TRANSLATING DEVELOPMENTAL TIME ACROSS MAMMALIAN SPECIES

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Abstract—Conservation of the order in which events occur in developing mammalian brains permits use of regression theory to model the timing of neural development. Following a small adjustment to account for a systematic variability in primate cortical and limbic systems, the model is used to generate a 95-event/nine-species matrix that predicts aspects of neurogenesis and axonal outgrowth in the brains of developing mice, hamsters, rats, spiny mice, rabbits, ferrets, cats, monkeys, and humans. Although data are compiled from species in which the timing of birth and the rate of maturation vary widely, the model proves statistically accurate, with practical implications for improving estimation of milestones of neural development, particularly for humans.

Using the three-factor model (species, neural events, and primate adjustments), we produce predictions for the timing of 493 neural occurrences in developing mammalian brains that either have not yet been, or cannot be, empirically derived. We also relate the timing of neural events across the nine species in the form of a reference table calibrated to the development of laboratory rats. This 'translation' table will assist in attempts to equate the neurodevelopmental literature across species with either large or small differences in gestation and maturation, and also permit studies done in a variety of mammals to be applied to better understand human development.

The comparative data indicate that humans, although conventionally considered an altricial species, are neurally advanced at birth relative to the other species studied. © 2001 IBRO. Published by Elsevier Science Ltd. All rights reserved.

Key words: axonal outgrowth, comparative development, cross-species development, humans, maturational timetables, neurogenesis.

A wealth of information on developing nervous systems has been obtained in a number of widely disparate mammalian species. Both development and evolution might be better understood if we could find a rigorous way to relate these data. For example, brain regions vary in elaboration and relative size across mammalian species (e.g., limbic regions, cortical areas) and it is helpful to know if there are different maturational timetables for the different neural systems. The ability to equate development across species has a very practical application. Researchers are repeatedly faced with the problem of relating neurodevelopmental studies done in one species to data obtained in a different species, as well as regularly questioned on how to apply non-human neural data to the developing human brain. If the timing of the developing neural events in the dissimilar species could be linked, accurate comparisons could be made of neural data derived from mammals whose brains vary in

maturational state on any given embryonic or post-conceptional (PC) day.

The ability to translate time would be most useful if it could equate across species whose neural development varies greatly or modestly. For example, it would permit the extensive literature on the well-studied rat to be applied to the recent burst of genetic studies done in mice. Although these rodents have a relatively small 3-day difference in gestation, it is not yet understood if similar neural events occur in a 4-day-old mouse and a 1-day-old rat. The ability to translate across greater differences in mammalian time would permit the vast numbers of non-human neural developmental studies to be applied to better understand development in the much less accessible human brain.

There is an aspect of development that is poorly understood in all mammals, including human infants – the relationship of birth to the maturational state of the brain. Conventionally, evolutionary biology ranks animals into immature (altricial) or more developed (precocial) species (MacArthur and Wilson, 1967). Humans are usually considered an altricial species (Clark et al., 1993; Ashwell et al., 1996; Morrissette and Heller, 1998), with our protracted maturation viewed as central to our unusual learning capacity (McKinney and McNamara, 1991; Bjorklund, 1997). The altricial designation, which reflects the relative dependence at birth (or hatching) and the length of the dependent period thereafter, is essentially a motoric one. However, behavioral studies docu-

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ment intellectual functions of the newborn or even *in utero* human brain (Gibson et al., 1979; Walker et al., 1980; Jusczyk et al., 1983; Meltzoff and Moore, 1983; Mehler et al., 1988; Meltzoff, 1990; Saffran et al., 1996). The relation of motor and cognitive maturation may be better understood if the timing of human neural events could be compared to neural development in other mammals.

In the limited number of previous studies that attempt to link developmental events across species, comparisons are made based on ratios between easily observed 'anchor events' such as eye opening (Dreher and Robinson, 1988; Robinson and Dreher, 1990) or weaning (Ashwell et al., 1996). In these studies, which emphasize the orderly sequence of some visual events across species (Dreher and Robinson, 1988; Robinson and Dreher, 1990) or compare development of fiber tracts to reproductive patterns (Ashwell et al., 1996), no attempt was made to predict events in other species, although the future possibility of such predictions was suggested (Robinson and Dreher, 1990).

In a different type of comparative study, the development of rats and humans was related using morphological observations (Bayer et al., 1993). However, extrapolation based on visual comparisons between these two species, no matter how detailed and carefully done, is likely to be somewhat difficult, especially given that the limbic and cortical components of rodent and human brains likely mature at different rates (Clancy et al., 2000).

In recent studies of our own, which use a multivariate method to link development, we document a striking stability in the order and relative timing of neural events across many mammalian species (Finlay and Darlington, 1995; Finlay et al., 1998; Darlington et al., 1999). Previously, we emphasized the implications of this finding for evolutionary theory (Finlay and Darlington, 1995; Finlay et al., 1998; Darlington et al., 1999). However, because the model is based on regression theory, it can be extended to produce predictions (Darlington, 1990). We recently applied the predictive power of the model to primate development and made some adjustments after noticing a systematic deviation in the expected timing of neurogenesis in limbic and cortical structures for primates versus other mammals (Clancy et al., 2000).

In this analysis, we use the model to generate predictions and confidence limits for the timing of unobserved event dates in a 95-event/nine-species matrix. We also generate a comprehensive timetable that permits the 'translation' of developmental time across the nine species. Portions of this study have been reported in abstract form (Clancy et al., 1999).

EXPERIMENTAL PROCEDURES

Data used to construct the comparative mammalian model

The model is based on empirical observations by many different researchers of the timing (measured in PC days) of 95 neurodevelopmental events obtained in nine mammalian species. Of the 95×9 or 855 species–event combinations covered by the

model, we found observations available in the literature for 362. No additional animals were killed. Data were obtained from Tables 1–5 of Robinson and Dreher (1990), Table 2 from Finlay and Darlington (1995), Tables 1–3 of Ashwell et al. (1996), data reported in Dunlop et al. (1997), Table 1 of Darlington et al. (1999), as well as from the general literature where noted. Data for the cortical events in this study refer to posterior (presumptive visual) cortex. Following the rostrolateral to posteromedial developmental gradient of cortical neurogenesis, this is one of the last neural areas to be born.

