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Commentary

Neural Development in Metatherian and Eutherian Mammals: Variation and Constraint

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ABSTRACT

A model for predicting the timing of neurogenesis in mammals (Finlay and Darlington [1995] Science 268:1578–1584) is here extended to an additional five metatherian species and to a variety of other events in neural development. The timing of both the outgrowth of axonal processes and the establishment and segregation of connections proves to be as highly predictable as neurogenesis. Expressed on a logarithmic scale, late developmental events are as predictable as early ones. The fundamental order of events is the same in eutherian and metatherian animals, but there is a curvilinear relation between the event scales of the two; for metatherians, later events are slowed relative to earlier events. Furthermore, in metatherians, the timing of developmental events is more variable than in eutherians. The slowing of late developmental events in metatherians is associated with their considerably longer time to weaning compared with eutherians. J. Comp. Neurol. 411:359–368, 1999.

Indexing terms: neurogenesis; placental mammal; marsupial mammal; neuronal connectivity; maturational timetables

Changes in brains require changes in development, and the work of comparative neurology is not only to understand the various organizations of existing brains, but how they got that way. Understanding differences in neural development across species is not only a large empirical undertaking, but also requires theoretical analysis of what events to compare, and how to compare them. Particularly, adequate multivariate statistical methods are required to reveal complex and contingent organization in numerous developmental events. In this commentary, we present analysis of some new data, along with discussion of the methods that can be used for cross-species comparison of developmental patterns.

We extend the work of Finlay and Darlington (1995) on the conservation of neurodevelopment schedules across mammalian species. Working with the post-conceptional dates of peak neurogenesis for 51 neural structures in six eutherian (placental) species, that paper showed that one can place the species studied on a scale of developmental speed, and place the neural structures on a scale of "earliness" in development, such that the date of development of any of these structures in any of these species can be predicted accurately from the corresponding species and structure scale values. These authors also included data from one metatherian (marsupial) species—the brush-tailed possum (*Trichosurus vulpecula*). These data seemed to fit the eutherian pattern in certain ways while differing in others.

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We extend the work of Finlay and Darlington (1995) in two major ways. First, we increase the number of eutherian species studied from six to nine (now including humans), and increase the number of metatherian species from one to six, thus allowing substantially greater confidence in our conclusions about the differences between eutherians and metatherians. Second, we investigate not only neurogenesis, but a variety of events in neural development, and increase the number of items in this category from 51 to 94. That is, we argue here that one can take a long list of events in neural development and place them on an "event scale." Then, from the scale value of any of these events, and the "species scale" value of any species studied, one can predict the post-conceptional day that event will occur in that species.

For these new data, we will argue that:

1. The same general model used by Finlay and Darlington (1995) also fits this broader set of species and events.
2. The principal difference between the developmental schedules of eutherians and metatherians is that later events slow down in metatherians relative to early events. Thus, for instance, the earliest events in neurogenesis occur earlier in the opossum than in the rabbit, but later events like eye-opening occur earlier in the rabbit.
3. Even allowing for the difference just described, metatherian developmental schedules seem to be less predictable than eutherian schedules. This may be due to greater variation across individuals among metatherians.
4. The analysis does not clearly support the view of Haeckel (1874) that the timing of later events is more variable than that of earlier events.
5. Events concerning cell generation and death seem to be neither more nor less predictable than events concerning connectivity between cell groups.
6. We will also argue for the efficacy of the type of analysis employed here compared to other kinds of analyses of developmental data.

Relationship of this modeling approach to methods using anchor events

Robinson and Dreher (1990) and Ashwell et al. (1996) have expressed the dates of developmental events as a proportion of the date for an "anchor" event. Robinson and Dreher used eye-opening as an anchor, whereas Ashwell et al. used weaning. That is certainly much simpler than the present approach, but we believe that our model has several advantages. First, the anchor event might not even be measured; dates of in utero eye-opening are unknown for many species. Second, the event chosen for an anchor might itself not scale well with other developmental events. If so, the scaling of all other events will be distorted. Third, even when the anchor event has been observed and does scale reasonably well with other events, the scaling of all other events is unduly influenced by possible random fluctuations in the measurement of the anchor event. By contrast, in our scaling approach, all available data contribute toward setting the score of each species on the species scale.

Fourth, the simpler anchor approaches, at least in their present forms, allow little or no flexibility in the way time is expressed in the model. We have found through experimentation that our model fits best if time is defined not simply as days since conception that an event occurs, but as $Y = \ln(\text{days} - 5.37)$. The use of natural logarithms (denoted *ln*) compresses differences between later events, so that for instance a difference of 8 days matters less between later events than between earlier events. We hypothesize that the subtraction of 5.37 improves the model because early organizational events such as implantation, blastulation, and differentiation of the basic germinal layers of the embryo take roughly that time in the mammalian species we have examined thus far, so differences in developmental schedule don't appear until after that point. Thus, if simple ratios were to be used, they might better be taken not from conception but from a date about 5 or 6 days after conception. Finlay and Darlington (1995) had estimated the subtractive constant at 7 days, and we assume our estimate will change again as new data are incorporated into the model.

DATA SOURCES AND SPECIES USED

Our analysis uses data from Tables 1–5 of Robinson and Dreher (1990), Table 2 from Finlay and Darlington (1995), and Tables 1–3 of Ashwell et al. (1996) plus data collected by Dunlop et al. (1997), supplemented by minor additions and corrections (Table 1). The analysis includes six metatherian and nine eutherian mammals, including humans. Of the metatherians, three are from the Order Polyprodonta, carnivorous marsupials including the fat-tailed dunnart *Sminthopsis crassicaudata* (a small shrew-like animal), the gray short-tailed opossum *Monodelphis domestica*, and the South American opossum *Didelphis virginia*. The rest are from the Order Diprodonta, herbivorous marsupials including the brush-tailed possum *Trichosursus vulpecula*, the quokka *Setonix brachyurus*, and the tammar wallaby, *Macropus eugenii*. Body size and various features of seasonality and maturation for these species appear in Table 2. Gestations in the marsupials range from 13 days in the South American opossum to 29 days in the tammar wallaby. Eutherian species include four rodents: the mouse *Mus musculus*, the hamster *Mesocricetus auratus*, the rat *Rattus norvegicus*, and the spiny mouse *Acomys cahirinus*. In addition, we have included the laboratory rabbit *Oryctolagus cuniculus*, the ferret *Mustela putorius furo*, the cat *Felis domestica*, the monkey *Macaca mulatta*, and the human *Homo sapiens*. Gestations in this group range from 15.5 days in hamster to 270 days in humans.

