The squid giant axon was an important preparation for studying the mechanisms underlying action potential generation.

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REVIEW

The emperor's new wardrobe: Rebalancing diversity of animal models in neuroscience research

Michael M. Yartsev

The neuroscience field is steaming ahead, fueled by a revolution in cutting-edge technologies. Concurrently, another revolution has been underway—the diversity of species utilized for neuroscience research is sharply declining, as the field converges on a few selected model organisms. Here, from the perspective of a young scientist, I naively ask: Is the great diversity of questions in neuroscience best studied in only a handful of animal models? I review some of the limitations the field is facing following this convergence and how these can be rectified by increasing the diversity of appropriate model species. I propose that at this exciting time of revolution in genetics and device technologies, neuroscience might be ready to diversify again, if provided the appropriate support.

"These must, indeed, be splendid clothes!" thought the Emperor. "Had I such a suit, I might at once find out what men in my realms are unfit for their office, and also be able to distinguish the wise from the foolish! This stuff must be woven for me immediately." And he caused large sums of money to be given to both the weavers in order that they might begin their work directly…"But the Emperor has nothing at all on!" said a little child. "Listen to the voice of innocence!" exclaimed his father; and what the child had said was whispered from one to another.

—Hans Christian Andersen, *The Emperor's New Clothes*

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Some say it was not too long ago that young neuroscientists beginning their academic careers would first carefully define the scientific question they were interested in and then venture outside the lab in search of the most suitable model system to address it (*1*). This approach has led to some of the most foundational discoveries in the history of neuroscience, many of which have generalized to "standard model systems" (including humans) and several of which have also been awarded the Nobel Prize in recognition of their broad importance (Fig. 1). Yet in the current landscape of neuroscience research (the "emperor"), this approach is rarely practiced, as the vast majority of neuroscience focuses on a handful of standard model organisms ("the clothes"). Indeed, it has already been a decade since more than 75% of research efforts were directed to the rat, mouse, or human (*2*), and this number has likely substantially increased. In light of this remarkable convergence, one can naively ask, why? Does the standard model system approach that the neuroscience field is taking also have some limitations that we should open our eyes to and carefully consider the costs of?

This piece is not written from the 10,000-foot perspective of a senior scientist but rather from the perspective of a junior professor trying to learn from the lessons of the past and look into the future. As such, more questions than answers are raised, with the hope of starting a discussion on the most appropriate way for the field of neuroscience to move forward effectively. I discuss the reasons for the convergence in animal models and why it represents a major deviation from core principles that have successfully guided the neuroscience field. The importance of diverse and appropriate model systems is discussed with respect to function specialization, comparative approach, and the role of diversity in both basic and translational neuroscience. The interplay between the notable advantages offered by both standard and nonstandard model systems would ultimately benefit the broad neuroscientific community. Yet for such interplay to be possible, some rebalancing in the neuroscience landscape is required.

The model system approach: past, present, and why things have changed

Over 8 million species reside on our planet (*3*), each possessing specialized skills and functions that have evolved to promote survival in their natural environment. Throughout history, neuroscientists have strategically taken advantage of this diversity to study the inner workings of the brain. The first questions one might ask are, how were species chosen to serve as model systems for different studies (Fig. 1) and what were they intended to model? A potential answer is centered

around a core principle in the field of neuroethology termed Krogh's principle, which states the following: "For a large number of problems there will be some animal of choice or a few such animals on which it can be most conveniently studied" (*4*). In other words, choose the most appropriate model system for the scientific question. A wonderful example is the work of Hodgkin and Huxley who utilized the squid to understand the mechanisms of action potential generation (*5*) (Fig. 1A). This species was chosen because of the huge size of its giant axon (~1 mm in diameter), which allowed recording of electrical potentials along most of the axon. The successful implementation of this approach necessitated a careful thought process and the identification of core homologies to support the direct link between the model (the squid's giant axon, in this case) and what it was intended to model (general mechanisms of action potential generation in axons).

Considering that the approach of assigning the model system for the scientific question has been so successful, why has neuroscience gradually moved away from it? Does it not seem sensible that the model system should be chosen for the scientific question rather than the other way around? Perhaps the benefits of converging on a handful of model organisms outweigh the costs. Indeed, this convergence has enabled the rapid development of a large arsenal of tools that facilitate interrogation of neural circuits at unprecedented levels of detail. The application of these technologies to questions where they can be of value has taken an increasing and valuable role in neuroscience. Furthermore, this convergence has enabled the standardization of animal procedures, such as housing and breeding, across labs and institutions, hence reducing costs and simplifying daily operations. The concentrated efforts of many laboratories utilizing similar animal models (and often asking similar questions) further facilitates collaborative efforts and provides an additional layer of scientific rigor, as findings can be carefully compared. Yet, despite these and other advantages, one might ask whether there are also limitations we fail to see or important aspects of scientific research that get lost in this process of standardization. In other words, is the emperor only partially dressed?

Is specialization of function important?

