Neuroinformatics

1539-2791/07/1–16/$30.00 (Online) 1559-0089
DOI: 10.1385/NI:5:1:1

Original Article

Web-Based Method for Translating Neurodevelopment From Laboratory Species to Humans

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Abstract

Biomedical researchers and medical professionals are regularly required to compare a vast quantity of neurodevelopmental literature obtained from an assortment of mammals whose brains grow at diverse rates, including fast developing experimental rodent species and slower developing humans. In this article, we introduce a database-driven website, which was created to address this problem using statistical-based algorithms to integrate hundreds of empirically derived developing neural events in 10 mammalian species (http://translatingtime.net/). The site, based on a statistical model that has evolved over the past decade, currently incorporates 102 different neurodevelopmental events obtained from 10 species: hamsters, mice, rats, rabbits, spiny mice, guinea pigs, ferrets, cats, rhesus monkeys, and humans. Data are arranged in a Structured Query Language database, which allows comparative brain development measured in postconception days to be converted and accessed in real time, using Hypertext Preprocessor language. Algorithms applied to the database also allow predictions for dates of specific neurodevelopmental events where empirical data are not available, including for the human embryo and fetus. By designing a web-based portal, we seek to make these comparative data readily available to all those who need to efficiently estimate the timing of neurodevelopmental events in the human fetus, laboratory species, or across several different species. In an effort to further refine and expand the applicability of this database, we include a mechanism to submit additional data.

Index Entries: Bioinformatics; comparative development; cross-species database; humans; maturational timetables.

(Neuroinformatics DOI: 10.1385/NI:5:1:1)

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Introduction

Studies that characterize the timing of mammalian neurodevelopment typically are accomplished in experimental animals chosen to satisfy a variety of scientific contingencies. There will always be multiple species reported in the scientific literature, with rodents the experimental species of choice and less-studied humans the species of most interest. However, comparative cross-species neural development data, especially for small increments of time, have never been available in an accessible, user-friendly, web-based format. To address this problem, we apply a mathematical model that has evolved over the past decade (Finlay and Darlington, 1995; Darlington, 1999; Clancy, 2000, 2001; Finlay, 2001) to a database of empirically-derived neurodevelopmental events, producing web-based access to timing of comparative postconception (PC) dates and to predictions of specific neurodevelopment events in 10 mammalian species at the site http://translatingtime.net/.

The Need for a Web-Based Database

Developmental neuroscientists, stymied by the prospect of translating data across different animal species and then extrapolating their findings to human development, have attempted a variety of methods ranging from morphological comparisons (Bayer, 1993) to "rules of thumb," e.g., PN7 to PN14 in rat equates to human year 1 (Andrews and Fitzgerald, 1997). These previous methods provide valuable information, but many are decades old (Dobbing, 1970; Dobbing, 1971; Dobbing and Sands, 1973; Dobbing, 1974; Dobbing and Sands, 1979), limited to rats vs human comparisons (Bayer, 1993) and typically compare only one or two variables (Dobbing, 1971; Dobbing, 1974; Dobbing and Sands, 1979). Often the selected variables are not clearly defined, or may have questionable relevance for brain development.

More recently, we have advanced multivariate statistical approaches, with foundations in evolutionary analysis (Finlay and Darlington, 1995; Darlington, 1999; Clancy, 2000, 2001; Finlay, 2001). A mathematical approach is possible because a primary biological mechanism coordinating mammalian neural development apparently arose early and was maintained across evolution (Finlay and Darlington, 1995; Beatty, 1997; Striedter, 2005). The value of a mathematical analysis of neural development lies in the ability to efficiently capture the overall regularity of development as well as identify and adjust for deviations. Yet journal data reporting these comparisons are relatively inaccessible for the clinicians who need to quickly and efficiently interpret animal experiments or researchers who need to design experiments corresponding to specific periods in human brain development where comparisons have not yet been published. The detail with which comparative cross-species data are conventionally presented is limited by journal space.

We now seek a higher level of applicability for modeled cross-species comparisons. We designed a web-based database to generate a comprehensive timetable that permits detailed "translation" of developmental time across 10 mammalian species, including humans. The database (Finlay and Darlington, 1995; Clancy, 2000, 2001) was updated to include a new species, guinea pig, and additional neural events. These data are presented using the Internet, the ideal way to develop and share a truly inclusive comparative model for cross species development. We suggest that such an approach is essential for the efficient interpretation of neurodevelopmental research, and may ultimately be applicable to studies of neurophysiology, neurotoxicology, teratology, molecular genetics, and behavioral development.