The total data set included 97 developmental events including birth, weaning, and eye-opening. However, earlier analyses had convinced us, together with Robinson and Dreher (1990), that birth did not fit well into the event scale, so it was not included in any analyses reported here. Unlike birth, weaning was found to fit the scale adequately, but we omitted it because it is not a neurological event, and our specific goal was to create a scale fitting neurological events. As explained more fully later, one other event was omitted because it was not measured in any placental species. This was the appearance of the fasciculus aberrans in the tammar wallaby, reported by Ashwell et al. (1996) to occur at 45 days. Since we omitted birth, weaning, and this other event, we used only $97 - 3$ or 94 events in our analyses. Using the eutherian data set described above, we further tested whether any of the 94 events exhibited larger modeling errors than other events, suggesting that such events should be omitted from the scaling procedure. No events fitted so poorly as to require

omission from the scaling analysis. If we had known the date of each of the 94 events in each of the 15 species, we would have had altogether 94 × 15 or 1,410 observations, but in fact we had only 398 observations, 349 on eutherians and 49 on metatherians.

MODELING PROCEDURES

Overview

Researchers have long considered how best to compare the timing of developmental events across species that differ widely in gestational length. As mentioned above, we use here the model proposed by Finlay and Darlington (1995). The basic idea in this model is to derive two scales. The first, which we call here the event scale, scales the timing of developmental events, with later events scored high. The second, which we call the species scale, scales species on the speed of neural development, with slow-developing species scored high. These scales are derived so that the sum of any event score and any species score can be used to predict the timing of that event in that species, measured in days since conception. For instance, by the model presented later in this paper, the cat exceeds the rat by .932 units on the species scale, and eye-opening exceeds the peak of neurogenesis of the nucleus accumbens by the same amount. Thus the model predicts that eye-opening will occur in the rat on the same post-conceptional day that peak neurogenesis for the nucleus accumbens will occur in the cat, since the sums of the relevant species and event scores are equal for those two cases.

When we say that the sum of an event score and a species score "can be used to predict" the time of that event in that species, we do not mean to imply that the sum equals that time. Rather, the model tries to make that sum equal some mathematical function of the time. The function that we have found to best fit the model is $Y = \ln(\text{postconceptional day} - 5.37)$. We explain later in this section how we chose this function; the model derives the species scale and the event scale to best predict Y as thus defined.

Since the publication of this modeling approach in Finlay and Darlington (1995), we have spent a great deal of effort exploring a variety of alternative models and model-fitting methods, including weighted least squares rather than regression (Finlay et al., 1998), and including a model that was fitted iteratively and in which scores on the species and event scales are multiplied rather than added. None of these more complex procedures turned out to produce noticeably better models than the original regression method, so we continue to use the regression model.

As explained more fully later, the regression model fitting the eutherian data seems to differ from the model best fitting the metatherian data, so we derived the models separately, starting with the larger eutherian data set. We emphasize that set in the rest of this section, and devote a later section to metatherians.

As is well known to statisticians, each observation's residual (error of prediction) in a regression model tends to underestimate the observation's residual from the unknown true model, because each observation tends to pull the observed model (the model derived in the sample) toward itself. Furthermore, some observations have more leverage than others to pull the model toward themselves, and their residuals are lowered more than other residuals. Statistics called leverage-corrected residuals (lcrs) can be computed to correct this problem, using a formula given by Darlington (1990, p. 357). Under the standard assumptions of regression, each observation's squared lcr value is an unbiased estimator of the observation's squared deviation from the unknown true model. Such lcr values were computed for all observations and are mentioned repeatedly in the Results section.

If we had had observations on all cells for the 94 × 9 matrix of possible eutherian observations, then, except for an unimportant additive constant, we could have defined the species and event scale values simply as the column means and row means of the Y-values in that matrix. The regression method is essentially a way to approximate that result even when many of the cells in that matrix are empty.

A closer look

This section is aimed at the reader who wants to understand our analytic method in detail, and perhaps apply it to other data sets.

Dummy variables. Multiple regression can be used to find the weighted average of two or more variables that correlates most highly with a dependent variable Y. Many discussions of multiple regression emphasize the use of continuous variables such as age or body size, but the predictor variables can also include dummy variables to represent dichotomies like sex. A dummy variable is simply scored 0 for one category (e.g., one sex) and 1 for the other category. Dummy variables are obviously not normally distributed, but regression includes no requirement that predictor variables be even approximately normally distributed.

Sex is a categorical variable with only two categories, but many categorical variables, such as species, have many categories. One can still include such variables in a regression by representing each category except the last one by a separate dummy variable. For instance, suppose we were working with just four species: cat, rat, macaque, and rabbit. We could make three dummy variables: one for cat, one for rat, and one for macaque. All observations for cats would score 1 on the first variable, all observations for rats would score 1 on the second variable, all observations for macaques would score 1 on the third variable, and all other scores would be 0. No variable is needed for rabbit, since that would produce a redundancy: any observation scoring 1 on any of the three variables cannot be for a rabbit, and any observation scoring 0 on all three variables must be for a rabbit. Thus the computer "knows" when an observation is for a rabbit, even though there is no separate variable for rabbits. If one attempted to include an additional dummy variable for rabbits, most regression computer programs would refuse to run, since they cannot work with redundancies.

Returning from the hypothetical four-species example to our actual data set, we had nine eutherian species, so we created eight dummy variables to represent species. We had 94 developmental events, so we created 93 dummy variables to represent them. We thus had 8 + 93 or 101 predictor variables altogether. We then ran a multiple regression predicting Y from these 101 variables across the 349 eutherian observations.

There is a widespread but erroneous belief that the number of predictor variables in a regression should not exceed 10% of the number of cases. Since we had 349 cases

TABLE 1. Database of Time of Events in Neural Development for Nine Eutherian and Six Metatherian Mammals