Species (listed in order of neurodevelopmental speed) include hamster *Mesocricetus auratus*, mouse *Mus musculus*, rat *Rattus norvegicus*, rabbit *Oryctolagus cuniculus*, spiny mouse *Acomys cahirinus*, ferret *Mustela putorius furo*, cat *Felis domestica*, monkey *Macaca mulatta*, and human *Homo sapiens*.

Eye opening and weaning are two non-neural events that have been used in prior studies in attempts to equate development across species (Dreher and Robinson, 1988; Robinson and Dreher, 1990; Ashwell et al., 1996) and whether they fit a linear scale generated from neural events was tested empirically. Eye opening fit the model well, and was then included as data in the model. Weaning was not well predicted by the model (e.g., humans were predicted to be weaned immediately following birth), so this event was not included. One neural event was also excluded, a surge in the production of synapses in the developing brain which begins just before birth in primates (Rakic et al., 1986; Zecevic and Rakic, 1991; Missler et al., 1993a,b; Bourgeois et al., 1994; Granger et al., 1995; Huttenlocher and Dabholkar, 1997) or eye opening in cats (Benhamida, 1987) and rats (Blue and Parnavelas, 1983) [whichever occurs last, reviewed in Bates et al. (in press)]. This is the only neural event we have found that systematically fails to fit into the conserved developmental sequences.

Data quality and coding

It should be noted that compilation of data on neural development collected across laboratories will necessarily introduce some errors of standardization, no matter how carefully the original data were collected and analyzed. For example, ideally we would assign 'starts', 'peaks' and 'ends' for neurogenesis dates that are consistent across studies. However, while some investigators publish histograms for which we can use consistent numerical criteria (Rakic, 1977; Bayer, 1980; Rakic and Nowakowski, 1981; Bayer and Altman, 1987, 1990), others report only onset or offset of neurogenesis, that is, the first or last day any neurons were generated (Robinson and Dreher, 1990). When possible, we counted as 'start' the day on which 5% of the neurons of a given structure were generated, and 'end' similarly, but this criterion is impossible to apply uniformly without some loss of data. When there was bimodality or no clear 'peak', we derived a midpoint.

Observation of some events in our data set, such as axon ingrowth, presents an additional problem, sampling 'delay'. This occurs because an event cannot be measured until after it has happened and even then the data point can only be as accurate as the sampling interval allows.

Measuring post-conceptional and postnatal days

For mathematical convenience, in this analysis the first 24-h period following conception is designated PC day 1. Some developmental studies refer to the first 24 h following conception as PC 0; these data were converted whenever necessary. For the first 24 h following birth, we retain the conventional designation of postnatal (P) day 0.

The model

The model predicts PC dates transformed to $Y = \ln(PC \text{ days} - 4.42)$. This is roughly the same as a log transform of PC days, though the subtraction of the constant (4.42) does noticeably improve the model's accuracy. We speculate that

the value of 4.42 may have real biological meaning, as the number of days required for very early events such as implantation, blastulation, and differentiation of the basic germinal layers likely take the same amount of time in all eutherian mammals (Finlay and Darlington, 1995). (Our first paper on this model used $Y = \log(\text{PC days} - 7)$ (Finlay and Darlington, 1995), but the current 4.42 constant is based on a data set over twice as large as we had then, i.e., 362 observations versus 159.)

Y is predicted by giving each event an event score (with later events having higher scores) and giving each species a species score (with slower-developing species having higher scores) using a general linear model described in detail in Darlington et al. (1999). Then Y is modeled as the sum of three terms: the event score, the species score, and a particular interaction between them, although the interaction is only necessary when the model is applied to primates.

Standard regression methods are used in computing this primate interaction, which is discussed in detail in a previous study (Clancy et al., 2000). Briefly, species are divided into primates and non-primates, and events are divided into cortical regions, limbic systems and non-cortical, non-limbic regions, with fiber tracts assigned according to the location of the cell bodies from which they originate. (Limbic events are defined per Levitt and Rakic (1982) as any of the spatially distributed neural regions that are positive for the limbic-associated membrane protein.) In the current analysis, this third factor adds 0.21722 to the estimated Y score of every primate cortical event, and subtracts 0.09031 from the estimated Y score of every primate limbic event. (These adjustments have changed slightly from their initial values as more events were added to our data base.)

With one exception, this model exhibits the desirable property of homoscedasticity. That is, on the average, errors in estimating Y are about equally large at high, medium, and low values of the factors, enabling equally confident predictions for both early and late neural events, and for all nine species in this study. The exception is human data, which at first seem to be predicted less accurately than other data. As discussed later, this may be an artifact.

Predicting neural events

To predict the timing of specific neural events, the equation $Y = \log(\text{PC days} - 4.42)$ is rearranged to yield PC days = $\exp(Y) + 4.42$. Thus, to predict PC days for some event, we add the relevant factors (species score, event score, and primate interaction when appropriate) to estimate Y, then use this new equation to estimate predicted PC days. For example, to predict the timing of the start of neurogenesis of cortical layer VI in humans, we add the human value of 2.5 on the species scale, the value of 1.244 on the event scale, and add +0.21722 for the brain region factor since humans are primates and the event in question is a cortical event. These three values sum to 3.96122, so the estimate for PC days is $\exp(3.96122) + 4.42 = 56.9$ days. To predict the same event in macaques, the species score is changed to the macaque score of 2.25, and the same formula including the brain region adjustment is applied, estimating $\exp(3.4940) + 4.42 = 45.5$ days. This prediction matches well with the observed (rounded) date of PC 45 (Robinson and Dreher, 1990).

Producing time translations

To generate cross-species time translations, we used the same formula described above – this time to produce Y values that correspond to 12- or 24-h intervals in development of the common laboratory rat. Human and macaque scores were computed three times, once each to include adjustments for the limbic and cortical interactions, as well as once without the interaction to account for non-cortical, non-limbic regions.

Confidence limits and standard errors of predictions

Each of our 855 cells has its own predicted value of Y, and each of those predictions comes with two standard errors. The smaller of the two is the standard error of estimate for estimating the true cell mean, and the larger is the standard error of estimate for estimating a single observation in that cell. To obtain the confidence limits on Y for any cell, we multiplied the appropriate standard error by the appropriate value of t from a t table, and added or subtracted the product from the estimated value of Y for that cell. For the present sample size and 95% confidence limits, the appropriate t is 1.97. These calculations are outlined in many textbooks on regression and linear models (e.g., Neter et al., 1990). To translate these confidence limits from Y values into PC days, we use the same formula described above: PC days = $\exp(Y) + 4.42$.