To our knowledge, this web-based bioinformatics model is the only available approach for

the conversion of neurodevelopmental data across mammalian species. It presents cross-species data for 102 unique neural events (397 totals in the ten species) such as neurogenesis peaks and axonal outgrowth milestones, in an easily accessible, highly detailed database that can be updated as new data become available. We have previously presented evidence to support the accuracy, precision, and reproducibility of this model, such that it can be used routinely for human infants (Clancy, 2000, 2001). Portions of this study have been presented in abstract form (Kersh, 2005).

Why a Statistical Model is Appropriate

The approach we take to clarify the relationship of neurodevelopmental timing in humans and research species is based on a statistical model originally formulated to help characterize evolutionary principles underlying species differences in brain size (Finlay and Darlington, 1995). It is possible to do this mathematically because despite somatic and motoric diversity, a remarkable similarity exists in the timing and sequence of events that occur during brain development, particularly in highly related mammalian species.

Mouse, Rat, and Human on the Day of Birth

This similarity of developmental schedules allows applications of the statistical general linear model, particularly multiple regression, to relate a database of brain development "events" across the 10 mammalian species currently included in the model, including hamster, house mouse, rat, rabbit, spiny mouse, guinea pig, ferret, cat, rhesus monkey, and human. These analyses are also able to predict the timing of neural events for which empirical data are currently unavailable (Darlington, 1990) as well as quantify, and adjust for variability in these predictions (Clancy, 2000, 2001).

How the Model Works

For those who want an in-depth explanation, the model applied at the website is explained in detail in methods, with additional detail reported in previous studies (Darlington, 1990, 1999; Clancy, 2000, 2001; Finlay, 2001). Briefly and in nonstatistical terms, regression theory models relationships across variables, and is used here to model the relationship between and across entries in a 10 species database. The database can be considered a worksheet of mathematical cells arranged in columns and rows. Columnar entries include the 10 "species," whereas row entries are a variety of "neural events," defined simply as empirically derived occurrences in brain development, such as when neurons destined for various cortical layers are born. Regression coefficients, which measure variability in linear relationships, are used to assign "scores" to the species—with slow-developing species (primates) having higher scores than fast-developing species (rodents). Scores are also assigned to neural events, with events that occur early in development, such as generation of cranial motor nuclei, assigned lower scores than those that occur later, such as the onset of synchronized activity in the retina or retinal "waves."

Thus, the model on which the algorithms used in the website are based includes a "species factor" and a "neural events factor." It also includes a third "primate factor." Earlier versions of the model allowed us to understand from a mathematical perspective that primate brain development is a bit different than that of other mammals. Specifically, primate cortical events (involved in "higher" cognitive processing) occur a bit later than would be predicted from a nonadjusted model and regions of the primate limbic system (involved in memory and emotions, e.g., amygdala; *see* website for complete list) develop a bit earlier than that those of the other mammals in this

study. Standard regression methods are also used in computing the primate interaction (Clancy, 2000), discussed next.

The model predicts PC dates transformed to the statistical term "Y" (simply a mathematically convenient term) as "Y = ln (PC days—k)." The constant (k), accounts for the fact that early events (blastulation, differentiation of basic germinal layers) likely take the same amount of time in all eutherian mammals. At the website, Y is modeled as the sum of three terms: the event score, the species score, and the primate interaction where appropriate, roughly the same as a log transform of PC days. This general linear model is fitted simultaneously to all cells with data, allowing cross-species comparisons. But the model also generates estimates for species-event combinations with no empirical data.

Methods

General System Configuration of "Translatingtime.Net"

The Translating Time website is hosted on a Dell PowerEdge SC430 computer running the Red Hat Linux ES version 4 operating system on a Pentium D microprocessor. The website was created using the Macromedia editor Dreamweaver 8, which allows for the site's construction, management, and task automation. The database was created in Structured Query Language (MySQL) and is stored in two tables: one for species and their respective scores, and the other for specific empirically derived neurodevelopmental events and their respective scores.

Algorithms derived from the statistical model are written in Hypertext Preprocessor language (PHP), a server-side embedded scripting language (HyperText Markup Language [HTML]). These serve as an intermediate level to communicate with the MySQL service on the backend of the system. Queries are sent to the database and output is generated from the PHP algorithms, displayed as either text (for cross species comparisons and some event predictions) or in HTML tabular format (for predictions).

Inference Engines in "Translatingtime.Net"

There are two inference engines: a cross-species comparison neurodevelopment "time translator" and a species-specific neurodevelopmental "event predictor."