	Placental mammals (Species scale value)									Marsupials (Species scale value)					
Event scale[1]	0.565 Hamster	0.619 Mouse	0.821 Rat	1.013 Rabbit	1.153 Spiny mouse	1.650 Ferret	1.753 Cat	2.285 Macaque	2.500 Human	0.736 Short-tailed opossum	1.098 Dunnart	1.119 S. Amer. opossum	1.440 Brush-tailed possum	1.603 Quokka	1.756 Tammar wallaby
0.789 Peak—cranial motor nuclei	—	9.0[4]	11.0[4]	—	—	—	—	—	—	—	—	—	—	—	—
0.952 Peak—locus coeruleus	—	—	11.0[4]	—	—	—	—	32.0[4]	—	—	—	—	—	—	—
0.971 Start—RGC generation	9.5[3]	10.5[3]	11.5[3]	13.0[3]	—	21.0[3]	19.5[3]	30.0[3]	—	—	—	—	—	—	—
0.992 Peak—inferior olivary nucleus	—	10.0[4]	12.0[4]	—	—	—	—	—	—	—	—	—	—	—	—
0.995 Peak—magnocellular basal forebrain	—	—	12.0	—	—	—	—	30.0[4]	—	—	—	—	—	—	—
1.060 Start—superficial SC laminae	11.0[3]	10.5[3]	12.5[3]	—	—	—	—	30.0[3]	—	—	—	—	—	—	—
1.071 Peak—red nucleus	—	—	12.0[4]	—	—	—	—	—	—	—	—	—	—	—	—
1.071 Peak—vestibular nuclei	—	—	12.0[4]	—	—	—	—	—	—	—	—	—	—	—	—
1.090 Peak—cranial sensory nuclei	—	11.0[4]	12.0[4]	—	—	—	—	—	—	—	—	—	—	—	—
1.096 Posterior commissure appears	13.0[2]	—	—	—	—	—	21.0[2]	35.0[2]	33.0[2]	—	—	—	—	—	30.0[2]
1.105 Start—LGNd generation	10.5[3]	10.5[3]	13.5[3]	—	—	—	21.5[3]	36.0[3]	—	—	—	—	—	—	—
1.139 Start—subcortical plate generation	11.5[3]	—	11.5[3]	—	—	20.5[3]	23.5[3]	39.5[3]	—	—	—	—	—	—	—
1.155 Peak—subplate	10.0[4]	11.0[4]	14.0[4]	—	14.0[4]	—	24.0[4]	43.0[4]	—	—	—	—	22.0[4]	—	—
1.155 Peak—raphe complex	—	13.5[4]	12.0[4]	—	—	—	—	30.0[4]	—	—	—	—	—	—	—
1.192 Peak—reticular nuclei	—	11.0[4]	13.0[4]	—	—	—	24.0[4]	—	—	—	—	—	—	—	—
1.194 Peak—Purkinje cells	—	10.5[4]	14.0[4]	—	—	—	—	39.0[4]	—	—	—	—	22.0[4]	—	—
1.198 Peak—medial geniculate nucleus	—	11.0[4]	13.0[4]	—	—	—	26.0[4]	—	—	—	—	—	26.0[4]	—	—
1.201 Mammillo-thalamic tract appears	—	—	14.0[2]	—	—	—	23.0[2]	—	44.0[2]	—	—	—	—	—	30.0[2]
1.206 Peak—deep cerebellar nuclei	—	—	13.0[4]	—	—	—	—	38.0[4]	—	—	—	—	—	—	—
1.208 Peak—preoptic nucleus	—	12.5[4]	12.0[4]	—	—	—	—	—	—	—	—	—	—	—	—
1.222 Peak—globus pallidus	—	11.0[4]	14.0[4]	—	—	—	—	—	—	—	—	—	22.0[4]	—	—
1.231 Medial forebrain bundle appears	14.0[2]	13.0[2]	13.0[2]	—	—	—	—	35.5[2]	33.0[2]	—	—	—	—	—	28.0[2]
1.232 Axons in optic stalk	—	12.3[5]	14.5[5]	—	—	24.0[5]	19.0[5]	—	51.0[5]	—	16.0[5]	—	—	—	—
1.241 Peak—ventrolateral geniculate nucleus	11.0[6]	11.5[4]	14.0[4]	—	—	—	26.0[4]	—	—	—	—	—	—	—	—
1.257 Start—lamina VI generation	11.5[3]	—	13.0[3]	14.5[3]	—	22.5[3]	26.5[3]	45.0[3]	—	—	—	—	—	—	—
1.287 Peak—LGNd	11.0[6]	12.0[4]	14.0[4]	—	—	—	27.0[4]	43.0[4]	—	—	—	—	26.0[4]	—	—
1.291 Fasc. retroflexus appears	14.0[2]	14.0[2]	12.0[2]	—	—	—	21.0[2]	40.0[2]	—	—	—	—	—	—	30.0[2]
1.304 Peak—cochlear nuclei	—	12.0[4]	14.0[4]	—	—	—	—	—	—	—	—	—	31.0[4]	—	—
1.305 Peak—suprachiasmatic nucleus	11.5[4]	13.0[4]	14.0[4]	—	—	—	25.0[4]	—	—	—	—	—	22.0[4]	—	—
1.317 Optic axons at chiasm/tract	—	13.0[5]	15.0[5]	—	—	24.0[5]	—	36.0[5]	—	18.0[5]	23.5[5]	—	—	31.0[5]	31.0[5]
1.319 Stria medullaris thaliami appears	—	—	14.0[2]	—	—	—	—	48.0[2]	44.0[2]	—	—	—	—	—	28.0[2]
1.325 Peak—amygdala	—	12.0[4]	15.0[4]	—	18.0[4]	—	—	38.0[4]	—	—	—	—	—	—	—
1.330 Peak—mitral cells	—	12.0[4]	14.0[4]	—	18.0[4]	—	—	—	—	—	—	—	—	—	—
1.337 Peak—substantia nigra	—	—	15.0[4]	—	—	—	—	39.0[4]	—	—	—	—	—	—	—
1.340 Peak—nucleus of lateral olfactory tract	—	12.5[4]	14.0[4]	—	—	—	—	—	—	—	—	—	—	—	—
1.340 Peak—VPL and VB	—	12.5[4]	14.0[4]	—	—	—	—	—	—	—	—	—	22.0	—	—
1.342 External capsule appears	—	—	—	—	—	—	—	40.0[2]	56.0[2]	—	—	—	—	—	40.0[2]
1.355 Peak—retinal horizontal cells	—	—	—	—	—	—	30.0[4]	40.0[4]	—	—	—	—	—	—	—
1.363 Rapid optic axon generation	—	—	15.0[3]	15.5[3]	—	—	27.5[2]	—	—	—	—	—	—	—	—
1.364 Peak—claustrum	—	12.5[4]	—	—	18.0[4]	—	—	—	—	—	—	—	22.0[4]	—	—
1.368 Peak—superior colliculus	12.0[4]	13.0[4]	15.0[4]	—	—	—	—	41.0[4]	—	—	—	—	29.0[4]	—	—
1.388 End—LGNd	11.5[3]	12.5[3]	15.5[3]	—	—	—	31.5[3]	43.0[3]	—	—	—	—	—	—	—
1.400 Peak—septal nuclei	—	13.0[4]	14.0[4]	—	19.0[4]	—	—	45.0[4]	—	—	—	—	—	—	—
1.402 Peak—anterior olfactory nucleus	—	13.5[4]	12.0[4]	—	22.0[4]	—	—	—	—	—	—	—	—	—	—
1.415 Peak—retinal ganglion cells	12.0[4]	13.0[4]	16.0[4]	—	—	—	30.0[4]	43.0[4]	—	—	—	—	—	—	—