<div align="center">RESULTS</div>

Predictions for specific neural events

Using the comparative mammalian model, we generated a matrix of predicted dates (measured in PC days) for 95 events in nine different species. The predictions appear in Table 1 in bold type, followed by empirical data where available, and references. The event scores used in the model are listed in the first column of numbers; species scores are included under the names of each mammal. When the 362 empirically derived dates in our data set are compared to the predictions generated by the model for the same events, the correlation is high: $R = 0.9900$.

Translating times across species

Sequences in which neural developmental time is equated across the nine species are listed in Table 2, with rat days listed in the first column. PC dates prior to birth are shown in bold type, dates following birth are shown in regular type as P days (e.g., P4). The increments between rows are 0.5 days each in 'rat days' up to 1 day following birth, after which the increments are 1 full day. Pre- and postnatal dates for non-primates are given to the nearest 0.1 days, while dates for primates are given to the nearest full day. The range of predicted dates corresponds to the dates of the earliest and latest neural events covered in our analysis, from the peak of neurogenesis of cranial motor nuclei to eye opening.

The table permits translation of neurodevelopmental times by following a line across the columns. For example, one can read that neural events occurring in a PC 19 rat brain are similar to those in a hamster brain on the day of birth, a mouse brain on PC 16.4 and a cat brain on PC 40.4, since those values are all on the same row. As described earlier, translations to primate time will be different for different brain regions, so we represent each primate species by three columns instead of one. Thus, PC 19 in the rat brain corresponds to PC 72 for the human limbic system, PC 94 for the human posterior cortex, and PC 78 for 'other' (non-limbic, non-cortical) neural events.

Typical gestation times for the nine species are shown in Table 2, both within the table ('Birth') and at the top of each column, preceded with a 'G'. For example, rat gestation is about 21.5 days, and cat gestation is about 65 days.

Table 1.

Predicted Dates of Neural Events in Post-conception Days

Neural Event	score	hamster 0.663 model	empir.	mouse 0.701 model	empir.	rat 0.897 model	empir.	rabbit 1.098 model	empir.	sp. mouse 1.177 model	empir.	ferret 1.714 model	empir.	cat 1.808 model	empir.	macaque 2.255 model	empir.	human 2.500 model	empir.
cranial motor nuclei - peak	0.903	9.2		9.4	9[h]	10.5	11[h]	11.8		12.4		18.1		19.5		27.9		34.5	
retinal ganglion cell generation - start	1.023	9.8	9.5[l]	10.0	10.5[l]	11.2	11.5[l]	12.8	13[l]	13.4		19.9	21[l]	21.4	19.5[l]	30.9	30[l]	38.3	
subplate - start	1.038	9.9	9[m]	10.1	10[c]	11.3	11.5[l]	12.9		13.6		20.1	20.5[l]	21.6	23.5[l]	37.9	39.5[l]	47.1	
locus coeruleus - peak	1.070	10.1		10.3		11.6	11[h]	13.2		13.9		20.6		22.2		29.8	32[b]	36.9	
inferior olivary nucleus - peak	1.073	10.1		10.3	10[h]	11.6	12[h]	13.2		13.9		20.7		22.3		32.3		40.0	
magnocellular basal forebrain - peak	1.103	10.3		10.5		11.8	12[h]	13.5		14.2		21.1		22.8		30.7	30[h]	38.0	
superficial SC laminae - start	1.126	10.4	11[l]	10.6	10.5[l]	12.0	12.5[l]	13.7		14.4		21.5		23.2		33.8	30[l]	42.0	
posterior commissure appears	1.126	10.4	13[a]	10.6		12.0		13.7		14.4		21.5		23.2	21[a]	33.8	35[a]	42.0	33[a]
red nucleus - peak	1.128	10.4		10.7		12.0	12[h]	13.7		14.4		21.6		23.3		33.9		42.1	
vestibular nuclei - peak	1.128	10.4		10.7		12.0	12[h]	13.7		14.4		21.6		23.3		33.9		42.1	
cranial sensory nuclei - peak	1.155	10.6		10.8	11[h]	12.2	12[h]	13.9		14.7		22.0		23.8		34.7		43.1	
dLGN - start	1.156	10.6	10.5[l]	10.8	10.5[l]	12.2	13.5[l]	14.0		14.7		22.1		23.8	21.5[l]	34.7	36[l]	43.1	
external capsule appears	1.163	10.6		10.9		12.3		14.0		14.8		22.2		23.9		42.3	40[a]	52.8	56[a]
subplate - peak	1.172	10.7	10[h]	10.9	11[h]	12.3	14[h]	14.1		14.9	14[h]	22.3		24.1	24[h]	42.7	43[h]	53.3	
reticular nuclei - peak	1.200	10.9		11.1	11[h]	12.6	13[h]	14.4		15.2		22.9		24.7	24[h]	33.3		41.4	
medial geniculate nucleus - peak	1.233	11.1		11.3	11[h]	12.8	13[h]	14.7		15.5		23.5		25.3	26[h]	37.1		46.2	
raphe complex - peak	1.237	11.1		11.4	13.5[h]	12.9	12[h]	14.8		15.6		23.5		25.4		34.4	30[h]	42.8	
cortical layer VI - start	1.244	11.1	11.5[l]	11.4	11[l]	12.9	13[l]	14.8	14.5[l]	15.7		23.7	22.5[l]	25.6	28[l]	45.5	45[l]	56.9	
mammillo-thalamic tract appears	1.248	11.2		11.4		13.0	14[a]	14.9		15.7		23.8		25.7	23[a]	34.8		43.2	44[a]
axons in optic stalk	1.250	11.2		11.5	12.3[g]	13.0	14.5[g]	14.9		15.7		23.8	24[g]	25.7	19[g]	37.7		46.9	51[g]
Purkinje cells - peak	1.251	11.2		11.5	10.5[h]	13.0	14[h]	14.9		15.8		23.8		25.7		37.7	39[h]	47.0	
deep cerebellar nuclei - peak	1.256	11.2		11.5		13.0	13[h]	14.9		15.8		23.9		25.8		37.9	38[h]	47.2	
preoptic nucleus - peak	1.258	11.2		11.5	12.5[h]	13.1	12[h]	15.0		15.8		24.0		25.9		35.1		43.6	
globus pallidus - peak	1.272	11.3		11.6	11[h]	13.2	14[h]	15.1		16.0		24.2		26.2		35.5		44.2	
vLGN - peak	1.276	11.4	11[f]	11.6	11.5[h]	13.2	14[h]	15.2		16.0		24.3		26.3	26[h]	38.6		48.0	
medial forebrain bundle appears	1.302	11.6	14[a]	11.8	13[a]	13.4	13[a]	15.5		16.3		24.8		26.9		36.5	35.5[a]	45.4	33[a]
internal capsule appears	1.305	11.6		11.9		13.5	15[a]	15.5		16.4		24.9		26.9		48.1	40[a]	60.2	63[a]
dLGN - peak	1.323	11.7	11[l]	12.0	12[h]	13.6	14[h]	15.7		16.6		25.3		27.3	27[h]	40.2	43[h]	50.2	
suprachiasmatic nucleus - peak	1.330	11.8	11.5[h]	12.0	13[h]	13.7	14[h]	15.8		16.7		25.4		27.5	25[h]	37.4		46.5	
fasciculus retroflexus appears	1.338	11.8	14[a]	12.1	14[a]	13.8	12.5[a]	15.9		16.8		25.6		27.7	21[a]	37.6	40[a]	46.8	
optic axons at chiasm of optic tract	1.342	11.8		12.1	13[g]	13.8	15[g]	15.9		16.8		25.7	24[g]	27.8		40.9	36[g]	51.0	
cochlear nuclei - peak	1.343	11.9		12.1	12[h]	13.8	14[h]	15.9		16.8		25.7		27.8		40.9		51.1	
rapid axon generation/optic nerve-start	1.366	12.0		12.3		14.0	15[l]	16.2	15.5[l]	17.1		26.2		28.3	27.5[a]	41.8		52.2	
mitral cells - peak	1.373	12.1		12.4	12[h]	14.1	14[h]	16.3		17.2	18[h]	26.3		28.5		42.0		52.5	
VP and VB nuclei - peak	1.375	12.1		12.4	12.5[h]	14.1	14[h]	16.3		17.2		26.4		28.6		42.1		52.6	
nucleus of lateral olfactory tract - peak	1.375	12.1		12.4	12.5[h]	14.1	14[h]	16.3		17.2		26.4		28.6		38.9		48.4	
retinal horizontal cells - peak	1.375	12.1		12.4		14.1		16.3		17.2		26.4		28.6	30[h]	42.1	40[h]	52.6	
amygdala - peak	1.392	12.2		12.5	12[h]	14.3	15[h]	16.5		17.5	18[h]	26.7		29.0		39.5	38[h]	49.2	
superior colliculus - peak	1.404	12.3	12[h]	12.6	13[h]	14.4	15[h]	16.6		17.6		27.0		29.3		43.2	41[h]	54.0	
claustrum - peak	1.410	12.4		12.7	12.5[h]	14.5		16.7		17.7	18[h]	27.2		29.4		43.5		54.3	
stria medullaris thalami appears	1.414	12.4	11.5[l]	12.7	12.5[l]	14.5	15.5[l]	16.8		17.8		27.2		29.5		40.2	48[a]	50.2	44[a]
dLGN - end	1.416	12.4		12.7	12.5[l]	14.5	15.5[l]	16.8		17.8		27.3		29.6	31.5[l]	43.7	43[l]	54.6	
substantia nigra - peak	1.420	12.4		12.8		14.6	14[h]	16.8		17.8		27.4		29.7		40.5	39[h]	50.5	
entorhinal cortex - peak	1.421	12.5		12.8	13[h]	14.6	13.5[h]	16.8		17.9		27.4		29.7		53.5	48[h]	67.1	
cortical layer V - start	1.422	12.5	12.5[l]	12.8	12[c]	14.6	13.5[l]	16.8		17.8	20[h]	27.4	27.5[l]	29.7	32.5[l]	53.5	58.5[l]	67.1	
retinal ganglion cells - peak	1.439	12.6	12[h]	12.9	13[h]	14.8	16[h]	17.1		18.1		27.8		30.1	30[h]	44.6	43[h]	55.8	