Inferring a Cross-Species Neurodevelopmental Time Translation

The time translator inference engine takes input from the user and resolves what specific queries equate to, for example: "What does 45 d PC in macaque neurodevelopment equal in human development?" It accepts input on the species the user wishes to translate from (Species One, or in this example, Macaques), and the species the user wishes to translate to (Species Two, or in this case, Humans), together with the day of interest in Species One (PC45). The output is then propagated and displayed as: "45 PC days in Macaque neurodevelopment equates to Human neurodevelopment as follows: cortical events: 70.9 PC d, limbic events: 52.3 PC d, and noncortical/limbic events: 56.3 PC d." Specific neurodevelopmental events for both selected species, and their accompanying brain regions (cortical, limbic or noncortical, and nonlimbic), are also displayed in HTML tabular format for each event currently listed in the database. The following data are also provided: gestation time, the respective species' scores and the allowed PC day data-ranges for which queries can be submitted. A species data range begins in the first neural event data point available in that species and ends at that species' unique day of eye-opening.

Inferring a Neurodevelopmental Event Prediction

The species-specific neurodevelopmental event predictor inference engine is based on

the same model described earlier, but resolves queries that ask, for example: "When does the peak of neurogenesis occur in the development of human amygdala?" The output is then propagated and responds with: "The amygdala—peak of neurogenesis—is predicted to occur at 49.4 d postconception." The specific brain region (if the requested species is a primate) of the event, along with the gestation time and day of which eye opening occurs is also displayed.

Database

The backend MySQL database consists of two basic tables, one listing the species and one listing neural events, together with their respective scores and adjustments for primate interactions. Data are pulled from tables and referenced in a PHP algorithm that is executed on the user's computer. Species included in the database were chosen for a variety of reasons specific to each experimenter, although rodents account for the most data because they are the experimental species of choice. The database includes data collated from published literature on brain development for dates of discrete neural events (measured in PC days) for hamster *Mesocricetus auratus*, house mouse *Mus musculus*, Norway rat *Rattus norvegicus*, guinea pig *Cavia porcellus*, Old World rabbit *Oryctolagus cuniculus*, spiny mouse *Acomys cahirinus*, ferret *Mustela putorius furo*, domestic cat *Felis domestica*, rhesus monkey *Macaca mulatta*, and human *Homo sapiens*. No additional animals were sacrificed.

Of the 102 × 10 (1020) potential data points, we include empirical data for 397, 15 of which are neural events for humans. Data were obtained from the general literature (Rakic, 1974; Kostovic, and Rakic, 1980; Caviness, 1982; Luskin and Shatz, 1985; Price and Blakemore, 1985; Rice, 1985; Brunjes, 1989; Bayer and Altman, 1990; Bayer and Altman, 1991; Meister, 1991; Woo, 1991; Langford and Sefton, 1992; Zhou, 1998) as well as compiled from previous publications (Tables 1–5 from Robinson and Dreher [1990], Table 2 from Finlay and Darlington [1995], Tables 1–3 from Ashwell [1996], data reported by Dunlop [1997], Table 1 from Darlington [1999], and Table 2 from Clancy [2001]).

To ensure consistency in our database, we converted all empirical data uniformly. In our model, the first 24-h period following conception is always given the designation PC 1, and the conventional designation of postnatal (PN) day 0 is given to the 24 h immediately following birth. For the neurogenesis data points, "start" date is the day on which 5% of the neurons of a given structure were generated, and "end" is assigned similarly. If bimodality, or no clear "peak," was evident in the empirical neurogenesis data, a midpoint was used. Limbic events were defined according to Horton and Levitt (1988) as any neural regions that are positive for the limbic-associated membrane protein, LAMP (*see* list on website link "Related Tables"). Fiber tracts were assigned to brain regions according to the location of the cell bodies from which they originated.

The Statistical Model

The first "Finlay/Darlington" model (Finlay and Darlington, 1995) actually started with a much smaller data set (174 observations spanning 51 events in 7 species); the present data set was accumulated over many years (Finlay and Darlington, 1995; Finlay, 1998; Darlington, 1999; Clancy, 2000, 2001; Finlay, 2001; Clancy, 2006). But for simplicity, the explanation describes the model as if the larger data set was used from the beginning.