1.419 Internal capsule appears	—	—	15.0[2]	—	—	—	—	40.0[2]	63.0[2]	—	—	—	—	—	42.0[2]
1.436 Peak—entorhinal cortex	—	13.0[4]	14.0[4]	—	20.0[4]	—	—	48.0[4]	—	—	—	—	—	—	—
1.437 Start—LGNd generation	12.5[3]	—	—	—	—	27.5[3]	30.5[3]	46.5[3]	—	—	—	—	—	—	—
1.443 Peak—inferior colliculus	—	—	16.0[4]	—	—	—	—	43.0[4]	—	—	—	—	25.0[4]	—	—
1.457 Peak—cortical layer VI	12.0[4]	12.5[4]	16.0[4]	—	18.0[4]	—	33.0[4]	53.0[4]	—	—	—	—	38.0[4]	—	—
1.460 Peak—AV, AM, and AD nuclei	—	13.5[4]	15.0[4]	—	—	—	—	—	—	—	—	—	—	—	—
1.471 Start—cortical lamina V	12.5[3]	—	13.5[3]	—	—	27.5[3]	32.5[3]	58.5[3]	—	—	—	—	—	—	—
1.476 Peak—caudoputamen	—	14.0[4]	15.0[4]	—	20.0[4]	—	—	45.0[4]	—	—	—	—	20.0[4]	—	—
1.488 Peak—subiculum	—	13.0[4]	16.0[4]	—	20.0[4]	—	—	48.0[4]	—	—	—	—	—	—	—
1.496 Peak—parasubiculum	—	13.5[4]	16.0[4]	—	—	—	—	48.0[4]	—	—	—	—	—	—	—
1.501 Fornix appears	—	14.0[2]	15.0[2]	—	—	—	—	48.0[2]	63.0[2]	—	—	—	—	—	36.0[2]
1.510 Peak—pontine nuclei	—	13.5[4]	16.0[4]	—	—	—	—	—	—	—	—	—	—	—	—
1.522 RGC axons reach LGNd and SC	—	14.5[3]	15.5[3]	—	—	28.5[3]	31.5[3]	—	—	—	—	—	—	—	—
1.526 Peak—presubiculum	—	13.5[4]	17.0[4]	—	—	—	—	48.0[4]	—	—	—	—	—	—	—
1.534 Stria terminalis appears	15.0[2]	13.5[2]	—	—	—	—	—	—	56.0[2]	—	—	—	—	—	42.0[2]
1.544 End—superficial SC laminae	12.0[3]	14.0[3]	17.5[3]	—	—	—	—	56.0[3]	—	—	—	—	—	—	—
1.549 Anterior commisure appears	13.0[2]	14.5[2]	—	—	—	—	—	48.0[2]	70.0[2]	19.0[2]	—	25.0	—	—	42.0[2]
1.556 Peak—dentate gyrus	—	—	16.0[4]	—	22.0[4]	—	—	48.0[4]	—	—	—	—	—	—	—
1.582 Optic axons invade visual centers	16.0[5]	15.5[5]	16.5[5]	—	—	26.0[5]	32.0[5]	—	60.0[5]	20.0[5]	28.5[5]	—	—	38.0[5]	38.5[5]
1.590 Peak—CA 1–2	—	15.0[4]	18.0[4]	—	20.0[4]	—	—	48.0[4]	—	—	—	—	—	—	—
1.599 Peak—cortical layer V	14.0[4]	13.0[4]	16.0[4]	—	20.0[4]	—	35.0[4]	70.0[4]	—	—	—	—	45.0[4]	—	—
1.615 Peak—cones	—	14.0[4]	—	—	—	—	36.0[4]	56.0[4]	—	—	—	—	—	—	—
1.633 Start—lamina IV generation	12.5[3]	—	15.5[3]	20.0	—	32.5[3]	37.0[3]	70.0[3]	—	—	—	—	—	—	—
1.647 Peak—nucleus accumbens	—	16.0[4]	19.0[4]	—	22.0[4]	—	—	45.0[4]	—	—	—	—	—	—	—
1.667 End—lamina VI generation	13.5[3]	—	15.5[3]	—	—	36.5[3]	37.5[3]	65.0[3]	—	—	—	—	—	—	—
1.669 Peak—retinal amacrine cells	14.0[4]	15.0[4]	16.0[4]	—	—	—	45.0[4]	56.0[4]	—	—	—	—	—	—	—
1.678 Peak—tufted cells	—	16.0[4]	17.0[4]	—	22.0[4]	—	—	—	—	—	—	—	—	—	—
1.688 Hippocampal commissure appears	—	15.0[2]	17.0[2]	—	—	—	37.0[2]	—	77.0[2]	—	—	—	—	—	63.0[2]
1.698 Peak—cortical layer IV	15.0[4]	14.0[4]	17.0[4]	—	20.0[4]	—	39.0[4]	80.0[4]	—	—	—	—	49.0[4]	—	—
1.722 End—RGC generation	14.0[3]	18.5[3]	18.5[3]	—	—	—	35.5[3]	57.0[3]	—	—	—	—	—	—	—
1.745 Peak—isles of Calleja	—	16.0[4]	—	—	—	—	—	—	—	—	—	—	—	—	—
1.754 End—cortical lamina V generation	15.5[3]	—	16.5[3]	19.0	—	38.5[3]	39.5[3]	75.0[3]	—	—	—	—	—	—	—
1.792 Corpus callosum appears	15.0[2]	17.0[2]	18.5[2]	—	—	—	39.0[2]	—	87.5[2]	—	—	—	—	—	—
1.836 LGNd axons in the subcortical plate	—	—	17.5[3]	—	—	—	41.5[3]	78.0[3]	—	—	—	—	—	—	—
1.857 Peak—cortical layer II–III	16.0[4]	15.0[4]	18.0[4]	—	22.0[4]	—	56.0[4]	90.0[4]	—	—	—	—	67.0[4]	—	—
1.860 Peak optic axon number	18.0[3]	—	19.5[3]	23.5[3]	—	—	38.5[3]	69.0[3]	—	—	—	—	—	—	—
1.867 Cortical axons reach LGNd	—	—	19.5[3]	24.5[3]	—	—	—	67.0[3]	—	—	—	—	—	—	—
1.869 End—lamina IV	15.5[3]	—	17.5[3]	—	—	42.5[3]	42.5[3]	85.0[3]	—	—	—	—	—	—	—
2.031 Cortical axons innervate LGNd	—	—	21.5[3]	27.5[3]	—	—	—	81.5[3]	—	—	—	—	—	—	—
2.135 Start—superficial SC laminae	—	—	24.5[3]	29.5[3]	—	—	—	86.0[3]	—	—	—	—	—	—	—
2.140 Peak—rods	—	19.0[4]	—	—	—	—	65.0[4]	85.0[4]	—	—	—	—	—	—	—
2.188 Cortical innervation of LGNd adult-like	—	—	24.5[3]	30.5[3]	—	—	—	96.0[3]	—	—	—	—	—	—	—
2.198 LGNd axons in lamina IV	—	—	25.0[3]	—	—	—	61.5[3]	91.0[3]	—	—	—	—	—	—	—
2.214 Peak—retinal bipolar cells	—	—	—	—	—	—	65.0[4]	85.0[4]	—	—	—	—	—	—	—
2.295 SC segregation	24.0[5]	24.0[5]	—	—	—	—	58.5[5]	—	175.0[5]	—	63.5[5]	53.5[5]	49.0[5]	78.0[5]	100.0[5]
2.300 VC axons in the superficial layers of SC	—	—	28.5[3]	34.5[3]	—	—	—	96.0[3]	—	—	—	—	—	—	—
2.316 Ipsi/contra segregation	23.5[3]	25.5[3]	28.5[3]	32.0[3]	—	56.0	60.5[3]	87.0[3]	175.0	—	—	—	—	—	—
2.316 End—rapid axon loss	31.5[3]	—	29.0[3]	32.5[3]	—	—	53.0[3]	110.0[3]	—	—	—	—	—	—	—
2.579 Eye opening	31.0[2,3,5]	30.0[5]	36.0[2,3,5]	43.0[5]	—	72.0[3,5]	72.0[2,3,5]	123.0[2,3,5]	182.0[2,5]	44.0[5]	58.5[5]	80.0[5]	105.0[5]	138.0[5]	168.0[5]

