuracy, and in subsequent versions it was expanded to include many more species, including humans and more classes of developmental events (Clancy et al., 1999, 2001; Darlington et al., 1999).

The model predicts post conception (PC) dates transformed to the mathematical term Y as $Y = \ln(\text{PC days} - 4.34)$. 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 greater separation, in absolute days, of late events in slow-developing species compared to the separation of same events in more rapidly developing species is the feature of the data reflected in the log function (contrasted with, for example, the inaccurate multiplicative 7× rule-of-thumb that is used to transform "dog years" to human years).

The term "Y" is the sum of three terms: an event score, a species score, and a primate interaction term where appropriate. Each neural event in the database is assigned an event score (with later events having higher scores), and each species assigned a species score (with faster-developing species having higher scores) produced from the general linear model described previously (Darlington, 1990; Finlay and Darlington, 1995). The primate interaction factor accounts for the fact that limbic and cortical components of primate versus other brains mature at different rates with respect to each other (Clancy et al., 2001). Therefore, for example, if you would like to know the postconceptional day when amacrine cells are first generated in the ferret, you look up the species score for ferrets, add it to the "first day of amacrine cell generation" event score to determine Y; and solve the first equation for PC day. The website automates these basic computations. We refer the reader interested in technical and qualitative evaluation of the model's structure and predictions to the various sources cited previously but note that the very high correlation ($r = 0.990223$) between observed values and the model's predictions gives this model much practical utility. The credit for its practical utility does not go to the model, but rather to the regularity of the empirical observations it represents, those collected from many laboratories. Even while the period of early construction of the brain and eyes can vary from about 12 days to 120 in the species we have accumulated, the rules for the transformation and placement of events are highly conserved and are captured well by the minimal two "species" and "event" values, with the "primate interaction factor" the only important qualification we have introduced thus far.

3.3. *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 1 is the presence of distinct gradients of neurogenesis and other aspects of maturation within single-cell classes (Rakic, 1974; Rapaport et al., 1992, 1996). In the model, each event, for example, retinal ganglion cell generation, is given as onset, peak or offset of the entire designated population. Some gradients of maturation are conspicuous in even the most rapidly developing species, and no claim is made that gradients are absent; however, the quantification of gradients was not standardized enough to allow meaningful comparison across species. In the retina, for example, there is a distinct gradient of neurogenesis from the center to the periphery of the retina observed in every mammal studied. It is most pronounced in the monkey – for example, 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).

These gradients allow the extracellular environment of groups of essentially identical 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 bipolars (Fig. 2), the early provision and cessation of precursor cells for specification in the central retina produces an abundance of retinal ganglion cells and cones and fewer rods, with the opposite case in the peripheral retina (Cepko et al., 1996; Finlay et al., 2005). The shorter distances and time available in the mouse retina appear to produce only the shallowest gradients of cell classes across the retina surface, while in the monkey, the gradient is pronounced enough to (possibly) never reach rod neurogenesis before neurogenesis terminates in the central retina (the eventual site of the fovea), and to produce an abundance of rods with virtually no cones in the very periphery. Insofar as the absence of rods might be a feature "initializing" the fovea and whatever new features of genetic specialization that come linked to it, there will be no real mouse homologue as the fovea is linked to a feature of retinal chronology that mice simply do not have.