The model was used to predict the timing of 95 neural events in each species, including events for which empirical data are available. Predictions (in bold type) and empirically derived data are reported in PC days. Start, stop, and peak refer to neurogenesis dates.

AD, anterior dorsal thalamus; AM, anteromedial thalamus; AV, anteroventral thalamus; empir., empirical; dLGN, dorsal lateral geniculate nucleus; vLGN, ventral lateral geniculate nucleus; SC, superior colliculus; VB, ventrobasal thalamus; VP, ventroposterial thalamus.

References: (a) Ashwell et al. (1996), Tables 1–3; (b) Bayer and Altman (1990); (c) Bayer and Altman (1991); (d) Brunjes et al. (1989); (e) Caviness (1982); (f) Darlington et al. (1999); (g) Dunlop et al. (1997); (h) Finlay and Darlington (1995), Table 2; (i) Kostovic and Rakic (1980); (j) Luskin and Shatz (1985); (k) Rakic (1974); (l) Robinson and Dreher (1990), Tables 1–5; (m) Woo et al. (1991).

Table 1 *(Continued).*

		hamster	mouse	rat	rabbit	sp. mouse	ferret	cat	macaque	human
anterior olfactory nucleus - peak	1.441	12.6	12.9 13.5 [l]	14.8 12 [h]	17.1	18.1 22 [h]	27.9	30.2	41.2	51.4
subplate - end	1.442	12.6	13.0 12 [l]	14.8 15 [b]	17.1	18.1 22 [d]	27.9	30.2 30 [l]	54.5 48 [l]	68.5
cortical layer VI peak	1.448	12.7 12 [h]	13.0 12.5 [h]	14.9 16 [h]	17.2	18.2 18 [h]	28.0	30.4 33 [h]	54.8 53 [h]	68.9
septal nuclei - peak	1.463	12.8	13.1 13 [h]	15.0 14 [b]	17.4	18.4 19 [h]	28.4	30.8	42.0 45 [h]	52.5
inferior colliculus - peak	1.475	12.9	13.2	15.1 16 [h]	17.5	18.6	28.7	31.1	46.1 43 [h]	57.7
AV, AM and AD nuclei - peak	1.483	13.0	13.3 13.5 [h]	15.2 15 [h]	17.6	18.7	28.9	31.3	42.8	53.5
optic axons reach dLGN and SC	1.519	13.3	13.6 14.5 [l]	15.6 15.5 [l]	18.1	19.2	29.8 28.5 [l]	32.3 31.5 [l]	47.9	60.0
pontine nuclei - peak	1.528	13.4	13.7 13.5 [h]	15.7 16 [h]	18.2	19.4	30.0	32.5	48.4	60.6
caudoputamen - peak	1.532	13.4	13.8 14 [h]	15.8 15 [h]	18.3	19.4 20 [h]	30.1	32.7	44.7 45 [h]	55.9
optic axons invade visual centers	1.542	13.5 16 [g]	13.8 15.5 [l]	15.9 16.5 [g]	18.4	19.6	30.4 26 [g]	32.9 32 [g]	59.8	75.2 60 [g]
subiculum - peak	1.545	13.5	13.9 13 [h]	15.9 16 [h]	18.5	19.6 20 [h]	30.4	33.0	45.2 48 [h]	56.6
parasubiculum - peak	1.556	13.6	14.0 13.5 [h]	16.0 16 [h]	18.6	19.8	30.7	33.3	45.7 48 [h]	57.2
superficial SC laminae - end	1.571	13.8 12 [l]	14.1 14 [l]	16.2 17.5 [l]	18.8	20.0	31.1	33.8	50.3 56 [l]	63.0
fornix appears	1.573	13.8	14.1 14 [a]	16.2 15 [a]	18.9	20.0	31.2	33.8	46.4 48 [a]	58.1 63 [a]
stria terminalis appears	1.578	13.8 15 [a]	14.2 13.5 [a]	16.3	19.0	20.1	31.3	34.0	46.6	58.4 56 [a]
cortical layer V - peak	1.582	13.9 14 [h]	14.2 13 [h]	16.3 16 [h]	19.0	20.2 20 [h]	31.4	34.1 35 [h]	62.0 70 [h]	78.0
presubiculum - peak	1.583	13.9	14.2 13.5 [h]	16.4 17 [h]	19.0	20.2	31.5	34.1	46.8 48 [h]	58.6
cortical lamina VI - end	1.596	14.0 13.5 [l]	14.4 13 [l]	16.5 15.5 [l]	19.2	20.4	31.8 36.5 [l]	34.5 37.5 [l]	62.9 65 [l]	79.1
cortical lamina IV - start	1.607	14.1 12.5 [l]	14.5 15 [e]	16.7 15.5 [l]	19.4 20 [h]	20.6	32.1 32.5 [l]	34.8 37 [l]	63.5 70 [l]	79.9
dentate gyrus - peak	1.617	14.2	14.6	16.8 16 [h]	19.5	20.8 22 [h]	32.4	35.2	48.3 48 [h]	60.5