[1]AD, anterodorsal nucleus of the thalamus; AM, anteromedial nucleus of the thalamus; AV, anteroventral nucleus of the thalamus; LGNd, dorsal lateral geniculate nucleus; RGC, retinal ganglion cells; SC, superior colliculus; VB, ventrobasal nucleus of the thalamus; VC, visual cortex; VPL, ventroposterolateral nucleus of the thalamus.
[2]Ashwell et al., 1996.
[3]Robinson and Dreher, 1990.
[4]Finlay and Darlington, 1995.
[5]Dunlop et al., 1997.
[6]Unpublished data.

TABLE 2. General Characteristics of Gestation, Parturition, and Development in the Polyprotodont and Diprotodont Marsupials of This Study

	Polyprotodonts			Diprotodonts		
	Sminthopsis crassicaudata (dunnart)	*Monodelphis domestica* (gray, short-tailed opossum)	*Didelphis virginiana* (S. American opossum)	*Trichosursus vulpecula* (brush-tailed possum)	*Setonix brachyurus* (quokka wallaby)	*Macropus eugenii* (tammar wallaby)
Adult female weight (g)	12–18	80–100	1,000–4,000	1,500–3,500	2,750	5,000
No. of teats	8–10	13	11–17	2	4	4
Litter size	2–10	3–14	3–13	1	1	1
Neonatal weight (mg)	10	100	130	200	350	370
First off teat (days)	43	14	48	94	87	105
Pouch/ventrum exit (days)	59–63	55–60	70	140–150	190	250
Weaning (days)	65–68	55–65	110	230	240	270
Sexual maturity (months)						
Female	4	4	5	12–24	9–12	8
Male	5	5	6	24	13	24
Birth season in captivity	All year	All year	Jan–Aug	Mar–Nov	Jan–Mar	Jan–June

and 101 variables, we did not come close to satisfying that rule. However, as explained by Darlington (1990, p. 131), the accuracy of a regression model is actually determined primarily by the difference between the number of cases and the number of predictor variables, not their ratio. In the present case that difference is 349 − 101 or 248, which is more than large enough.

The regression method derives a regression coefficient *b* for each predictor variable. As in any regression model, predictions of *Y* are derived by multiplying each *b* by the score on the corresponding variable and summing these products across the variables. However, consider the eight dummy variables, which tell the computer to which of the nine eutherian species a particular observation applies. For any given observation on one of the species with its own dummy variable, seven of those eight scores are 0 because they are for species other than the one on which the observation was made. When *b* is multiplied by 0, the product is of course 0, so these seven products do not contribute to the sum. On the one remaining variable, the observation's score is 1, so the product ($b \times$ score) is simply *b*. Therefore the contribution of the eight species variables to the predicted *Y* is simply the single value *b* for the species on which that observation was made.

The same is true for the 93 "event" dummy variables: the contribution of those variables to each observation's predicted *Y* is simply the regression slope *b* computed for that particular event. Since the 8 "species" variables and the 93 "event" variables together constitute all the predictor variables, each observation's predicted *Y* is simply the sum of two values of *b*: one for its species, and one for its event. However, that is exactly the property that we wanted our scale values to have: we wanted to predict the timing of any event in any species from the sum of the corresponding species and event values. Thus the regression slopes of dummy variables can be interpreted as scale values. This gives us a scale value for each species, and a scale value for each event, except for the one species and one event that were omitted to avoid redundancy. After the regression has been run, these can be added to the appropriate scales with scale values of 0. In this paragraph we have for simplicity ignored the regression's additive constant; it is discussed shortly.

This procedure requires a regression program capable of handling (in this instance) over 100 predictor variables. Also, the process is far easier if the regression program has special commands for generating dummy variables. This capability is called the general linear model. Programs with this ability include SYSTAT, SAS, and the latest versions of Minitab and SPSS. The program we actually used is GAUSS, a linear-algebra program used mainly by professional statisticians.

Adjusting scale values to convenient ranges. The event and species with no dummy variable can be called the base event and base species. If one happened to choose the first-occurring event, and the fastest developing species, as the base event and species, then, since their scale values would be 0, all other events and species would have positive scale values. However, if one chose any other event or species as the base values, then some of the scale values would be negative. This is merely an inconvenience, not a real flaw in the model, since in data like these the additive constant in the regression will be chosen by the computer to make all predicted values of *Y* positive. However, the scales are more appealing if the additive constant in the regression is folded into the scales themselves so it need not appear as a separate term in the model. Also, one might prefer to do this in such a way that all scores on both scales will be positive. For instance, if the additive constant were 5, one might arbitrarily add 2 points to all scores on the species scale, and 3 points to all scores on the event scale, to eliminate the need for an additive constant. Furthermore, one could determine the split so as to make all scale values positive.

We made the split in such a way as to make the value for humans on the species scale be 2.5. The main reason for this is that we found that this choice not only makes all scores on both scales positive, it makes them all far enough above 0 so that, if new events and species are added at the low end of the scale, they are unlikely to get negative scores on either scale. There is no sense in which 2.5 is a maximum on the species scale; if data from whales or elephants became available and were integrated into the analysis, those species would presumably score above humans because of their longer developmental periods.

