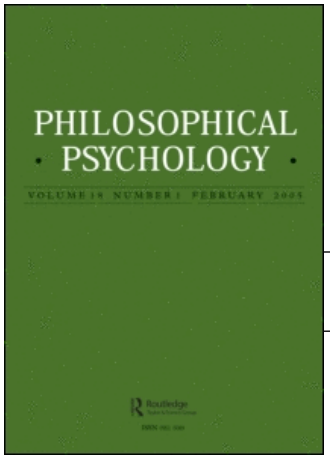

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The Comparative Biology of Human Nature

Jason Scott Robert

Model organismism—the over-reliance on model organisms without sufficient attention to the adequacy of the models—continues to hobble our understanding of human brains and behaviors. I outline the problem of model organismism in contemporary biology and biomedicine, and discuss the virtues of a genuinely comparative biology for understanding ourselves, our evolutionary history, and our place in nature.

Keywords: Model Organisms; Nature vs. Nurture; Neuroscience

1. Introduction

The sun has long since set on the heyday of the nature–nurture controversy. There are virtually no hard-line genetic or socio-environmental determinists anymore. Geneticists and social scientists both recognize the context-sensitivity of gene action and activation, and the multiple determination of phenotypes through the interactions of biological and social factors. Indeed, a kind of compromise position has emerged, an 'interactionist consensus' according to which ''nature *versus* nurture'' has been jettisoned in favor of ''nature *via* nurture'' (Ridley, 2003) or, slightly more happily, ''nature *and* nurture in complex interplay'' (e.g., Gray, 1992; Oyama, 2000; Kitcher, 2001; Moore, 2002; Robert, 2003, 2004a; Rutter, 2006). Yet despite this apparent breakthrough, pressing and challenging tasks remain in contemporary biology and psychology. Chief among them are the need to unpack the interactionist consensus and to interrogate the mechanisms of organismal and behavioral development and their evolution (Robert, 2004a, in press-a).

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In this essay, I explore one persistent obstacle for moving beyond the sterile sequelae of the nature–nurture disputes in understanding human beings, and especially human brains: the over-reliance on model organisms. I will briefly discuss the limits of model organism-based human biology, and then elaborate the promise of a more comparative approach for shedding light on ourselves, our history, and our relationships with other animals. This is a programmatic exercise in the practical philosophy of science—and specifically neuroscience, neuropsychology, and psychobiology—which I hope will serve to provoke further and more detailed studies at the leading edge of contemporary science.

2. Studying Human Nature by Studying Nonhuman Animals

In November 2006, the National Academy of Sciences sponsored a prestigious Sackler Colloquium on *The New Comparative Biology of Human Nature*. The aims were 2-fold, one primary and substantive and the other secondary and more pragmatic. The primary, substantive aim was to explore the benefits and limitations of model organisms in understanding the human brain, and so to determine the desirability and even the necessity for comparative studies (especially with our closest living relatives). The secondary, more pragmatic aim was to assess levels of scientific support for large-scale comparative research with chimpanzees, which might require overturning the National Institutes of Health's moratorium on captive breeding of chimpanzees. The format of the meeting was as follows: (1) frame the topic from the perspective of the history and philosophy of science; (2) solicit scientific presentations focused on the justification of research programs (why model organisms? why *this* model organism? why comparative approaches? why *these* particular comparisons?); and (3) generate philosophical, historical, and scientific reflection on (2) on the basis of (1). I was a plenary speaker at this meeting, along with my colleague Jane Maienschein, as well as Cheryl Logan of the University of North Carolina at Greensboro; we were primarily responsible for (1), that is, for framing the issues historically and philosophically.

Unfortunately, despite significant interest in the driving questions we laid out, and despite the participation of excellent scientists, the colloquium was not as successful as we had hoped in meeting either of the articulated aims. Though the framing session proceeded as planned, the ensuing scientific presentations failed to address the key questions, but rather, for the most part, focused on the researchers' own particular experimental data. Instead of *reflecting on* and *justifying* their research programs/approaches/techniques/choices, the presenters mainly *described* their findings. This had two negative effects for the colloquium: first, the primary, substantive aim simply was not met; second and accordingly, there was little motivation to support the more pragmatic aim, as no one was able to explain why more comparative research is a good thing for science or for society. (That said, the science presented was interesting and first-rate. I learned a lot at this meeting. But the content of the presentations was not what we had expected.)