anterior commisure appears	1.620	14.2 13 [a]	14.6 14.5 [a]	16.8	19.6	20.8	32.5	35.2	48.4 48 [a]	60.7 70 [a]
cones - peak	1.630	14.3	14.7 14 [b]	16.9	19.7	21.0	32.8	35.6 36 [h]	53.1 56 [l]	66.6
CA1, CA2 - peak	1.637	14.4	14.8 15 [h]	17.0 18 [h]	19.8	21.1 20 [h]	33.0	35.8	49.2 48 [h]	61.6
retinal amacrine cells - peak	1.678	14.8 14 [h]	15.2 15 [h]	17.6 16 [h]	20.5	21.8	34.1	37.1 45 [h]	55.5 56 [h]	69.7
cortical layer II/III - start	1.681	14.8	15.3	17.6 16 [c]	20.5	21.8 18 [d]	34.2	37.2 42 [l]	68.1 85.5 [k]	85.8
cortical layer V - end	1.689	14.9 15.5 [l]	15.3 14 [l]	17.7 16.5 [l]	20.7 19 [l]	22.0	34.5 38.5 [l]	37.5 39.5 [l]	68.6 75 [l]	86.4
nucleus accumbens - peak	1.690	14.9	15.3 14 [h]	17.7 19 [h]	20.7	22.0 22 [h]	34.5	37.5	51.6 45 [h]	64.7
tufted cells - peak	1.691	14.9	15.4 16 [h]	17.7 17 [h]	20.7	22.0 22 [h]	34.5	37.5	51.7	64.8
cortical layer IV - peak	1.703	15.1 14 [m]	15.5 17 [c]	17.9 17 [h]	20.9	22.2 20 [h]	34.9	37.9 39 [h]	69.5 80 [h]	87.6
hippocampal commisure appears	1.711	15.2	15.6 15 [a]	18.0 17 [a]	21.0	22.4	35.1	38.2 37 [a]	52.6	66.0 77 [a]
retinal ganglion cell generation - end	1.725	15.3 14 [l]	15.7 18.5 [l]	18.2 18.5 [l]	21.2	22.6	35.6	38.6 35.5 [l]	57.9 57 [l]	72.8
corpus callosum appears	1.742	15.5 15 [a]	15.9 17 [a]	18.4 18.5 [a]	21.5	22.9	36.1	39.3 39 [a]	72.1	90.9 87.5 [a]
isles of Calleja - peak	1.748	15.6	16.0 16 [h]	18.5	21.6	23.0	36.3	39.5	54.4	68.3
LGN axons in subplate	1.768	15.8	16.2	18.8 17.5 [l]	22.0	23.4	37.0	40.2 41.5 [l]	73.8 78 [l]	93.1
cortical axons reach dLGN	1.794	16.1	16.5	19.2 19.5 [l]	22.5 24.5 [l]	23.9	37.8	41.1	75.6 67 [l]	95.4
cortical layer II/III - peak	1.826	16.5 16 [h]	16.9 15 [h]	19.7 18 [h]	23.0	24.6 22 [h]	38.9	42.3 56 [h]	78.0 90 [h]	98.4
cortical layer IV - end	1.839	16.6 15.5 [l]	17.1 17 [e]	19.8 17.5 [l]	23.3	24.8	39.3 42.5 [l]	42.8 47 [l]	78.9 85 [l]	99.6
optic nerve axon number - peak	1.849	16.7 18 [l]	17.2	20.0 19.5 [l]	23.5 23.5 [l]	25.0	39.7	43.2 38.5 [l]	65.0 69 [l]	81.8
cortical layer II/III - end	1.929	17.8	18.3	21.3 19 [c]	25.1	26.7 22 [d]	42.6	46.4 57 [l]	85.9 100 [k]	108.6
cortical axons innervate dLGN	2.005	18.8	19.4	22.6 21.5 [l]	26.7 27.5 [l]	28.5	45.7	49.7	92.4 81.5 [l]	116.9
adultlike cortical innervation of dLGN	2.103	20.3	20.9	24.5 24.5 [l]	29.0 30.5 [l]	31.0	49.9	54.4	101.5 96 [l]	128.5
LGN axons in cortical layer IV	2.117	20.5	21.2	24.8 25 [l]	29.3	31.4	50.5	55.1 61.5 [l]	102.8 91 [l]	130.2
superficial SC - start of lamination	2.124	20.7	21.3	24.9 24.5 [l]	29.5 29.5 [l]	31.6	50.9	55.5	84.2 86 [l]	106.4
rods - peak	2.136	20.8	21.5 19 [h]	25.2	29.8	31.9	51.4	56.1 65 [h]	85.1 85 [l]	107.6
visual cortical axons in SC	2.212	22.1	22.8	26.8 28.5 [l]	31.8 34.5 [l]	34.0	55.1	60.1	112.6 96 [l]	142.6
retinal bipolar cells - peak	2.215	22.2	22.9	26.9	31.9	34.1	55.3	60.3 65 [h]	91.8 85 [l]	116.0
ipsi/contra segregation in LGN and SC	2.298	23.7 23.5 [l]	24.5 25.5 [l]	28.8 28.5 [l]	34.3 32 [l]	36.7	59.7 56 [l]	65.1 60.5 [l]	99.3 87 [l]	125.6 175 [l]
rapid axon loss in optic nerve ends	2.331	24.4 31.5 [l]	25.2	29.7 29 [l]	35.3 32.5 [l]	37.8	61.6	67.2 53 [l]	102.5 110 [l]	129.8
eye opening	2.546	29.2 31 [a,g,l]	30.2 30 [g]	35.7 36 [a,g,l]	42.7 43 [g]	45.8	75.3 72 [g,l]	82.3 72 [a,g,l]	126.1 123 [a,g,l]	159.9 182 [a,g,l]