When the scales are adjusted in this way, one gets the very same scale value for each event and each species, regardless of which event and which species were chosen as the base event and species. We arbitrarily chose the peak neurogenesis of the magnocellular basal forebrain as the base event, and the spiny mouse as the base species. With this arbitrary choice, values on the event scale ran from − .206 (peak—cranial motor nuclei) to 1.584 (eye-opening), values on the species scale ran from -.588 (hamster) to 1.347 (human), and the regression's additive constant was 2.148. To eliminate the need for an additive constant when using the scales, we could choose any two constants a(event) and a(species) that sum to 2.148. To

make all scale values positive, we also had to make a(event) at least .206, and make a(species) at least .588. We chose to set a(event) = .995 and a(species) = 1.153; these two values sum to the requisite value of 2.148, the 1.153 makes the human scale value be exactly 2.5, and the split makes all adjusted scale values positive. These adjusted values appear in Table 1.

Defining Y. The adequacy of a regression model can be measured in several ways, but one of the most common is the multiple correlation—the correlation between the actual values of the dependent variable *Y* and the values as predicted from the regression model. We found that ln (postconceptional days) could be predicted from a regression model far more accurately than simply the days themselves. We then experimented with values of *k* in the formula $Y = \ln(\text{days} - k)$. Using the remarkable power of modern computers, we fitted a separate regression model using every value of *k* from 0–10, in increments of .01. In the present eutherian data set, the value of *k* yielding the highest multiple correlation was 5.37. Using the same approach in a substantially smaller data set, Finlay and Darlington (1995) had found a *k* of 7. We assume that our estimate of *k* will continue to change as more data become available.

RESULTS

Eutherian mammals

When the 349 eutherian observations were used to derive species and event scales, the model values of (species scale + event scale) were found to correlate .98926 with values of *Y*, across the 349 eutherian observations. A graph of the fit of data to the model for eutherian mammals is shown in Figure 1A. The 349 absolute values of lcr were found to have a median of .0828, a mean of .1055, and a root mean square (RMS) of .1385. Thus, the typical observation is predicted with an error of about 10% of its difference from 5.37. For example, an event predicted to occur at the 25th postconceptional day has a 95% confidence interval of about ±2 days. The mean squared error (MSE), computed using standard regression formulas, was .01987. The standard error of estimate (SEE) is the square root of MSE, or .1410. That value should closely match the RMS of lcr values, and it does; RMS was .1385. Thus two quite dissimilar methods of computing event variability yield comparable results.

The nine eutherian species scaled as indicated by "species scale value" along the top of Table 1; this is an estimate of the relative duration over all the developmental events studied for each species, with the value for humans set arbitrarily at 2.5. The 94 developmental events in the analysis scaled as "event scale value" in Table 1; this gives the order, within each species, of each developmental event listed. When an event is described as "Peak," followed by the name of a neural structure, the event is the peak of neuronal birthdays for the structure named, as described by Finlay and Darlington (1995).

Are early events in neurogenesis more predictable than later ones? Each of the 349 eutherian observations pertains to a particular event with a particular scale value (e.g., 2.579 for eye opening). If late events were more variable than early ones, the absolute values of leverage-corrected residuals should correlate positively with those scale values. In fact, however, the correlation was very slightly negative (r = −.048). Thus there is no tendency for later events to be less predictable than early events on our logarithmic scale *Y*. Later we suggest that this finding does not contradict the views of Haeckel (1874) as directly as it might seem to.

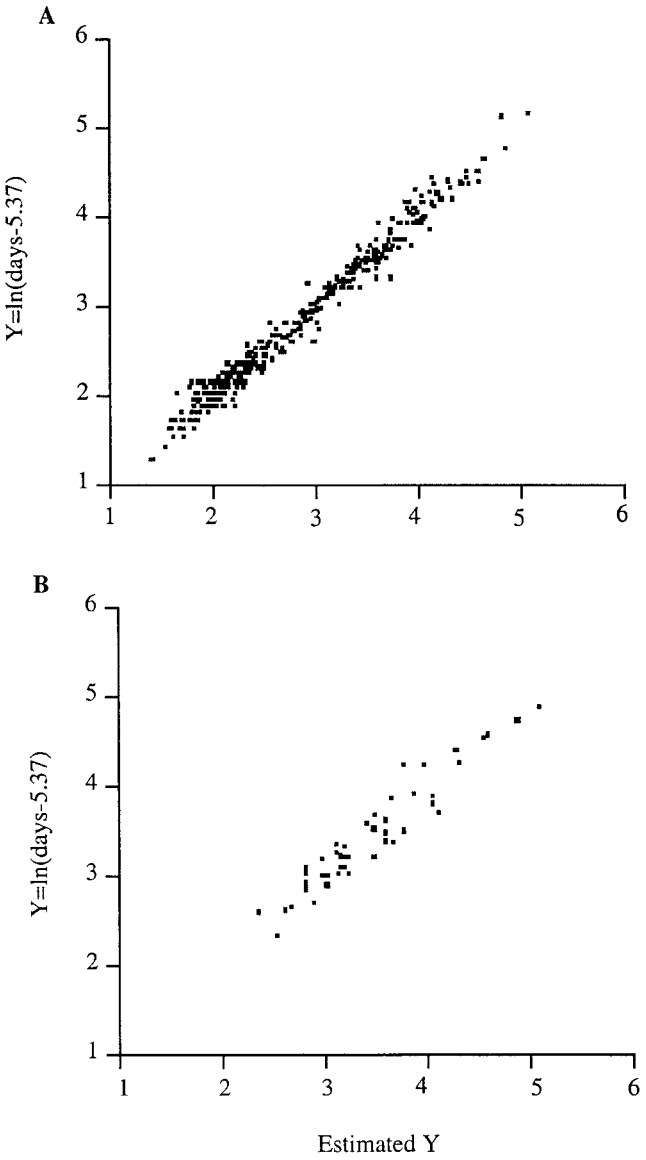

Fig. 1. Actual versus estimated values of *Y* (predicted day of event) for 349 placental observations (**A**) and 49 marsupial observations (**B**).