First, all 397 observed dates were expressed as "days since conception" on a logarithmic scale. Using multiple regression, we predicted this variable from a large number of "dummy" or indicator variables, one for each species and one for each neurodevelopmental event. These variables were coded 1 for the event or species

in question and 0 otherwise. For instance, the "rat" variable is coded 1 for all observations involving rats, and 0 for all other observations. The regression coefficients of these variables are actually the "scale values" mentioned earlier. We then tried many modifications of this simple model, but only three noticeably improved the model's fit to the data. One was adjusting the logarithmic scale to start 4.34 d after conception. The other two were the adjustments for cortical and limbic events in primates that produced the model we now use. Currently, these primate factors add 0.248683 to the estimated Y-score of every primate cortical event, and subtract 0.079280 from the estimated Y-score of every primate limbic event. The statistical details are described by Darlington and colleagues in several previous publications (Darlington, 1999; Clancy, 2000, 2001). Readers might notice that some values are slightly modified from our previous studies. This occurs because the database is dynamic, as the number of entries increases, scores change slightly, thus improving the model.

Testing for Variability

Using Systat 10, we computed standard statistical correlation coefficients, mean square errors (MSE) (unbiased estimates of true residual variances), and standard errors of estimate. Confidence limits (90% and 95%) were also computed using standard statistical techniques.

Supporting Data

Supporting data tables are linked on the website as "Related Tables," including confidence limits for each included neural event in each of the 10 species. A table listing the empirical data on which the model is based is also included, as are tables listing specific "limbic" events and any abbreviations included in the events tables.

Images

Figure 1 and the photographs on the website were obtained using a Canon D20 (Tokyo, Japan) digital camera. The images were cropped and edited in Photoshop CS2 (Adobe Inc., San Jose, CA). The photo of the human infant is reproduced with permission.

Results

Using algorithms based on the Finlay/Darlington model, we generate comparative dates (measured in PC days) in increments of single days in human development for all species included in the model. Examples of these comparative data appear in Table 1. The table is not inclusive in this printed version owing to space limitations, however, detailed time increments for each species are available at the website.

Predicted Dates of Representative Neurodevelopmental Events

How to Use the Database

Comparative Data

At the site, the user can enter a postconception date within the range of data on which the model is based for any of the 10 species in the model. The time translation page is accessed by clicking on either the "Translate Neurodevelopmental Time Across Mammalian Species" button on the home page or the "Translate" button in the menu bar. In mouse, for example, the data range from postconception day 9.4 to postconception day 29.6 (standardizing day of birth as PN day 0, this equates to PN 10). The user can read that the comparable time in PC days for any other species, including for the human fetus (data range from PC 34.5 to PC 200). The model computes that the brain of a hamster at PC15 is at the same stage of development as the brain of a cat fetus at PC 37.7 d, and a human fetus at PC 65, PC 89, or PC 70, depending (for humans) on whether

Fig. 1. Mouse, rat, and human on the day of birth. Clinicians and researchers currently struggle to equate the timing of neurodevelopmental events across various mammalian species. Rats and mice have only 2-d difference in gestation time, but how do we apply this limited knowledge to compare development across rodent brains with human brains, for example, on the day of birth? Scale bar divisions equal approx 1 mm (mouse and rat) or 1" (human).

the brain region is limbic, cortical, or nonlimbic noncortical (other), respectively. As mentioned earlier, for humans and macaques, a systematic deviation in cortical and limbic neurodevelopmental scheduling we find only in primates (Clancy, 2000) requires that three predicted dates are generated to account for this.

Web Page Reproduction

Predict Neurodevelopmental Events

Predictions, using web-based algorithms based on the Finlay/Darlington model for the 623 neural events lacking empirical data, are also generated on the web platform; 87 of these predictions are for events in the relatively inaccessible developing human brain. This capability is accessed on the home page by clicking on the "Predict Neurodevelopmental Events" button. The user can then select any one of the 10 species, and any of the 102 events and the model's estimate of the timing of that event in that species is displayed. Again, space limits the examples listed in Fig. 2, but all data are available on the website.

Variability

Statistical accuracy is high. The correlation coefficient between all observed and predicted data is 0.990223, a value that indicates remarkable correspondence. The estimate of true residual variance, MSE, is 0.01516 for all species in the model, a value that is reasonably close to the ideal (0.00). The standard error of estimate (SEE) (square root of MSE) is 0.1231. Using t values of 1.968 and 1.650, we computed 90% and 95% confidence levels. These are available on the website.