Table 2.

Translating Time Across Species

rat (G21.5)	hamster (G15.5)	mouse (G18.5)	rabbit (G31)	spiny mouse (G39)	ferret (G41)	cat (G65)	macaque (G165)			human (G270)		
							limbic	other	cortex	limbic	other	cortex
9.0	8.1	8.3	9.9	10.4	13.9	14.7	19	20	23	23	25	29
9.5	8.5	8.7	10.5	11.1	15.0	16.0	21	22	26	26	27	32
10.0	8.9	9.1	11.1	11.8	16.2	17.3	23	24	28	28	30	35
10.5	9.3	9.5	11.7	12.5	17.4	18.6	24	26	31	30	33	39
11.0	9.7	9.9	12.4	13.2	18.6	19.8	26	28	33	33	35	42
11.5	10.1	10.3	13.0	13.8	19.7	21.1	28	30	36	35	38	45
12.0	10.4	10.7	13.6	14.5	20.9	22.4	30	32	38	38	41	48
12.5	10.8	11.1	14.2	15.2	22.1	23.7	32	34	41	40	43	52
13.0	11.2	11.5	14.9	15.9	23.2	25.0	34	36	43	43	46	55
13.5	11.6	11.9	15.5	16.6	24.4	26.3	35	38	45	45	48	58
14.0	12.0	12.3	16.1	17.3	25.6	27.6	37	40	48	47	51	61
14.5	12.4	12.7	16.7	18.0	26.8	28.8	39	42	50	50	54	65
15.0	12.7	13.2	17.3	18.7	27.9	30.1	41	44	53	52	56	68
15.5	13.1	13.6	18.0	19.4	29.1	31.4	43	46	55	55	59	71
16.0	13.5	14.0	18.6	20.1	30.3	32.7	45	48	58	57	62	74
16.5	13.9	14.4	19.2	20.8	31.4	34.0	47	50	60	60	64	78
17.0	14.3	14.8	19.8	21.5	32.6	35.3	48	52	63	62	67	81
17.5	14.6	15.2	20.5	22.1	33.8	36.5	50	54	65	64	70	84
18.0	15.0	15.6	21.1	22.8	34.9	37.8	52	56	68	67	72	87
18.5	15.4	16.0	21.7	23.5	36.1	39.1	54	58	70	69	75	91
19.0	BIRTH	16.4	22.3	24.2	37.3	40.4	56	60	73	72	78	94
19.5	P0.7	16.8	22.9	24.9	38.5	41.7	58	62	75	74	80	97
20.0	P1.1	17.2	23.6	25.6	39.6	43.0	60	64	78	77	83	100
20.5	P1.4	17.6	24.2	26.3	BIRTH	44.3	61	66	80	79	86	104
21.0	P1.8	18.0	24.8	27.0	P1	45.5	63	68	82	82	88	107
BIRTH	P2.2	BIRTH	25.4	27.7	P2.1	46.8	65	70	85	84	91	110
P1	P3	P0.7	26.7	29.1	P4.5	49.4	69	74	90	89	96	117
P2	P3.7	P1.5	27.9	30.4	P6.8	52.0	72	78	95	94	101	123
P3	P4.5	P2.3	29.2	31.8	P9.2	54.5	76	82	100	99	107	130
P4	P5.3	P3.1	BIRTH	33.2	P11.5	57.1	80	86	105	103	112	136
P5	P6	P3.9	P0.6	34.6	P13.9	59.7	84	90	110	108	117	143
P6	P6.8	P4.8	P1.9	36.0	P16.2	62.2	87	94	114	113	123	149
P7	P7.6	P5.6	P3.1	37.4	P18.5	BIRTH	91	98	119	118	128	155
P8	P8.3	P6.4	P4.4	BIRTH	P20.9	P2.4	95	102	124	123	133	162
P9	P9.1	P7.2	P5.6	P1.1	P23.2	P5	98	107	129	128	139	168
P10	P9.9	P8	P6.9	P2.5	P25.6	P7.5	102	111	134	133	144	175
P11	P10.6	P8.8	P8.1	P3.9	P27.9	P10.1	106	115	139	138	149	181
P12	P11.4	P9.6	P9.4	P5.3	P30.3	P12.7	109	119	144	142	154	188
P13	P12.2	P10.4	P10.6	P6.6	P32.6	P15.2	113	123	149	147	160	194
P14	P12.9	P11.2	P11.8	P8	P34.9	P17.8	117	127	154	152	165	201
							122	133	161	159	173	211
							126	137	BIRTH	164	178	217
										169	184	224
										174	189	230
										179	194	237
										184	199	243
										189	205	250
										194	210	256
										198	215	263
										203	221	BIRTH

The model was used to predict neural developmental time equated across the nine species, calibrated to the development of the rat (first column). The table permits translation by following a line across the columns. Dates prior to birth (bold type) are in PC days; dates following birth (regular typeface) are listed as P days. Gestation times are listed at the top of each column preceded with a 'G'. If neural development at birth corresponded to the same stage across all species, the birthdate entries within the table would all be on the same row. The table shows how widely they diverge.