One plausible hypothesis to explain the failings of this colloquium is that, beyond their particular research paradigm, scientists may be insufficiently equipped to ask and answer conceptual, epistemological, and methodological questions about their research program—at least in this kind of forum. This hypothesis, if true, would be somewhat worrisome, given that much of this research is supported through publicly-funded grants. Another plausible hypothesis is that Maienschein, Logan, and I failed to motivate the discussion, or simply failed to elucidate the sheer importance of the discussion for contemporary biology and biomedicine. In case that were so, my brief here is to make the argument more strongly.

3. Model Organismism in Biology and Biomedicine

Biologists, historians, and philosophers have generated a large and fascinating literature on the use of experimental creatures (rodents, mammals, fish, bacteria, viruses, plants, and so on) as 'model organisms' (e.g., Ankeny, 2000, 2001; Bolker, 1995; Bolker & Raff, 1997; Burian, 1993; Creager, 2001; Gest, 1995; Gilbert, 2001; Gilbert & Jorgensen, 1998; Jenner & Wills, 2007; Kohler, 1994; Logan, 2002; Preuss, 2000; Rader, 2004; Robert, 2004b; Saikkonen, Lehtonen, Helander, Koricheva, & Faeth, 2006; Schaffner, 1998). There are a variety of uses of 'model' at play in these and related discussions. For instance, models may be 'real' or theoretical—the latter would include mathematical models, for instance. Here, 'real' models are of interest: physical instantiations of target phenomena. Moreover, a 'disease model' may be quite distinct from a 'model of synapse formation' or a 'model of limb development.' Though both are designed to facilitate experimentation and generalization, their epistemological and methodological roles differ. The former is meant to serve as a proxy, as a living replica (however inaccurate) of some disease process in humans; to cure the disease model is (putatively) to go some way toward curing the disease. The latter are meant instead as a kind of prototype or archetype for understanding normal function or behavior, whether in humans, mammals, vertebrates, or whatever. Also, not all experimental animals are animal models, and not all animal models are model organisms—the latter honorific tends to be applied only to those officially sanctioned by the National Institutes of Health or other funders and around which a model 'system' has grown (including research networks, literatures, databases, and so on).

In developmental biology, for instance, only a few experimental animals have achieved feature performer status as model organisms, including mice, frogs, chicks, and zebrafish. Rats are especially popular in psychology, fruit flies and nematodes in genetics and molecular and cellular biology, and so on. While there are all sorts of contingent historical reasons for the establishment of these particular animals, there are also contingent epistemological reasons at work.

First, model organisms thrive in laboratory contexts and are generally inexpensive to raise and maintain—they are *lab-friendly*. Second, model organisms yield to laboratory analysis—they are experimentally *tractable*. Third, model organisms are *standard*—the organisms that everyone uses. These features help to explain the

pragmatic advantages afforded by model organism research. But they also introduce a range of distinct disadvantages, including developmental simplicity that does not always translate well to more developmentally complex organisms. Indeed, model organisms are tailor-made (literally custom-produced) for analysis, and are "both selected and selectively fashioned in order to make experiments work" (Robert, 2004b, p. 1008). Accordingly, they may exhibit characteristics (mechanisms, morphologies, behaviors) that are available on demand in the lab and yet nonexistent in nature. Also, these standardized characteristics that are reliably elicited on demand tend not to evince any of the variation naturally exhibited by other organisms. Moreover, where the organisms selected as model organisms are not developmentally simple, they may nonetheless be developmentally *different* in interesting ways—and this may be the reason they were anointed in the first place (Bolker, 1995).