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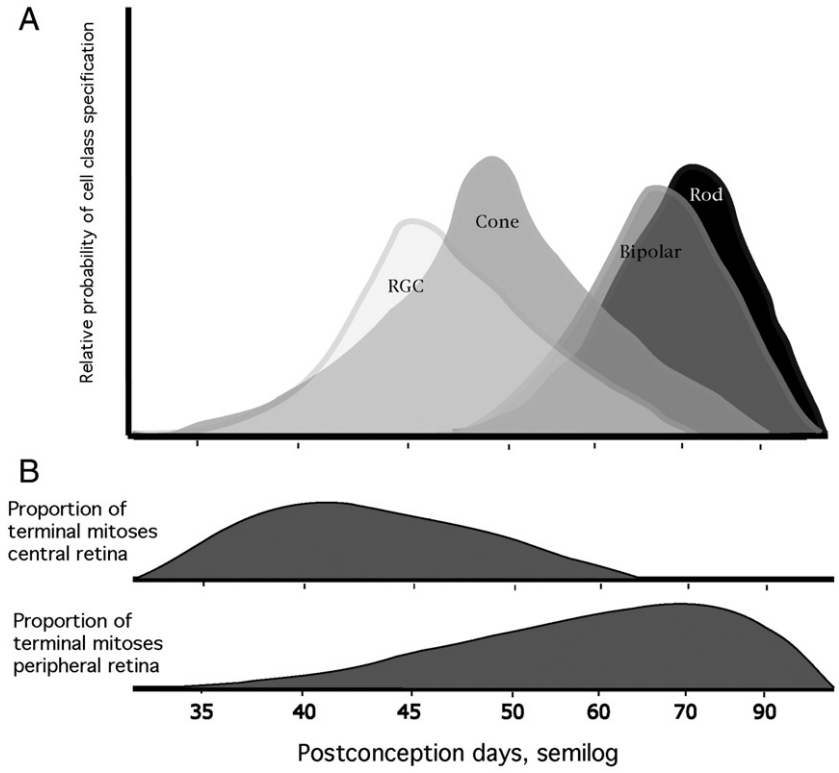

Fig. 2 – (A) Order of production of retinal ganglion cells, cones, bipolar cells and rods in the retina of rhesus macaque. For the two types of neurons omitted from this map, horizontal cells virtually overlap cones; amacrine cells lead bipolars slightly. The abscissa shows the postconceptional day of terminal cell division, the ordinate the per cent of each cell class produced on that day. (B) The spatial gradient in the probability of exit of precursor cells in central retina (top) versus peripheral retina (bottom). The graph in "A" and those in panel B share the same abscissa. Replotted and schematized from Rapaport et al. (1996). Reprinted with permission from Kremers' *The Primate Visual System* 2005.

3.4. *What evolutionary variability suggest we should look for in mouse models of the developing visual systems*

We are entering a relatively unexplored field when we ask what the relationship is between 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 contrasts with 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 between evolutionary variation, individual variation, naturally occurring pathology and induced pathology depending on the view of the genome we hold. We have several potential examples of mechanisms of coordination of neurogenesis that would appear to resolve problems of relative scaling for size relevant both for individual development and for cross-species scaling.

3.5. *Scaling the eye, particularly considering rods versus cones*

The requirements for scaling of rods and cones in eyes of varying sizes are not the same to maintain their particular functions. As mentioned earlier, the eyes of diurnal primates are absolutely large compared to most mammals and scale allometrically with body size at a fairly low slope (Ross, 2000), ranging from around 10 mm in diameter in the smallest monkeys to around 30 mm in various anthropoid apes and in humans. Scaling an organ (made of cells of constrained size), which 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 relative 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, absolute retinal thickness may not vary much, due 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 is necessary in the number of cones to retain the same visual acuity – since the retina is flooded with photons in

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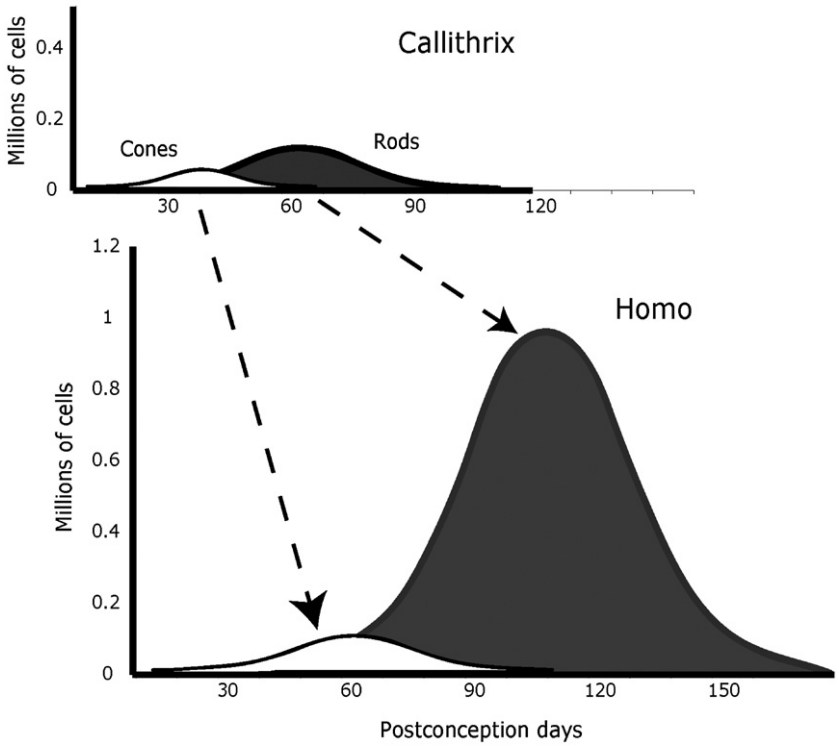