As discussed in detail next, these values do not have the same meaning as they might have in typical statistical analyses because the empirical observations that the model is based on are typically mean values for several observations. Therefore, although empirical data, particularly for humans, include sources of unavoidable variability, the model is able to

Table 1
Predicted Dates of Representative Neurodevelopmental Events

		Hamster *0.675*		**Mouse** *0.716*		**Rat** *0.906*		**Ferret** *1.718*		**Cat** *1.817*		**Macaque** *2.255*		**Human** *2.500*	
Event	Score	Model	Empir.	Model	Empir.	Model	Empir.	Model	Empir.	Model	Empir.	Model	Empir.	Model	Empir.
Cranial motor nuclei—peak	0.906	9.2		9.4	9.0[4*]	10.5	11.0[4]	18.1		19.6		27.9		34.5	
Retinal ganglion cell generation—start	1.018	9.8	9.5[32]	10.0	10.5[32]	11.2	11.5[32]	19.8	21.0[32]	21.4	19.5[32]	30.7	30.0[32]	38.1	
Inferior olivary nucleus—peak	1.073	10.1		10.3	10.0[4]	11.6	12.0[4]	20.6		22.3		32.2		40.0	
Posterior commisure appears	1.125	10.4	13.0[33]	10.6		12.0		21.5		23.3	21.0[33]	33.7	35.0[33]	41.9	33.0[33]
Cranial sensory nuclei—peak	1.154	10.6		10.8	11.0[4]	12.2	12.0[4]	22.0		23.9		34.6		43.0	
Medial geniculate nucleus—peak	1.230	11.1		11.3	11.0[4]	12.8	13.0[4]	23.4		25.4	26.0[4]	37.0		46.0	
Neurogenesis cortical layer VI—start (VC)	1.232	11.1	11.5[32]	11.4	11.0[22]	12.8	13.0[32]	23.4	22.5[32]	25.4	28.0[32]	46.3	45.0[32]	57.9	
Purkinje cells—peak	1.251	11.2		11.5	10.5[4]	13.0	14.0[4]	23.8		25.8		37.7	39.0[4]	46.9	
Axons in optic stalk	1.281	11.4		11.7	12.3[26]	13.3	14.5[26]	24.4	24.0[26]	26.5	19.0[26]	38.7		48.2	51.0[26]
Medial forebrain bundle appears	1.303	11.5	14.0[33]	11.8	13.0[33]	13.4	13.0[33]	24.7		26.8		36.5	35.5[33]	45.5	33.0[33]
Suprachisamatic nucleus—peak	1.326	11.7	11.5[4]	12.0	13.0[4]	13.7	14.0[4]	25.3		27.5	25.04	37.5		46.7	
Cochlear nuclei—peak	1.340	11.9		12.2	12.0[4]	13.8	14.0[4]	25.6		27.9		40.8		50.9	
Amygdala—peak	1.387	12.2		12.5	12.0[4]	14.2	15.0[4]	26.7		29.0		39.6	38.0[4]	49.4	
Superior colliculus—peak	1.402	12.3	12.0[4]	12.7	13.0[4]	14.4	15.0[4]	27.0		29.3		43.1	41.0[4]	53.8	

Retinal ganglion cells—peak	1.435	12.6	12.0[4]	12.9	13.0[4]	14.7	16.04	27.7		30.2	30.0[4]	44.4	43.0[4]	55.5	
Anterior olfactory nucleus—peak	1.438	12.6		13.0	13.5[4]	14.8	12.0[4]	27.8		30.3		41.5		51.7	
Neurogenesis cortical layer VI—peak (VC)	1.449	12.6	12.0[4]	13.0	12.5[4]	14.8	16.0[4]	27.9		30.3	33.0[4]	56.0	53.0[4]	70.3	
Dentate gyrus—peak	1.612	14.2		14.6		16.7	16.0[4]	32.3		35.2		48.5	48.0[4]	60.8	
Anterior commisure	1.612	14.2	13.0[33]	14.6	14.5[33]	16.8		32.3		35.2		48.6	48.0[33]	60.8	70.0[33]
Cones—peak	1.626	14.3		14.7	14.0[4]	16.9		32.7		35.6	36.0[4]	52.8	56.0[4]	66.3	
Neurogenesis cortical layer IV—peak	1.694	15.0	14.0[29]	15.5	17.0[22]	17.8	17.0[4]	34.7		37.8	39.0[4]	70.9	80.0[4]	89.3	
Hippocampal commisure appears	1.704	15.1		15.6	15.0[33]	17.9	17.0[33]	35.0		38.2	37.0[33]	52.8		66.2	77.0[33]
Retinal ganglion cell generation—end	1.720	15.3	14.0[32]	15.8	18.5[32]	18.2	18.5[32]	35.5		38.7	35.5[32]	57.6	57.0[32]	72.4	
Corpus callosum appears	1.731	15.4	15.0[33]	15.9	17.0[33]	18.3	18.5[33]	35.8		39.1	39.0[33]	73.4		92.5	87.5[33]
Neurogenesis cortical layer IV—end	1.829	16.6	15.5[32]	17.1	17.0[22]	19.8	17.5[32]	39.1	42.5[32]	42.7	47.0[32]	80.5	85.0[32]	101.6	
Optic nerve axon number—peak	1.838	16.7	18.0[32]	17.2		19.9	19.5[32]	39.4		43.0	38.5[32]	64.3	69.0[32]	80.9	
Onset of retinal waves	2.073	20.0		20.6		24.0		48.6	47.0[26]	53.3	52.0[26]	80.2		101.2	
Onset of barrels (S1)	2.096	20.3	19.0[31]	21.0	22.0[31]	24.5	24.0[31]	49.7		54.4					
Rods—peak of neurogenesis	2.130	20.9		21.6	19.0[4]	25.2		51.2		56.1	65.0[4]	84.6	85.0[4]	6.9	
Eye opening	2.517	28.7	31.0[32,33]	29.7	30.0[26]	35.0	36.0[32,33]	73.8	72.0[32,33]	80.6	72.0[32,33]	122.5	123.0[32,33]	155.3	157.5[38,39]

