Animal Models of Human Behavioral and Social Processes:

What is a Good Animal Model?

Dario Maestripieri

Criteria for assessing the validity of animal models of human behavioral research

Face validity: perceived resemblance between the animal model and the situation or process in humans (qualitative)

Predictive validity: accuracy with which the animal model predicts the course or outcome of the human phenomenon (empirical)

Construct validity: the extent to which both the animal model and the human phenomenon can be explained (e.g. in terms of origin, underlying mechanisms, and function) by the same theory (theoretical)

P. Willner (1984). The validity of animal models of depression. Psychopharmacology

Face validity

Vulnerable to anthropomorphism? Bias? Arbitrariness?

Example: mouse models of autism

“Genetically engineered mice that carry a triple dose of the *Ube3a* gene showed abnormalities in behavior that are the mouse equivalent of the three cardinal features of autism, providing us with a robust model of disease. Like patients with autism, the mice showed reduced social interaction with others (spent more time sitting in a corner of the cage) and communicated with them less (sniffed them less often). And the stereotyped repetitive behaviors of autism spectrum disorder were mimicked in the mice as evidenced by increased self-grooming.”

Predictive validity

This criterion is not useful in informing and driving the process of selection and development of an animal model.

Clearly, if the data produced by research with the animal model do not match the data produced by human research (i.e. the animal model has no predictive value), the model should be discarded, just as any scientific hypothesis that is not supported by the data should be discarded.

But the confirmatory data cannot be used to generate the hypothesis in the first place (and to develop the animal model).

Hypotheses (and animal models) must be developed from theories.

Construct validity

What general theory can explain the origin, underlying mechanisms, and function of similar behavioral processes in animals and humans?

Animals and humans are biological entities.

Theodosius Dobzhansky (1900-1975):

“Nothing in biology makes sense

except in the light of evolution”

Evolutionary processes that produce phenotypic similarities in humans and animals

Convergent evolution:

Similar morphological, physiological, behavioral, and psychological traits can evolve independently by natural selection in different species in response to similar environmental pressures. These traits serve analogous functions in different species and are therefore called analogous.

Phylogenetic inheritance:

Morphological, physiological, behavioral, and psychological traits can be similar in different species because these species have inherited these traits from a common ancestor. These traits are called homologous. Therefore, homologous traits have, by definition, a common phylogenetic history and are produced by similar developmental processes

The Various Roles of Animal Models in Understanding Human Development

Gilbert Gottlieb, *University of North Carolina at Chapel Hill*, and Robert Lickliter, *Florida International University*

Abstract

In this article, the authors take a very conservative view of the contribution of animal models to an understanding of human development. We do not think that homologies can be readily documented with even our most closely related relatives' behavior and psychological functioning. The major contribution of animal models is their provision of food for thought (hypotheses, not facts) about human development and general principles of development, and we describe some of the more significant and interesting of these at length. We also briefly discuss the other applications of animal research toward understanding the development and evolution of behavior, more generally speaking.

On the Importance of Comparative Research for the Understanding of Human Behavior and Development: A Reply to Gottlieb & Lickliter (2004)

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Abstract

Comparative behavioral research is important for a number of reasons and can contribute to the understanding of human behavior and development in many different ways. Research with animal models of human behavior and development can be a source not only of general principles and testable hypotheses but also of empirical information that may be extrapolated to humans.

How evolutionary principles can guide the development of animal models. I: Choice of model organism

- Example #1, topic: reproductive physiology and motivation/behavior
  - Question#1: estrogen and female sexual motivation across the cycle
  - Question#2: prolactin, oxytocin, and maternal motivation
  - Question#3: testosterone and male sexual motivation
    - Analogous models: none
    - Homologous models: mammals (for males, also birds and other organisms)
- Example #2, topic: complex cognitive processes
  - Question#1: assoc. learning, memory, or spatial orientation skills
    - Analogous models: insects, birds, mammals
    - Homologous models: primates
  - Question#2: complex social cognition
    - Analogous models: some birds, some mammals, some primates
    - Homologous models: OW monkeys and apes
  - Question#3: autism
    - Analogous models: none?
    - Homologous models: none?

How evolutionary principles can guide the development of animal models. I: Choice of model organism

Example #3, topic: developmental processes

- Question#1: biological mechanisms through which experience influences language acquisition
  - Analogous models: singing birds
  - Homologous models: none ?
- Question#2: effects of aging on cognitive function
  - Analogous models: any long-lived organisms (reptiles, birds, large mammals)
  - Homologous models: OW monkeys and apes

Example #4, topic: social processes

- Question#1: dyadic relationships involving pair-bonding and cooperation
  - Analogous models: any pair-bonded organisms (e.g. birds or mammals)
  - Homologous models: none
- Question#2: agonistic alliances with unrelated individuals
  - Analogous models: some mammals, some OW monkeys and apes
  - Homologous models: some OW monkeys and apes

How knowledge of a species' behavior and ecology can guide the selection of a particular process as an animal model.