Is the timing of neurogenesis more predictable than that of other events? Using our 349 eutherian observations, we classified 67 of the 94 events as cell generation and death events, 26 as process outgrowth and connection events, and one (eye-opening) as neither type. To test whether the first type was more predictable than the second, we used the same leverage-corrected residuals to measure unpredictability. As shown in Figure 2, the distribution of the two classes of events appears quite similar. We had 240 individual absolute values of residuals for generation and death events, with a mean of .101, an RMS of .130, and a maximum of .411. There were 101 individual absolute values of residuals for process outgrowth and

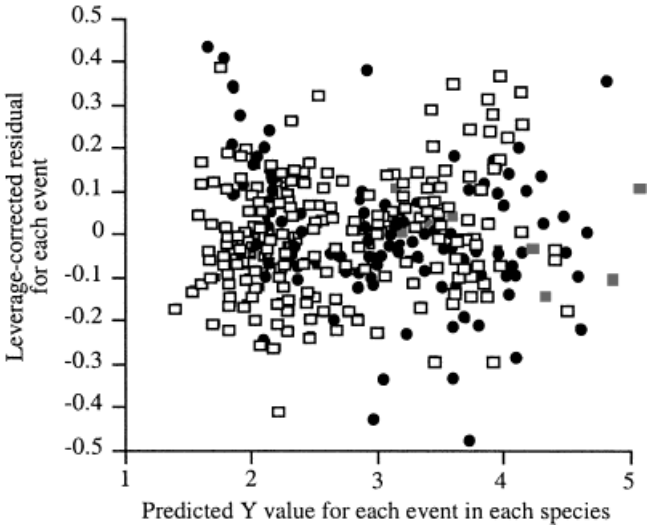

Fig. 2. Leverage-corrected event residuals by class of event. Squares, generation and death events; filled circles, process and connection events; gray squares, eye opening.

connection events, with a mean of .109, an RMS of .160, and a maximum of .478. Thus the two means, the two RMS values, and the two maxima all differ at least slightly in the direction predicted by the hypothesis. However, we also looked at all the 240 × 101 or 24,240 possible comparisons between individual residuals of the two types. Only 52.1% of these comparisons—essentially just half—were in the direction predicted by the hypothesis. Also, by a standard t-test, the absolute lcr values were not significantly larger for process and connection events than for generation and death events. We conclude that for all practical purposes, the two types of event fit the model equally well.

Adapting the model to metatherians

Our ability to model metatherian data is constrained by the nature of our data. In comparison with the 349 eutherian observations, we have just 50 metatherian observations, spanning 33 different events and six species. One of the 50 had to be dropped, for reasons about to be explained, leaving the 49 observations mentioned earlier. The 50 observations are distributed as follows: dunnart 5, short-tailed opossum 4, South American opossum 3, brush-tailed possum 18, quokka 5, and tammar 15. Furthermore, 28 of the 33 events are observed in only one species each. If we were to try to derive a model based entirely on metatherian data (i.e., without using the eutherian event scale), those 28 cases would be useless in fitting a species scale, since they provide no comparisons among species. Thus the species scale would be based entirely on 22 (i.e., 50 − 28) observations spanning five events, which is too little data to fit a useful model. Therefore, at least until new data become available, we are forced to use the eutherian event scale, with the tentative assumption that events occur in metatherians in the same order as in eutherians.

As explained earlier, one of our 50 metatherian observations was of an event that had not been measured in any eutherian species, and it was thus dropped, leaving the 49 metatherian observations we discuss.

TABLE 3. Timing of Reproductive Events in Metatherian Mammals

Species	Estrus (days)	Gestation (days)	Post-partum estrus	Embryonic diapause
Polyprotodonts				
S. crassicaudata (dunnart)	31	13.5	No	No
M. domestica (gray short-tailed opossum)	32.3	13.5	No	No
D. virginiana (S. American opossum)	25.5	13	No	No
Diprotodonts				
T. vulpecula (brush-tailed possum)	25.7	17.5	No	No
S. brachyurus (quokka)	28	27	Yes	Yes
M. eugenii (tammar)	30.6	29.3	Yes	Yes

A further possible complication in some metatherians is the presence of embryonic diapause, in which the embryo can be held indefinitely as a unilaminar blastocyst—a stage prior to all of the 94 events in our data set. The length of diapause depends indirectly on environmental conditions and can vary from pregnancy to pregnancy, so that even talking about a "mean" diapause length for a species is of questionable validity. If there were such a thing, it would affect the additive constant in our model. Actually, the diapause is a characteristic of the macropod diprotodonts (the kangaroos and wallabies) and not the polyprotodonts, and in our six species it exists only for the quokka and tammar (Table 3). However, that does affect 20 of our 50 observations. In sum, we have less confidence in the metatherian model about to be described than in the eutherian model already described. However, the model does seem to be of some interest.

The species scale for metatherians is shown in Table 1. The model's R was .9551 and SEE was .1964. Both these measures indicate a good fit, though noticeably worse than the fit for eutherians, for which R was .9893 and SEE was .1410 (Fig. 1B). The regression slope for the metatherian event scale was 1.2155 with a standard error of .0650. This slope is therefore significantly above its value of exactly 1.0 for eutherians, although the actual size of the difference is not dramatic.

Several variations of the model were tried and found to yield only trivial and nonsignificant improvements in fit. These included changing k, in the expression $Y = \ln(\text{days} - k)$, from the value of 5.37 that had been found for eutherians; allowing the event scale to have different slopes for diprotodonts and polyprotodonts; and adding nonlinear forms of the event scale—specifically, squares and square roots of the event-scale values. Since none of these modifications seemed useful, the results reported above apply to the model without these modifications.

The finding of a coefficient above 1 for the metatherian event scale means essentially that later events are delayed relative to earlier events. This matches an observation made by Robinson and Dreher (1990): "Nevertheless, it is quite apparent that developmental events in the first half of the CP (caecal period—the period from conception to eye-opening, measured in postconceptional days) generally occur much earlier (relative to eye-opening) in marsupials than they do in eutherian mammals....By contrast, most of the events that occur during the second half of the CP do so at about the same stage (i.e., the same proportion of the CP) in both marsupials and mammals." Figure 3 illustrates this quality of the data; it shows the postconceptional days at which various developmental events will occur for the rabbit versus the opossum, according to our model. The opossum has a smaller brain weight and thus

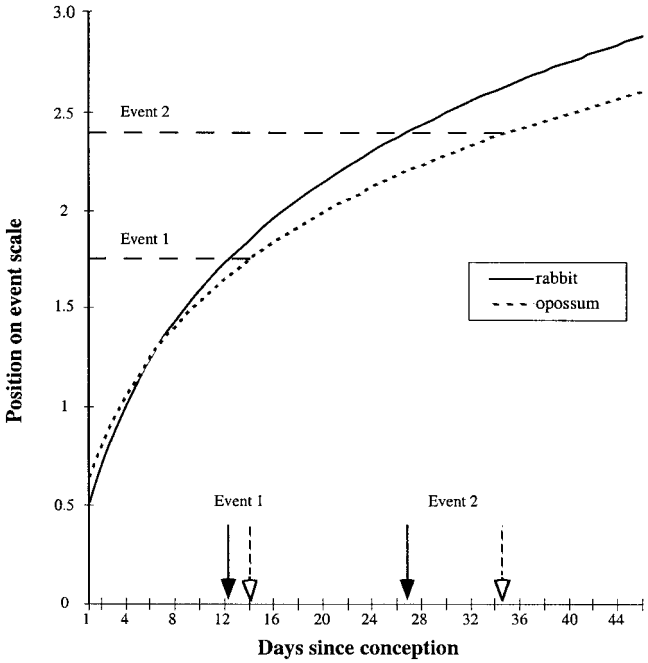

Fig. 3. Maturational rates of the rabbit versus the opossum.

might be expected to mature faster than the rabbit. As Figure 3 shows, this does, in fact, occur for early events in maturation, but not for later events since the two curves cross. Since the model uses a single slope for each order (eutherian or marsupial), such crossings will not occur within an order.