Table 1 is a condensed example of data available on the website. The first two columns lists representative neurodevelopmental events and scores followed by the model's predictions for postconception dates on which these events likely occur. Representative predictions for specific neural events in each developing species are listed in bold type, followed, when available, by empirical data and references. Species scores are included under the names of each mammal. The database includes a total of 102 neurodevelopmental events in 10 mammalian species. Inclusive data for all species are available on the website. VC, visual cortex (defined on website as S1).

*Superscript numbers correspond to reference numbers on website.

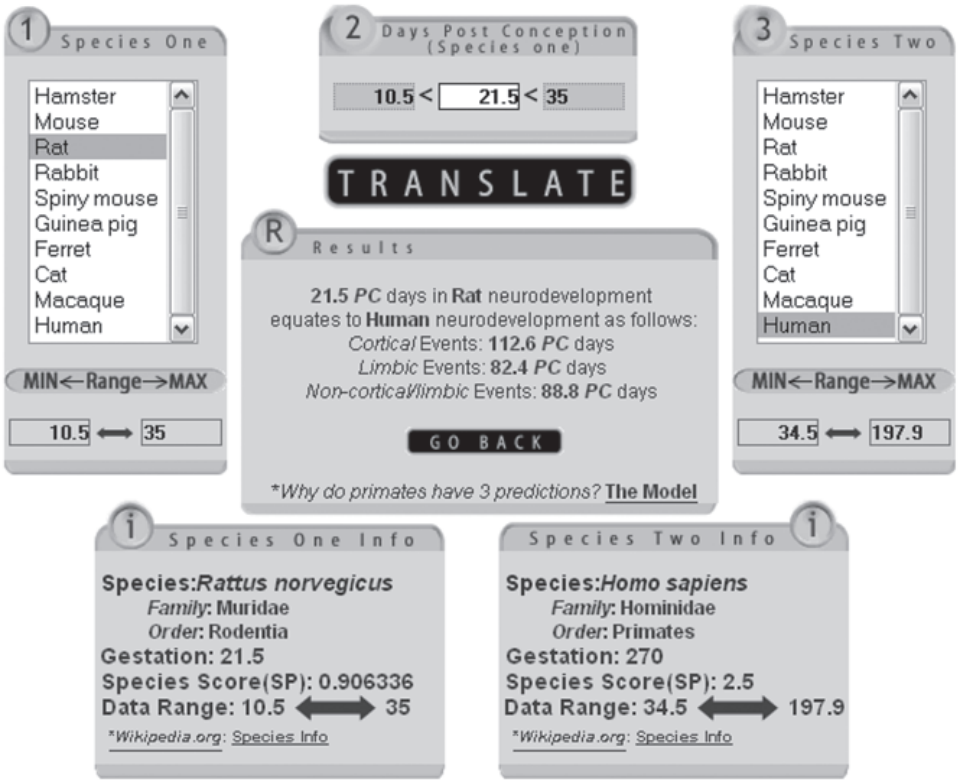

Fig. 2. Web page reproduction. This representative web page depicts a "translation" from rat on the day of birth (P0) to human neurodevelopmental time.

compensate for these inconsistencies (*see* Clancy et al., 2001 and discussion next), making the model's predictions reliable estimates despite inconsistencies.