Additionally, while the continuity of material resources across labs makes it much easier for scientists to replicate (or disconfirm) each others' results, this also introduces a kind of insularity and even one-dimensionality into contemporary biology: scientists who use model organisms are limited to studying only those aspects of biology that are reproducible in those particular organisms—at the expense of studying everything else in nature. Sometimes, general lessons can be extracted, but any scientific inference on the basis of model organism research must be cautiously drawn. If the model organism—or even all model organisms taken together—were a model of everything of interest, then this would be less of an issue. But no model organism is a *model* model in this sense, and the current set of model organisms is phylogenetically skewed enough to cast serious doubt on the capacity of model organism-based research to reveal the intricacies of genetics, development, or evolution in any comprehensive way. (See Jenner & Wills, 2007 for a demonstration of the uneven phylogenetic distribution of the six major model organisms in developmental biology.)

As indicated above, remarks such as these are not new under the sun. And yet *model organismism* persists as the guiding framework of contemporary biomedicine and some parts of biology, too. Why that should be the case is a fascinating sociological and epistemological question, to which future research must be squarely directed. For now, let us stipulate that model organismism refers to the research methodology according to which scientists use model organisms in experimental research to accomplish pragmatic aims—making experiments work—in the absence of adequate attention to whether those experiments hook on to anything in the world, let alone the phenomenon of experimental interest. When we forget the limits of model organisms in explaining, say, development, we are prone to errors in inference that are both subtle and powerful in biasing our understanding. Of course, not every model organism experimentalist is a model organismist. But, it seems, plenty of them are.

How does model organismism matter to the debates about nature and nurture? First, it encourages a potentially inappropriate reductionism (not just methodological but epistemological and even ontological) about development, according to which development is nothing but gene activation, whether in *E. coli*, elephants,

or you and me (Robert, 2003; see also Robert, 2004a). This is because the animals are selected and bred to be robust in the laboratory and so insensitive to environmental factors; they are specifically designed to exhibit genetically manipulable characters on demand (e.g., Gilbert & Jorgensen, 1998). Second, it places undue emphasis on the putative similarity between organisms—and the putative universality of developmental mechanisms—as against the differences between organisms that might justify another approach. Third, and as a result of these first two influences, it biases not just what we do know but even what we *can* know by validating some research questions and approaches and invalidating others. In particular, one key fallout of model organismism is the subtle translation of the original problem or question into a new question that is tractable via model organisms but non-identical to the problem or question of interest (see Robert, 2003; cf Wimsatt, 1986). In the next section, I explore how this happens in the special case of model organismal approaches to human disease, but the lesson is more general than that.

4. Model Organismism in Practice: The Case of Parkinson's Disease

Consider the case of Parkinson's Disease (PD). Cell transplant research for PD is premised on the notion that a hallmark feature of PD—the loss of dopaminergic neurons in the substantia nigra—may potentially be mediated by the transfer of new dopaminergic neurons, or of other cells that would promote the production or prevent the loss of dopaminergic neurons. While some clinical studies of cell transplant research for PD have been undertaken with fetal ventral mesencephalic cells harvested from aborted fetuses, the results have been equivocal (Freed et al., 2001; Olanow et al., 2003; cf Mendez et al. 2002, 2005). As this research continues, a new paradigm is emerging: using neural stem cells derived from embryonic or other sources. As part of the Model Systems Strategic Research Network funded by the Canadian Stem Cell Network, Françoise Baylis and I convened a series of collaborative workshops with stem cell researchers interested in cell transplant research. We focused on PD given its perceived status as 'low-hanging fruit' in the domain of neural stem cell research. Beyond the intricacies and challenges of cell transplantation, a more basic concern came into focus through the workshops: How well is PD understood on the basis of nonhuman animal models of the disease? And how is our current understanding of PD in humans biased by our animal models?

PD researchers primarily use variants of two animal models, both of which happen also to be model organisms: the 6-hydroxydopamine (6-OHDA) rat model and the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) nonhuman primate model, which is typically a rhesus macaque (Emborg, 2004). While there are other animal models in use in PD research, rat and macaque models have pride of place. We hosted collaborative workshops first with those who study 6-OHDA rat models, and then with those who study MPTP macaque models. The results were interesting, though not at all surprising: at the former workshop, investigators

emphasized that we already have proof of principle in primates that rodent models are suitable, and perhaps that there is no need for non-human primate models; at the latter workshop, investigators emphasized the distinct limitations of rodent models, and insisted on the propriety—indeed, the necessity—of nonhuman primate research. The *differences* between humans and both rodents and nonhuman primates were only rarely emphasized, perhaps because of the ongoing penchant to anthropomorphize inappropriately (Povinelli, 2004) and to indiscriminately lump together nonhomologous behaviors and traits (Robert, 2004a).

