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Extrapolating brain development from experimental species to humans

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Abstract

To better understand the neurotoxic effects of diverse hazards on the developing human nervous system, researchers and clinicians rely on data collected from a number of model species that develop and mature at varying rates. We review the methods commonly used to extrapolate the timing of brain development from experimental mammalian species to humans, including morphological comparisons, ''rules of thumb'' and ''event-based'' analyses. Most are unavoidably limited in range or detail, many are necessarily restricted to rat/human comparisons, and few can identify brain regions that develop at different rates. We suggest this issue is best addressed using ''neuroinformatics'', an analysis that combines neuroscience, evolutionary science, statistical modeling and computer science. A current use of this approach relates numeric values assigned to 10 mammalian species and hundreds of empirically derived developing neural events, including specific evolutionary advances in primates. The result is an accessible, online resource (http://www.translatingtime.net/) that can be used to equate dates in the neurodevelopmental literature across laboratory species to humans, predict neurodevelopmental events for which data are lacking in humans, and help to develop clinically relevant experimental models.

Keywords: Brain maturation; Comparative development; Cross-species development; Humans; Neurodevelopment

1. Introduction

Neurotoxicologists, developmental researchers, and pediatric clinicians use animal models to gather information about brain development and its disruptions, cellular or molecular mechanisms underlying neurotoxic effects, and potential interventions that cannot be studied directly in humans, but must be optimally timed for maximum safety and effectiveness. How best to relate data obtained from the nervous systems of diverse experimental species to humans is one of the most important challenges facing both basic and applied research (Fig. 1).

Not only must we be able to extrapolate from non-humans to humans for efficient biomedical research, we must also integrate data across experimental species. A specific animal model might be chosen for any conjunction of widely varying reasons. Accessibility of embryos, cost of acquiring or maintaining animals, availability of genomic analyses or probes, and/or close similarity to human physiology might factor in the design of a laboratory experiment. The result is a variety of data obtained in species born at a wide range of developmental stages and maturing at different rates, but with little explicit agreement or common understanding on how to relate them to humans. For example, how might we best study the effects of toxicants on the crucial first-generated cortical cells (subplate cells) when initial studies describing these cells were done in macaques (Kostovic and Rakic, 1980), later studies used cats (Chun and Shatz, 1989; Ghosh et al., 1990), rats (Bayer and Altman, 1990) and hamsters (Miller et al., 1993; Woo and Finlay, 1996), and future studies are likely to be accomplished in mice?

2. Model species

Although horses, elk and lions were at one time ''model species'' for medical research (Logan, 2002), modern science

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Fig. 1. Despite the challenges, it is essential to find a way to relate neural development across experimental species to humans.

has settled on some standard species. The chart in Fig. 2 depicts a distribution used in neurodevelopmental research in articles published 2005–2006 in nine model mammals. The base of knowledge developed for each species itself quickly becomes a factor in the choice of which species to use, particularly if there is no convenient way to closely compare results between species.

Each experimental species has its own advantages. Rodent dams have large litters that are easy to care for, generally disease-resistant, and have no agricultural uses. Rat pups are born after a short gestation (22.5 d), and have long been the general species of choice such that rat macro- and micro-neuroanatomy, neurophysiology, and assessments of behavior are well-mapped. Mice (gestation 19.5 d) are currently considered most amenable to genetic manipulations, initially chosen because manipulations were clearly reflected in their physical appearance (Nishioka, 1995). Hamster pups (gestation 15.5 d) are born earlier in their somatic development than other rodents so it is easier to study their early neurological development. These three species are considered altricial—born at relatively underdeveloped stages with eyes shut, and many neurogenic events occur postnatally.

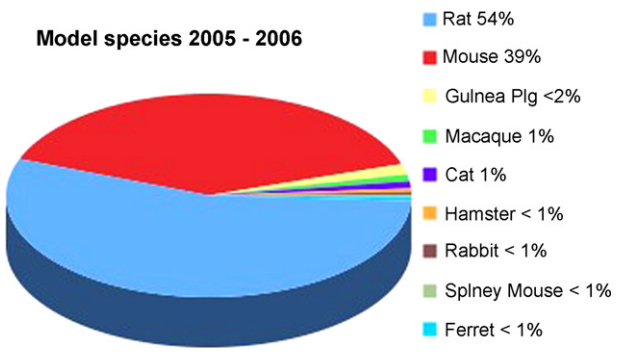

Fig. 2. The chart depicts the proportion of recent studies performed in nine of the most commonly used species (2005–2006 to date; Medline title search).

Ferrets (gestation 42 d) are also born early in development, but have larger brains, more comparable to humans. Cats, also with large brains, have visual systems that resemble humans, and are born at a somewhat later developmental point (gestation 65 d). Rabbits (gestation 31 d) were the initial species of choice for toxicology studies because the absence of tear ducts permits contaminant responses to develop quickly.

In contrast, guinea pigs (gestation 65 d) and spiny mice (gestation 40 d) are ‘‘precocial’’—close to independence at birth. Born with eyes open, guinea pigs even shed their baby teeth *in utero*, and are useful for studies of behavioral abilities that may develop without experience. Rhesus macaques, the leading laboratory primate species (gestation 165 d), are also considered precocial. Babies are born with eyes open and relatively advanced motoric abilities; they are most directly related to humans with (95% genome homology) (Rogers et al., 2006).

Researchers are thus required to assimilate a perplexing quantity of data collected at varying times across a wide developmental spectrum (Fig. 3) and relate it to developing humans (gestation 280 d). The nature of human development further confuses any comparison with laboratory models. Human newborns, if classified by the immature development of their body and motoric skills, should be considered an altricial species, but the relatively advanced development of the human brain and many aspects of perceptual systems at birth clearly places human neural development in a precocial category (Clancy et al., 2000; Verley, 1977).

Moreover, a significant calibration problem is developing in the rodent literature. Although rats dominate, the recent surge of genomic studies in mice means they represent an increasing proportion of experimental studies (8 years ago, mice