Discussion

A neuroinformatics approach enables us to maximally coordinate existing information, identify problematic empirical measurements, and describe covarying subcomponents (such as the primate limbic system) within overarching developmental schedules. Our analyses indicate that some conventional "rules of thumb" may need reconsideration. For example, our model does not support the conventional notion that rat development from PN7 to PN14 equates to the first year of human life. Such vague rules of thumb typically concatenate neural and somatic maturation, whereas the predictions generated by this model are specific for neurodevelopmental events, which may be substantially decoupled from somatic maturation.

How a Large Database and a Statistical Approach Improve Accuracy

Multivariate statistical analysis can sometimes produce predictions that are more accurate than the empirical data that generates them as a result of what statisticians call "the bootstrap effect." Our mathematical model takes into account the relationships between every available data point in every species included

in the model, identifies similarities, adjusts estimates to account for species differences, and thus calculates an equivalent degree of neurodevelopment in a reliable and reproducible manner. Essentially, each prediction generated by the model is based on all the observations used to build the model, thus errors are minimized, making the model's predictions better estimates of the true cell entries than the values from the literature, particularly for human data (Clancy, 2001). For example, some of the empirical values for humans are "noisy" because they are based on unavoidably small sample sizes and/or inaccurate estimates of conception.

The "bootstrapping effect" was recently corroborated for eye-opening in the human fetus. Incorporated into our initial models for this event was the conventional date reported in the literature, PC184 (Ashwell, 1996). However, our neuroinformatics approach consistently indicated that eye opening actually occurred at 156 d postconception (Clancy, 2000, 2001). The model's accuracy was recently confirmed when 4-dimensional ultrasonography probes placed human eye opening at 155–158 d (Kurjak et al., 2003; Kurjak, 2004; Campbell, 2005).

How Accurate Are These Estimates?

In most statistical analyses in biology, medicine, or psychology, the unit of analysis is an individual human or animal. But each of the 397 "observations" in our model is itself typically a mean score for several individuals. Thus the confidence limits on predictions made from ordinary regression formulas don't have their usual implication. However, we can consider the confidence limits to be meaningful if we make one extra-assumption, which we believe is reasonable. The parameter estimated by the usual MSE statistic (in our current model, MSE is 0.01516) is made up of three major factors:

1. Error in the mathematical form of our model—for instance if the true model contains interaction terms other than the primate-cortical and primate-limbic terms in our model.
2. Variation among individuals in a species
3. Measurement error in each individual, for example, an event occurred at 15 d in one individual but was recorded as 16 d owing to experimental error.

We assume that the last of these factors is the largest one because the experimental error can be expected to deviate systematically from the true value—be observed too late, for example, rather than assume that individual variation would be systematically biased away from the mean. With that assumption, the "true" value for each individual is essentially the "true" value for the species as a whole, and the same confidence limits apply to each. The confidence limits on this website are based on that assumption.

Similarly, the SEE we compute in our model (0.1231) is not at all analogous to typical values of SEE because, as noted earlier, each "observation" in our model is typically itself a mean across many individuals. SEE for our model is essentially a measure of how well these observations fit our model.

It should also be noted that the relative sparseness of the data in humans (e.g.) will cause the human data to have less "leverage" in setting the model's parameters in the first place, and then symmetrically have more error in back-predicting unknown human dates. In addition, because the model uses ln (day), there will be more deviation in the latest dates of species with the longest gestation times (primates).

Previous Applications of the Model

Despite its relative inaccessibility, this statistical model has been used and supported in about 70 diverse experimental studies to date. These include fetal alcohol exposure (Zhou, 2003), PN auditory projections (Leake, 2002), as well as for clinical studies reporting stereotactic comparisons of child and adult brains (Burgund et al., 2002) or language development (Bates, 2002). Studies of the amphibian spinal cord (Schlosser, 2003), periventricular regions

(Alvarez-Buylla and Garcia-Verdugo, 2002), and cerebellar neurogenesis (Karam, 2001) have also followed from this model.

Future Applications of the Website

Over the past decades, the survival of preterm and full-term neonates has improved drastically, mainly by improving the outcomes from respiratory, cardiovascular, infectious, and surgical conditions. Relatively less success has occurred with regard to neurodevelopmental outcomes, with modest gains from the treatment or prevention of intraventricular hemorrhage, periventricular leukomalacia, white matter damage (Volpe, 1997a,b), neonatal stroke, birth asphyxia (Smith et al., 1988) meningitis, encephalitis, congenital infections, or other conditions (Epstein and Gelbard, 1999; Dammann, 2002) affecting the immature brain. A deeper understanding of the mechanisms by which these conditions affect brain development and neurodevelopmental outcomes holds great promise for novel therapeutic approaches or preventive strategies. There is also increasing concern that conditions during early development may alter the susceptibility to major adult diseases by fetal programming of nutritional or metabolic or behavioral patterns (Gluckman and Hanson, 2004). Animal models targeted to highly specific developmental periods are required for experimental research in these conditions, and for other areas such as neurotoxicology, neuroteratology, or gene therapy. Major differences in developmental periods and rates of development between animal and humans brains have generated much controversy regarding to the applicability of experimental findings to human development (Todd, 2004).