At both workshops, and in our own deliberations, we explored the further possibility that neither the rodent nor the primate model of PD is particularly good. What these models model or, rather, approximate, is a subset of the motor symptoms of PD induced primarily via acute lesion. That is, they model some of the motor deficits of traumatically-induced parkinsonism, a motor phenotype that looks like PD in some respects but may be fundamentally different. PD in humans is (a) more than just these motor deficits, including as well cognitive and affective components, and (b) chronic and degenerative, not acute and static. Accordingly, if cell transplantation 'works' in rats or macaques to 'cure' some motor symptoms, we may not thereby be licensed to infer anything about cell transplantation in humans as a treatment for PD. That is, treating parkinsonism in these animal models is simply not comparable, let alone equivalent, to treating PD in humans.

Some symptoms of parkinsonism are resolvable via model organisms and these particular animal models are a case in point. But they bias our understanding and skew the research enterprise. For the task was never to resolve some symptoms of parkinsonism; it was, instead, to understand, treat, and even cure PD. Phenotypic parkinsonism in model organisms is not equivalent to PD in humans, and we should not delude ourselves into believing that the models resolve the original problem (PD) rather than resolving something else (parkinsonism). And yet, with research energy focused on these at-best partial models of the disease, the complexities of human PD are ignored—which helps to explain the lack of dramatic progress toward better treatments and cures for PD (Philips, 2004).

5. Beyond Model Organismism

Differences between species tend to be ignored and similarities tend to be overemphasized within model organismism. These twin tendencies suggest that comparisons are implicit and limited rather than explicit and more comprehensive. Where the quest for universal mechanisms is undertaken in the absence of a similar quest for (evolved) specializations, there are obvious limits to what we will learn. The presumption of similarity is dangerous, blinding us to the importance of understanding difference—the very essence of life.[1] Todd Preuss raises an interesting problem in this regard:

> The ubiquity of variation seems to pose a challenge to animal research, for if every species is unique, how can we hope to learn anything about humans by studying

> other animals? I suggest that this dilemma is more apparent than real. The fact that variation is extensive does not mean that there are no important cross-species commonalities. After all, rats do possess many features of cortical organization found widely among mammals. The problem is that we cannot be sure that any *particular* feature of rats is a widespread feature of mammalian organization by studying rats alone. (Preuss, 2000, p. 295)

But neither will comparing rats with mice or monkeys, given that all of these models have often been selected for experimentation for extra-scientific reasons, and on the assumption of fundamental similarity. Barely comparative biology is the most that model organismism typically affords; here, various model organisms (or their genomes) may be compared with one another, against the backdrop of the assumption of universal sameness.

An interesting feature of some scientific discussions of the model organismal approach in understanding life is the repeated reference to Hans Krebs' invocation of the 'August Krogh principle' that "for many problems there is an animal on which it can be most conveniently studied" as a justification for model organismism (Krebs, 1975; for discussion, see especially Gest (1995) and Jørgensen (2001)). Although many scientists (especially but not exclusively physiologists) interpret this as model organismal *carte blanche*—to study autism in voles, neural development in worms, or anything whatsoever in mice—they have also often either misinterpreted the principle or restated it so as to misrepresent its meaning (as intended by Krebs or by Krogh). Jørgensen (2001) cites telling examples, such as Feder and Watt's (1992) assertion that Krogh maintained that 'for every biological question is an organism best suited to its solution' and Randall, Burggren, and French's (1997) more elaborate (and fundamentally misleading) claim that:

> One of the reasons for Krogh's extraordinary success as a physiologist was his uncanny ability to choose just the right experimental animal with which to test his hypotheses. His view was that for every defined physiological problem, there was an optimally suited animal that would most efficiently yield an answer. (Randall, Burggren, & French, 1997, p. 15)

Jørgensen returns to Krogh's 1929 address to the International Physiology Congress to show instead that Krogh was not only not a model organismist, but was a comparative physiologist to the core: for Krogh, understanding 'the essential characteristics of matter in the living state' will require 'the study of the vital functions in all their aspects throughout the myriads of organisms'; moreover, he maintained, "we will find out before very long the essential mechanisms of mammalian kidney function, but the general problem of excretion can be solved only when excretory organs are studied wherever we find them and in all their essential modifications" (Krogh, 1929, as cited by Jørgensen, 2001, pp. 59–60).