Relative variability of species and events

As would be expected from the high correlation between data and model, and as comparisons of the predicted dates and observed dates listed in Table 1 indicate, most of the predicted dates are very close to the observed dates, and many match exactly. However, several fit less well and a few vary considerably and we examined those.

T-residuals. T-residuals were used to measure the model's fit to each observation; a high t-residual means the model fits that one observation worse than it fits most others. The root mean square (RMS) t-residual for all 362 observations is 0.9939. The RMS t-residual value for the different species are as follows: hamster, 1.273; mouse, 0.827; rat, 0.820; rabbit, 0.601; spiny mouse, 1.181; ferret, 0.772; cat, 1.187; macaque, 0.880; human, 1.664.

Confidence limits and standard errors. We calculated standard errors for the true means and for single cases for each neural event in each species, as well as confidence limits for each prediction. Complete details of these data are available as supplementary material on our web site (www.psych.cornell.edu/psychology/finlay/finlaylab.html). The highest unpredictability in structure comes from two sources, the appearance of fiber bundles and the duration of neurogenesis of cortical layer II/III. Ten total observations fall outside 'outer' confidence limits (limits for single observations), and eight of these are observations of the appearance of fiber bundles – three in hamsters, two in cats, one in macaques, and two in humans. The two fiber bundle events outside the confidence limits in humans (optic axons invading visual centers and the ipsi/contra segregation in the lateral geniculate nucleus and the superior colliculus) are the same events as two in hamster, although the direction is opposed. Of the 14 total observations of the duration of genesis for cortical layer II/III (start, peak, and stop dates), 12 are outside the inner confidence limits (limits for true cell means).

DISCUSSION

The main message of our comparative mammalian analyses is the high conservation of the sequence of neurodevelopmental events across species (Finlay and Darlington, 1995; Darlington et al., 1999). This conservation permits use of a three-factor statistical model (species, neural event, and primate interaction) to accurately predict the timing of neural events across a variety of mammalian species. The primate interaction used for cortical and limbic regions maps directly onto the relative size of the primate isocortex (larger) and limbic system (smaller) when compared to similar regions in non-primate mammalian species (Finlay et al., 1998; Clancy et al., 2000) (although it should be noted that the data sets used in our model include only two primates – macaques and humans).

Variability in the model's predictions

Event variability. The events for which predicted dates vary the most from the empirical data are related to the duration of cortical layer II/III (note: it is almost impossible to distinguish where layer II ends and layer III begins; these layers are typically combined). Twelve of the 14 empirically derived dates for start, stop, or peak of neurogenesis of this layer are outside the 'inner' confidence limits of the predictions. It is possible that the timing of genesis of layer II/III is a factor in this variability. It is the last-generated layer of the cortex, which itself is born relatively late in neural development.

Various aspects of fiber tract development are the neural events that most often lie outside the 'outer' confidence limits (eight of the total 10). While it is possible that this feature is intrinsically more variable, it is our suspicion that observational variability, especially sampling delay, is the most likely cause. In addition, descriptions of tract maturation (i.e., adult-like) are less quantitative and more subjective than some other events. The initial observation itself is difficult; the small diameter of axon fibers often places them at the very limit of resolution of a light microscope and their ingrowth into a neural area may begin so slightly as to be almost unnoticeable.

Species variability. The species with the largest RMS t-residual is the slowest developing species, humans (RMS = 1.664). This value of 1.664 is 2.40 times as far above the mean of 0.9939 as the second highest value (hamster), indicating more variability in humans than in the other species. There are several likely sources, one obvious right from the outset – the precise date of conception for the human infants upon which empirical studies are based is seldom known (Bayer et al., 1993). Moreover, the number of human data points in our model is necessarily limited; it includes only eye opening and fiber tract appearance. The nature of fiber tract data derived from human embryos and fetuses would suggest that observational error, rather than 'real' variability, could account for the larger error of estimate. A crown to rump length is often used to 'age' a human fetus, but this measurement can be confusing between studies (Humphrey, 1968; Rakic and Yakovlev, 1968) and variable even within studies (Rakic and Yakovlev, 1968). The 'delay' factor is likely to be unusually large for human observations, as intervals between ages used in an individual developmental study may be relatively large (Hewitt, 1961; Zilles et al., 1986; Mojsilovic and Zecevic, 1991; Arnold and Trojanowski, 1996).

Translating time

The cross-species translations listed in Table 2 will assist in comparisons across the many neurodevelopmental studies performed in the brains of various mammals in which the length of development and the placement of birth with respect to neurodevelopment vary widely. These mammals are utilized in developmental studies

for a wide variety of reasons. Although rats are often the mammal of choice, particularly because their neuroanatomy and neurophysiology have been well characterized, many genetic studies are now accomplished in the neural systems of mice. Developmental studies also utilize hamsters for their short gestation and rapid postnatal development, and ferrets, which are also born in a relatively altricial state yet experience a lengthy postnatal development. Spiny mice present an interesting contrast in developmental studies due to their prolonged gestation and relatively advanced maturation at birth. Cats and macaques are often studied for their complex visual system, with the larger brains of macaques developing over a relatively lengthy gestational period, similar to the brains of humans.

Understanding human neural development

One value of cross-species comparisons is the potential to relate the abundant knowledge of development gleaned from other mammals to the much less accessible human neural system. Indeed, the drive to understand the human brain underlies much neuroscience research, regardless of the species in which the empirical data are gathered. One conclusion we might draw from the time translations is that, despite the somatic immaturity of the human infant, the human brain is relatively developed at birth. Two months prior to parturition, humans are at or above the neural maturational level of newborn macaques, and more neurally developed than a week-old kitten or a 2-week-old rat. This relatively advanced state of human neural tissue prior to the last trimester of gestation is supported by human histological data. Lemire et al. (1975) report over 280 morphological observations in the human brain, ranging from the fusion of the neural folds to myelination of subcortical fibers. Eighty-eight percent of these morphological events are observed in the first third of human gestation; only 1% occur during the last trimester.