Example: the rhesus monkey

Example #1, topic: effects of early psychosocial stress of offspring behavioral and physiological development

- Model #1: maternally-deprived, isolation- or peer-reared infants
- Model #2: infant monkeys reared by physically abusive mothers

Example #2, topic: effects of chronic social subordination on behavior and physiology

- Model #1: pairs of adult males housed in small cages
- Model #2: low- and high-ranking females living in the same group

Example #3, topic: effects of social variables on gene expression

- Model #1: all-female groups in which rank depends on order of introduction
- Model #2: loss of dominance rank following male immigration into a new group

Social environment is associated with gene regulatory variation in the rhesus macaque immune system

Jenny Tung[a,1,2], Luis B. Barreiro[a,3], Zachary P. Johnson[b], Kasper D. Hansen[c], Vasiliki Michopoulos[b], Donna Toufexis[b,d], Katelyn Michelini[a], Mark E. Wilson[b], and Yoav Gilad[a,1]

Constraints on the use of particular animal models

- Availability, housing and maintenance requirements, breeding, welfare issues, etc.
- Cost
- Time
- Training
- Opportunity to do invasive/or manipulative research
- Previous knowledge of the species
- Number of people already using the animal model
- Probability of funding
- Other

Reliability of an animal model (Geyer & Markou 2000)

•Consistency and stability with which the variables of interest are observed. This consistency should be evident at the following levels:

•a) ability to manipulate the independent variable with a high degree of precision;

•b) ability to measure the dependent variable objectively;

•c) small within-subject variability of the dependent variable;

•d) small between-subject variability of the dependent variable;

•e) reproducibility of the phenomenon under maximally similar conditions;

•f) reproducibility of the effects of manipulations.

"Having a reliable and reproducible experimental system is essential to scientific study. Although small within- and between-subject variability is usually desirable, it should be emphasized that there are cases in which the study of the variability of the model system could lead to a better understanding of the phenomenon. Variability cannot always be considered as error."

THIS IS THE CASE FOR MODELS OF HUMAN BEHAVIORAL AND SOCIAL PROCESSES!

Developing animal models on the basis of sound theoretical principles instead of constraints

Traditionally decisions about the development and use of animal models for human behavioral and biomedical research have been driven by constraints rather than by theoretical principles or knowledge.

The same way much scientific research is guided and driven by technology (what's available? What's possible?) rather than by interesting questions or theories.

Researchers should be encouraged to develop theoretically relevant, original, and interesting new models of human behavioral processes. Who can help with this?

- the researchers themselves, through the peer review process
- research institutions, through support for appropriate facilities
- the funding agencies, through encouragement of exploratory, high-risk high payoff approaches to the use of animal models

One example of an area in which we need new animal models: population-based research on behavioral and social processes

Examples of questions for which we need an animal model:

•Effects of group size and socio-demographic structure on social and cognitive development in early life

•Effects of social support provided by large kin networks on health in mid-life

•Effects of competition-related psychosocial stress on reproductive function & health in women

•Genetic and environmental maternal effects mediating the intergenerational transmission of maladaptive social behavior

•Effects of social stratification, hierarchies, and allostatic load resulting from chronic psychosocial stress on health and aging

Nonhuman primates such as macaques and baboons are excellent animal models for population-based research on behavioral and social processes because:

They are similar to humans in:

- Genetic, anatomical, and physiological characteristics
- Life history traits: long period of slow growth, late age of reproductive maturation, low reproductive output in adulthood, long gestation length, long lifespan
- Competitive, stratified social environment in which social support plays a crucial role in survival, reproduction, psychological well-being and health
- Behavioral processes at the individual, dyadic, family, group, and population level

and

- They are available in large numbers
- They survive and breed well in a wide range of environments
- They are relatively easy to handle
- Their lifespan is shorter than ours
- In some cases, their entire genome has been mapped

The challenges of population-based bio-behavioral research with rhesus monkeys:

- Funding
- Logistic difficulties
- Time investment
- Training and skills
- Getting the research published

The Field Station of the Yerkes NPRC in Atlanta, GA:

> 1,500 rhesus monkeys in large social groups)

The rewards:

- Ecological validity of findings
- Their extrapolability to humans
- Opportunity to understand biology-environment interactions
- Opportunity to understand effects of social environment on behavior, physiology, health
- Opportunity to use a lifespan approach to behavior, physiology, and health
- Opportunity to study phenomena at the population level (distribution, maintenance, transmission of phenotypes and genotypes)

The island of Cayo Santiago, PR (Caribbean Primate Center): 1,000 free-ranging rhesus monkeys studied since 1960s