This is, of course, not to deny that certain organisms really are well-suited to particular lines of inquiry, problem agendas, or experimental designs. But no organism is uniquely suited to all of these, and whether any particular organism is well-suited in any particular situation depends entirely on the details of that situation: What do we already know, what do we want to know, and how are we

going to go about knowing it? As Krebs (1975) pointed out 30 years ago, 'A general lesson to be learned from these considerations is the importance of looking out for a good experimental material when trying to tackle a specific biological problem'. And yet that general lesson has not been universally well learned, as scientists too often alter the question to suit the model rather than selecting an appropriate model to suit the question.

How else to explain the continued penchant not only for a small number of model organisms, but also resistance to the establishment of new models, and even attempts to further narrow the number of sanctioned model organisms within the biomedical research enterprise? With regard to the latter, consider the limitation of 'nonhuman primate' research to macaque monkeys (and, where budget is an issue, to marmosets), and also the rise of transgenically humanized mice as putatively universal models for all biological and biomedical phenomena of interest (Shultz, Ishikawa, & Greiner, 2007; cf Rissman, 2005). In the background, there are ethical concerns at play, especially regarding invasive research with many animals, not least with nonhuman primates—though it is often unclear why noninvasive experimental or even observational research with nonhuman animals should be in question. While ethical deliberations, and political pressure, may eventually decide the limits of scientific experimentation, there are at present more scientific options than mouse, macaque, marmoset, man, or bust.

In her excellent study of the limits of model organisms in developmental biology, Jessica Bolker argues that the assumption of universality 'has consequences at two levels':

> At the level of data accumulation, we lack knowledge of the existing diversity in developmental patterns and processes. At the conceptual level, our ignorance of developmental variability and diversity leads to an overly deterministic view of development, and to a concomitant narrowing of focus to proximate, internal mechanisms. (Bolker, 1995, p. 453)

Sound inferences are, accordingly, unlikely at best. The dearth of comparative data, coupled with genetic reductionism and ignorance of the total ecology of the genome—that is, that there is more to an organism than its genome, and that the genome has meaning only in developmental and environmental context—suggests that our understanding of fundamental biology based on model organisms is not only incomplete but fundamentally biased (Robert, 2004a; see also West & King, 1987, on the 'ontogenetic niche').[2]

6. Toward a More Comparative Biology and Biomedicine

Mere comparisons are not enough to move us beyond this lacuna. For comparing apples with apples, or with oranges or watermelons, tells us nothing about other kinds of fruit, let alone vegetables, legumes, or anything else under the sun. Only a rigorously comparative biology and biomedicine, operating at multiple levels of

organization and analysis, and grounded in both ecological context and in evolutionary considerations about relatedness and divergence, can begin to shed adequate light on life itself, and on our peculiarly human form of it.

While it is of course possible to make comparisons absent evolutionary hypotheses and phylogenetic frameworks, this is not advisable as a way forward in biology and biomedicine. Neither is it advisable simply to make assumptions about evolutionary history (say, about similarity or universality of forms or functions). Taking evolution seriously is critical here (in press-a, in press-b). So too is taking development seriously (Robert, 2004a).