Fig. 3 – Schematic to demonstrate how extension of the period of retina neurogenesis may disproportionately increase the numbers of later-generated cell groups by allowing disproportionate increase in the precursor pool from which later cell groups are drawn. Neuron numbers and developmental durations drawn from Finlay et al. (2000) and Clancy et al. (2000). Reprinted with permission from Kremers' *The Primate Visual System* 2005.

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 of course 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 at 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 et al., 2005).

How is this consistent within- and across-species scaling necessity executed in the schedule of neurogenesis of the retina? As mentioned earlier in "Case 3" 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 to cell groups exiting early. Although the precise kinetics remains to be worked out, the schedule of neurogenesis in the retina is arranged such that extension of the period of embryogenesis will automatically produce 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 (Fig. 3). Those cell types that must change in number exponentially with eye diameter, rods and their attendant bipolar cells are located last in order of differentiation, and those that need not change much in number are produced first and are insulated from the effects of extended neurogenesis. Those unfortunate ancestors with the opposite order of neurogenesis in the retina who might have had a selective advantage at a larger body size, but who became automatically blind in the dark as a result, presumably had 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 specific mechanisms that might produce excess rods, exactly like those researchers looking for the gene that produces a large frontal cortex. We hypothesize that there will be no such effect, except for the genetic event which causes the overall extension of neurogenesis for the entire brain, because the change in the relative numbers of rods and cones in larger eyes falls directly out of the kinetics of cell division and the longer period of neurogenesis required for larger retinas. This is an empirical prediction and extension of the argument made earlier for the control of retinal ganglion cell number. Contrasting possibilities that together or separately could produce similar changes

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are increasing and decreasing the pool of progenitor cells at particular time points by regulation of the number of asymmetric and symmetric divisions, or by cell death in the precursor pool or after differentiation, or in the particular case of rods, ensuring that retinal progenitors leaving the cell cycle late produce only rods. A number or mechanisms may prove to contribute to the total cell complement, but we emphasize here all cell groups in the retina have an aspect of control that is the same as total brain size, though identifiable cell groups scale with different exponents.

4. Kinds of control

We have asked about the locus of control of some basic aspects of retinal cell number and morphology, and it is interesting that the answer that emerges is not a principled one, but depends on the pattern of variability seen within and across species. Considering total retinal cell number, its very close relationship to brain size suggests a common locus of control, but if our interest were olfactory bulb, by contrast, we would find markedly less linkage (Finlay et al., 2001). If a nocturnal animal has markedly more rods than a diurnal close relative, we have suggested that the best place to look for control would be in cross-retinal control of timing, not alteration of the control of the rod population separately. Some forms of variation may be extremely common, and species-specific, like change in the amino acid composition of photopigments, but may be masked by convergence of photoreceptors and other epigenetic mechanisms until its conjunction with the fovea produces a new functionality. Extended development may produce some singularities. The initial event of production of a central rod-free area might have been an inevitable consequence of an extended developmental period that secondarily became the point where the several unusual cellular events associated with the postnatal development of the primate fovea were attached (Finlay et al., 2005). Therefore, initial events specifying the fovea might only derive from species-general timing constraints, but secondary events like compaction of the outer segments of the cones and displacement of cell bodies would require a local explanation.

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 ubiquity of size differences both within species and between species, the filter of evolution appears to have positioned the orders of cytogenesis to make functional sense with respect to the 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. Change in the duration of single events, such as neurogenesis or axon extension, may allow early and late components to systematically encounter different extracellular environments, giving species with long periods of neurodevelopment a source of differentiation unavailable to briefer ones. But what sets the overall duration of neurogenesis, and the developmental "clock" overall? Are there chronology mutants in mice which complete cytogenesis in abnormally short or long times, what covaries with this property, and what controls it? These aspects of cell cycle regulation, yet to be identified, are absolutely fundamental to our understanding of both development and evolution.

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