A number of observations about human infants support the message suggested by the values in Table 2 – unlike altricial mammals, humans at birth possess a precocial brain, although somewhat disguised by an unwieldy body. For example, features of language structure can be learned by the human fetus *in utero* (Jusczyk et al., 1983; Mehler et al., 1988). At birth, complex sensory dimensions can be learned and acted upon (Meltzoff and Moore, 1983; Meltzoff, 1990) and postnatal appreciation of the affordances of the environment and intermodal interactions are very rapid (Gibson et al., 1979; Walker et al., 1980). Statistical regularities of speech are also learned with extreme rapidity (Walker et al., 1980; Saffran et al., 1996).

Technical evaluation of the model's predictions

Utilizing a regression model to formulate predictions is an uncommon tool in developmental neurobiology and so we include the following discussion in which the model's accuracy is evaluated. Some portions are particularly technical and are included for the benefit of investigators who may wish to apply similar methods in other analyses (see also Darlington et al., 1999).

Fitting any mathematical model involves two steps: (i) selecting the variables to include in the model together with the general way they will be combined (e.g., additively, multiplicatively), and (ii) estimating the specific numerical values to be used in the model. In this section we assume that we have the correct overall form for the model; we base that assumption primarily on the high correlation of 0.9900 between observed values and the model's predictions. However, the specific numerical values predicted by the model do not always exactly match the available empirical data, particularly in the human data. Based on the assumption just mentioned, what can be said about the model's accuracy?

Bootstrap effect

Investigators who report observations typically recognize that these figures can be subject to individual variation and observational error, and this is especially true for the human data (Robinson and Dreher, 1990; Ashwell et al., 1996). However, when numerous error-plagued figures are averaged, the average is likely to be more accurate than the individual figures. The same is true when building a model. Since the estimates generated by the model are each based on all the observations used to build the model, errors can average out, making the model's estimates more accurate than the individual observations on which the model was based. This principle, well known to statisticians, has been called the 'bootstrap effect' by Cronbach and Meehl (1955).

The simplest example of the bootstrap effect comes in simple regression. Suppose a regression has been derived in a sample of 200 monkeys, predicting an animal's weight from its age in days, for ages running from 180 days to 1 year. To estimate the average weight of monkeys at 240 days, you could use the regression model, entering age = 240, or you could average the weights of the one or two monkeys in the sample who happened to be exactly 240 days of age when studied. Assuming a linear relation, the regression model is likely to give a far more accurate estimate of the value of interest than an average of one or two weights. The same point applies to more complex regression models, such as the one described in this article.

Because of the difficulty encountered when working with humans, published figures for human data appear to contain about twice as much error as figures for other species. Thus the model should be particularly useful for estimating neural dates in humans – not because the model estimates dates for humans better than for other species (it does not), but because the alternatives may be so much worse. Due to the fact that each predicted event is based not simply on data available for that particular species, but on data available for all species, the model is less restricted than might be expected by the limited – or even inaccurate – data set of humans.

Summary of the model's estimated accuracy relative to a model-free approach

The model's estimated accuracy varies from cell to cell of the 95×9 table of estimated dates. It is most accurate for a cell combination if the event (i) has been observed for many species, many events have been observed for the species (j), and if there has actually been an empirical observation for the particular ij combination. However, we estimate the model's accuracy to be high enough and consistent enough so that it should be used routinely – even when an observation is available for the particular event–species combination of interest. This is especially true for human data. To describe the relative accuracy of estimates made from the model versus the model-free approach (the simple use of empirical data for each event in each species), we will assume the purpose is to estimate the true average Y value for each event–species combination. Let SEM_{ij} denote the standard error with which the mean Y value is estimated by the model for event i and species j. Let SEF_{ij} denote the standard error of the model-free approach for that cell. Then define $SER_{ij} = SEF_{ij}/SEM_{ij}$. Thus if $SER_{ij} > 1$, the standard errors suggest the model's estimate would be superior to that of a strictly empirical approach even if there were an observation available for that approach to use. The farther above 1 SER_{ij} falls, the greater the superiority.

The SER statistic is actually biased against the model in three ways. The most obvious way is that it pretends that the model-free approach has an observation to work with even when it does not. Second, if that extra observation were available, we could have incorporated it into the derivation of the model, thus improving the model's accuracy. Thus SER actually compares the model as it exists today to a hypothetical future version of the model-free approach based on complete data, ignoring the fact that the same new data would allow us to improve the model.

The third bias against the model is that the standard errors of most estimates are inversely proportional to the square root of N, so that to cut a standard error in half you must typically quadruple the sample size. Thus when we say later that the model's estimates are on the average almost twice as good as model-free estimates because the median SER is almost 2, we could reasonably have reported 2^2 or 4. However, we feel that the standard error itself, rather than its square, is closer to what most people mean by the goodness of an estimate, so we shall use SER.

We now summarize the 855 values of SER. As a close inspection of Table 1 indicates, three of the 95 events studied were observed in only one species each (one in the mouse, two in the rat). For any such event–species combination, the cancellation of errors cannot occur, so the model cannot be expected to outperform a model-free approach. In fact, for these three combinations, the model's estimate of Y is exactly the same as that of the model-free approach, so SER is exactly 1.0 for those three combinations.

Of the 362 observations, there are $362 - 3$ or 359 cases for which the model had a chance to outperform the model-free approach. SER values for these 359 combinations range from 1.378 to 2.632, with a median of 1.939. (Additional SER data are available on our web site at www.psych.cornell.edu/psychology/finlay/finlaylab.html). Thus we can say that for these 359 event–species combinations, the model's estimates are on average almost twice as good as those of a model-free approach.

For the cancellation-of-errors effect to occur in species–event combinations for which no observation is available, there must be observations of at least two species for the event in question. There are 469 combinations meeting these conditions. SER values for these range from 1.234 to 2.213, with a median of 1.618. Thus we can say that even when no estimate at all is possible from the model-free approach, but the model has some chance of canceling out observational errors, it turns out to be on average about 1.6 times as good as an observation in that cell would have been if it had been available.

Finally we consider the event–species combinations for which no observation was available, and for which the model cannot gain from cancellation of errors because the event in question was observed for only one species. As already mentioned, there are three such events, and eight species for which each of these events was not observed, making 24 such combinations. For these 24 combinations, SER values range from 0.936 to 0.986 with a median of 0.964. Since these values are only slightly below 1, it appears that even for these combinations, the model can estimate the true date nearly as accurately as the model-free approach would have done if an observation had been available.

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