In the specific context of the brain sciences, Povinelli (2004) laments the current status of comparative neuroscience:

> Comparisons of the brains of humans and apes have traditionally been limited to gross considerations such as size and surface features (such as lobes and sulcus patterns). Remarkably, the details of the internal organization of human and great ape brain systems and structures have been largely ignored, in part because it's so difficult to study these brains, but also because most neuroscientists have frequently assumed that despite great differences in size, all mammalian brains are organized pretty much the same. (Povinelli, 2004, p. 31)

Continuing in the same vein, Preuss (1995, 2000, 2006) is similarly concerned about the limits of our current understanding. The abstract of his chapter in a key textbook of cognitive neurosciences exemplifies this perspective:

> Traditionally, many neuroscientists have supposed that all mammals possess variants of the same brain which differ only in size and degree of elaboration. Under this model, the brains of nonhuman species can be treated as simplified versions or models of the human brain. However, there is evidence that mammalian cerebral organization is much more variable than is commonly acknowledged. The diversity of mammalian brain organization implies that neuroscientists can make better inferences about human brain organization by comparing multiple species chosen based on their evolutionary relationships to humans, than by studying individual 'model' or 'representative' species. The existence of neural diversity also suggests that nonhuman species have evolved cognitive specializations that are absent in humans. (Preuss, 1995, p. 1227)

Accordingly, as Gilbert Gottlieb and Robert Lickliter have observed, it is ''dubious that nonhuman primates can serve as models for the most distinctive of human cognitive abilities, any more than we could serve as good models for their distinctive traits'' (Gottlieb & Lickliter, 2004, p. 317).

A rigorously comparative approach to neuroscience would overcome the limits of model organismism by beginning with an assumption of neural diversity across mammals and other animals, and by selecting a broad range of experimental organisms for study on the basis of phylogeny and not just ideology, convention, or laboratory-friendliness. The question—not the research material—would drive the investigation. Detailed analysis would be undertaken at various levels of organization across multiple disciplines, and under systematically serially varied ecological and

developmental conditions. Experimental designs would challenge key assumptions, query orthodoxies, and yield results that would reveal the virtues and biases of our current knowledge base in the neurosciences.

My claims here are not intended as a condemnation, but rather as a challenge: to reinvent the biological and biomedical research enterprise so as to generate genuine understanding of human and nonhuman-animal nature, cognition, development, and evolution, in sickness and in health. The challenge is, obviously, an immense one. Sometimes, model organisms or other animal models will prove particularly useful to the task at hand; not all research with model organisms is necessarily problematic. But where such research presumes rather than demonstrates similarity (or dissimilarity), constrains the research agenda, or otherwise biases our knowledge, a different approach is in order—as many others before me have presciently but vainly maintained. The nature of this different approach remains to be fully elucidated, in part empirically, in part conceptually, in part methodologically, but also in part ethically. For if, at the end of the day, there is no substitute for research with our closest nonhuman primate relatives or, indeed, with humans ourselves, then the *moral* and not merely epistemic justification of scientific research will take on ever greater significance.

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Notes

[1] Similarity and difference are, of course, complex concepts. Judgments of similarity or difference are a function of the resolution and the presumed background for comparison. Things that appear dramatically similar from a distance may appear totally different up close; things that appear dramatically different against one background may appear significantly similar to each other against another. Indeed, how like or unlike entities actually are may be indeterminate, subject to variation based not only on resolution and background but also methods and research strategies. This is not a problem unique to model organismism and comparative neuroscience, but rather a generic philosophical issue. Thanks to Karola Stotz for discussion of these issues (personal communication, February 27, 2008).

[2] This last point is especially important, though not unique to model organismism: any laboratory experiment involves simplification of the developmental (rearing) context, and this, too, may bias our knowledge base. Biases may occur where the simplifications are noted for the record but ignored for interpretive purposes (Robert, 2003; Robert, 2004a), or when the experimental set-up appears benign but turns out to be problematic. As an example of the latter, Gilbert (2001) reports on research with methoprene, a juvenile hormone

mimicking substance present in pesticides. The pesticides appear entirely harmless when lab organisms (in this case, *Xenopus* eggs) are exposed to them. But methoprene functions as a teratogen when exposed to sunlight, generating deformities in tadpoles in the wild. So, what we thought was true under laboratory conditions turns out to be false under ecologically realistic conditions. How widespread or significant such biases remains to be fully explored, but initial evidence suggests the need for correctives (Gilbert, 2001; West & King, 1987).

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