Our goal is to provide another tool to help in identifying the precise timing of developmental events across different mammalian species that are used for designing mechanistic studies of neonatal neurological conditions. In addition, because the long-term effects of fetal or neonatal insults depend on the developmental events occurring at the time of the insult, the ability to select corresponding periods of development in the human and, for example, rodent species is critical. Diagnostic tests or intervention strategies in neonates can also be assessed in different animal models at clinically relevant stages of brain development.

Differences in Primate Development

The "primate" factor that we have incorporated is unique to cross-species comparisons and one we feel is particularly important because extrapolating from rodents to humans is a profound question in neural developmental research. The factor fine-tunes the model by accommodating a systematic deviation in neurodevelopmental scheduling seen in primates (Clancy, 2000). In primates (including humans), the neocortex is much larger and the distributed limbic system, including the olfactory bulb, is proportionally smaller than would be expected for other mammals with similarly sized brains. These differences can be accounted for, at least partially, by differences in the periods of neurogenesis required for these two structures. In primate brains, the period of cortical neurogenesis is correspondingly extended, whereas neurogenesis for the limbic system is compressed (Finlay, 1998, 2001). Correction factors for the cortical and limbic system development were therefore included in our mathematical model to adjust for specific patterns of primate brain development. A list of limbic events is available from the "Related Tables" link on the website. It is possible that as our database grows to incorporate new species and events, other such factors will be identified.

Limitations

Although we are confident the predictions and comparisons for the neural events that are included in our database will be of value, we

must also caution against overeager interpretations until more data become available. For example, prolonged anesthesia alters neuronal cell survival in the developing rat brain (Ikonomidou et al., 1999; Jevtovic-Todorovic et al., 2003; Olney, 2004) but rodent studies cannot tell us how long human infants can be anesthetized safely without similar morphological or developmental consequences (Anand and Soriano, 2004; Soriano, 2005). At this point, the model cannot accurately predict an answer because the current database does not yet incorporate data from potentially influential items such as metabolic rates, cytokine expression, glial cell or vascular development, gene expression, axonal transport, or other developmentally regulated factors that may or may not fit the comparative model.

However, as new data are added, the precision of the model will be improved and the applicability of our statistical algorithms will be broadened. Accumulating data will also improve our understanding of some inconsistencies across ontogeny and phylogeny. For example, time cycles for mechanisms such as action potentials are similar across species, yet it is clear that intervals between the relatively large-scale events in our database become longer from rodent to human. Furthermore, the developmental predictions from these algorithms will only be as accurate as the data that they are based on. Multivariate modeling techniques, however, provide some protection from gross errors in estimation as discussed earlier.

Submitting New Data

There is a link on the home page, under "Provide Feedback," to a form "Submit New Data." The expectation is that researchers can submit peer-reviewed data that, following evaluation, will be compiled by the authors of this article and incorporated into the database. Although this process will take time to evolve, it will eventually provide a large amount of additional information as well as higher precision in the database. For example, when the new date for human eye opening was added to the database, small changes occurred in the scores for the event "eye opening," and for human species. But in fact, the scores for the entire database changed, although the changes were barely perceptible adjustments of several decimal places. But because every new or amended entry in the database serves to improve the accuracy of the model, this feedback mechanism holds much promise.

Future Directions of This Approach

Our ultimate plan is to maintain a user-friendly cross-species database where researchers and clinicians worldwide can add new species and new developing neural events on a regular basis, refining the model to include such items as sleep/wake cycles, metabolic rates, gene expression patterns and neurochemical comparisons, as well as PN human data. The timing is optimal to use the power of large, computer-based databases for acquisition as well as analysis, such that increasingly more precise predictions and broader applications can be produced and accessed from a web-based portal.

Acknowledgments

The authors wish to thank Julie Staudinger, David Davies, Kim Light, Thomas Kieber-Emmons, George Markham and Roger Hall. This project was supported by NIH Grant Number P20 RR-16460 from the IDeA Networks of Biomedical Research Excellence (INBRE) Program of the National Center for Research Resources.

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