DISCUSSION

Since our model provides reasonably good fit to the available data from all 15 species studied so far, it is reasonable to assume that it will fit many other species as well. However, that statement falls far short of the claim that it will fit all species. In particular, it would not be reasonable to conclude on the basis of this data set that there are no eutherian brains that have slow maturational rates, or metatherian brains with rapid rates. A search for deviations in maturational rate in either group would be informative about how evolution in rate and duration of maturational events has occurred.

Estimating event dates for species not yet widely studied

Our analyses suggest that if the date of eye-opening or any other single scalable event is measured accurately for a eutherian species, then that one date could be used to place that species on our species scale with moderate accuracy, so that the dates of all the other developmental events for that species could then be estimated from our model. For instance, the model says Y = species scale + event scale, and the event scale for eye-opening is 2.579, so for any species we can write:

$$\text{Estimated species scale value} = Y(\text{eye-opening}) - 2.579$$

This equation could be used to estimate the species scale value for any eutherian species from its date of eye-opening. The date of any other neuroembryological event for that species could then be estimated from the model. These estimates would not be as accurate as might be obtained by including the species in a full scaling analysis as presented here. However, the estimates should be more accurate than can be derived by any other method except direct observation of each date for that species, and could be usefully employed, for example, to select a time for a developmental manipulation in a species that had not yet been systematically studied.

Order of events in vertebrate brain development; variability in rate and duration

In our prior study of neurogenesis in a sample consisting primarily of eutherian mammals (Finlay and Darlington, 1995), we showed that there was a remarkable degree of conservation of the relative order of developmental events, in the context of a nearly tenfold variation in the duration of neurogenesis. The greater duration of neurogenesis produced a directly proportional increase in overall brain size and differential effects on the size of brain components, depending on their order of generation: late-generated structures become disproportionately large in large brains. The one metatherian included in that sample showed the same slowing in the timing of events for the metatherians described here. The present analysis shows that the rate of neurogenesis can also be variable across the mammalian class (i.e., both metatherians and eutherians); in the metatherians, the number of neurons produced is lowered, and the procession of events slowed in real time compared with the eutherians.

The slowing of timing in brain development observed in metatherians presumably relates to the considerably longer times to weaning compared with eutherians. Thus, for similarly sized animals, weaning occurs at 50 days in the gray short-tailed opossum but at only 21 days in the hamster and at 230 days in the quokka but at only 20 days in the rabbit. (Table 2; Eisenberg, 1981; Green, 1984; Tyndale-Biscoe and Renfree, 1987). Metatherian reproductive strategy is characterized by very short gestations, with nutrient supply via a placenta, but extended periods of lactation. Thus, for comparable body sizes, the total time from conception to weaning in metatherians by far exceeds that in eutherians. The greater overall time to independence in metatherians suggests that nutrient transfer is less effective via lactation than via a placenta (S.D. Bradshaw, personal communication). Possibly the slowing of late developmental events in metatherians reflects changes in milk composition with time such that carbohydrate content falls while lipids and total solids increase (Green and Merchant, 1987).

We find considerably more variation in the timing of events in the metatherian compared to with eutherian brain. The variation shown by metatherians may reflect an ability to adapt parturition to variable and hostile climates, which may in turn result in some variability during subsequent neural development

What would be the consequence of a slower rate of development? Not all events are slowed: presumably action potentials and most basic events concerned with neuronal physiology take the same amount of time in homeotherms. If a car manufacturer were to take twice the amount of time to build two cars of similar proportions, everything else equal, we might guess that the more slowly built car was the better car. Possibly the marsupial brain

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. It would be interesting to contrast some features of development of metatherian and eutherian mammals with this feature in mind.

Lack of pronounced variability in event order by type and timing

Our original choice to investigate only neurogenesis when investigating alterations of event timing in evolution (Finlay and Darlington, 1995) was guided by the theoretical reason that we were interested primarily in alteration of events that controlled brain size; in addition, there was the practical reason that the peak of neurogenesis was an easily measured event, comparable between laboratories. A priori, it also seemed that axon extension and projection segregation events might be controlled by more variable and local factors than neurogenesis. For this reason, we found it surprising that the generation and establishment of early connectivity in the brain appeared to be nearly as predictable as cell generation. The slight trend for greater variability in connectivity events might entirely be accounted for by the difficulty of fixing a precise date to inherently continuous events, like process segregation in the isocortex, versus the easily measurability of peak of neurogenesis for a certain cell class. The regularity we describe is not a simple case of a clocklike maturation of neurons going through standard maturational states repeatedly throughout the nervous system. To take the case of axonogenesis in the isocortex alone, some neurons extend axons while migrating, and some in situ; subpopulations extend axons at grossly different rates; and various transient connections are made and lost (Miller et al., 1993; Kageyama and Robertson, 1993). The observation of stability of the basic timing of connectivity events over millions of years of mammalian evolution suggests that these locally idiosyncratic arrangements are also conserved.

For the most part, this observation is borne out by the practitioners of developmental research, such that investigators reasonably propose any particular mammal as a model for generic mammalian neurodevelopment (for example, Harman and Beazley, 1986; Reynolds et al., 1985; Krause and Saunders, 1994). This is not to say that interesting deviations do not occur: for example, thalamocortical axons in metatherians do not undergo a waiting period in the subplate as eutherians do (Harman et al., 1995). Perhaps most notably, metatherians do not possess a corpus callosum. It is not the intent of this paper to argue that there is no variability in development, but to quantify that variability so that deviations may show in best relief.

The hypothesis that late events in development should be more variable than early ones derives fundamentally from Haeckel (1874): that after a variable early organizational period, vertebrate embryos pass through a period of common morphology and that deviations occur by alterations or additions to the end of development. The Haeckelian view has recently undergone challenge from two directions. First, Richardson et al. (1997) suggest that the embryonic observation itself is overstated: deviations in morphology, when they occur, can be seen at any maturational stage. Second, Allman et al. (1994) suggest that late events in development, i.e. reproductive maturity and death, can be as predictable as early organogenesis. Our finding adds one more piece to that mosaic. Overall, as Raff (1992) has observed, it seems that both evolutionary biologists and developmental biologists lack the necessary evidentiary base from which to make claims about conservation and variation in the evolution of development. As it is traditional to conclude, more information is needed.

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