Many animals are capable of diverse sets of behaviors and functions, but it seems inherently flawed to assume that all can be studied in any single (or a few) model organism(s). This discussion varies on a continuous scale, ranging from functions which are only possessed by certain species to functions exhibited by a wide variety of organisms but to different degrees of specialization.

At the extreme end are functions that standard animal models simply do not possess. In such cases, converging on the standard model system approach implies that these functions will not be studied. One example is the capacity of vocal learning, the core mechanism believed to underlie the human ability to acquire a language (*6*). Although humans are expert vocal learners, a remarkably sparse subset of animals share this capacity (*6*–*9*), which has only been demonstrated in songbirds (*6*) and, among mammals, potentially only demonstrated in cetaceans (*7*), elephants (*8*), nonhuman primates (*10*), and bats (*11*). The neural mechanisms supporting this function have been primarily studied in songbirds (*6*). The development of genetic and device technologies in nonhuman primates and bats (*12*–*14*) could enable studies in mammals for the first time. If the capacity of vocal learning is indeed limited to this set of model systems, then in their absence it will not be understood, despite its important potential relevance for humans (*15*).

But what about capacities that are possessed by many animals? Should these only be studied using standard model organisms? Such studies would also greatly benefit from the interplay between "specialist" and standard species, especially in cases where humans belong to the specialist group. Focusing exclusively on nonspecialist animal models may not only limit accurate translation to humans but further limit the development of therapeutic approaches by being blind to the solutions that specialists have found. An example is the neurobiological investigation of aging and associated neurological disorders. The life span of most animals correlates strongly with body size, such that larger species tend to live longer (*16*). Standard laboratory mammals do not deviate from this correlation (and, in some cases, fall beneath it), but some creatures do, including humans, who live longer than expected given their body mass (*16*). An extreme longevity specialist is the naked mole rat (*Heterocephalus glaber*) (*17*, *18*). Despite being the size of a mouse, it can live for over 30 years (approximately an order of magnitude longer than similarly sized rodents), making it the longest-living rodent on the planet. Understanding why these (and other) creatures live so long can provide important insights into the secrets of longevity, which may not be revealed in short-lived laboratory animals. For instance, the naked mole rat is faced with the necessity of maintaining proper health of its cells (including neurons) for decades, much like humans but unlike short-lived laboratory rodents. Indeed, studies have already begun to reveal remarkable properties that could facilitate such long-term survival of cells, including adaptations in cellular proliferation and stability of gene families involved in DNA repair and detoxification processes (*18*, *19*). Additional adaptations that have evolved in this long-lived species and are the subject of research include their extreme hypoxia tolerance (a major concern for victims of stroke, where the blood supply to the brain is interrupted), specialized nerve-fiber adaptation that enables a high tolerance for pain, and a complete immunity to cancer (*17*–*19*).

"...the vast majority of neuroscience focuses on a handful of standard model organisms..."

Following this logic, should we propose that brain function should only be studied in specialized organisms? Of course not, and, on the contrary, in cases where standard laboratory animal models provide a sensible preparation, it would be unreasonable not to capitalize on the great benefits that they provide. Yet, it is important to consider that standard laboratory model systems were not originally chosen for any particular specialized function or specific behavioral trait but rather for their breeding patterns and ease of maintenance, which were important for fields such as genetics and developmental biology (*20*, *21*). As such, there is still much to learn about these standard model systems. Taking more of an ethological approach, where the behavioral problems the animal needs to solve as well as the algorithms by which it solves them are considered, will promote a more efficient utilization of their accompanying technologies (*22*). Considering the known limitations and advantages offered by each approach, wouldn't it be most productive if these went hand in hand rather than narrowing down on the standard model system approach alone?

Is a comparative approach important?

One of the main goals of neuroscience research is to identify generalizable mechanisms that could perhaps illuminate functions (and dysfunctions) of the human brain. Thus, should we be satisfied with discoveries made in a single model organism, or is it necessary to study similar functions across a diverse set of relevant species? This captures a core concept of the comparative approach, which has traditionally served as an important tool in neuroscience (*23*, *24*). Converging on a fixed set of model organisms, either standard or not, precludes the degree to which scientific findings generalize beyond these species. In the absence of comparative studies, an entire field may be lead astray by observations that are either species specific or misinterpreted in the absence of comparative data. An example of the importance of comparative neurobiology is the study of sound localization and its underlying neural mechanisms, which are of great importance to a wide range of organisms, including humans (*25*). Initial seminal discoveries in the barn owl revealed that neural computations of this function followed nearly precisely the Jeffress model of the 1940s (*26*), which was based on coincidence detection of excitatory inputs arriving from the two ears (*25*). Yet in rodents, which have been shown to face the same challenge of sound localization [such as the Mongolian gerbil (*27*)], the problem is solved by using inhibitory inputs that adjust the temporal sensitivity of coincidence-detection neurons (*25*), thus underscoring the importance of reexamining general hypotheses across species.

Are the benefits of the comparative approach restricted to validating or disproving the generalization of scientific discoveries? Not at all—this approach also plays an inherent and crucial part in promoting the discovery itself. Such was the case in the field of adult neurogenesis, where initial findings in rodents were met with skepticism until clear evidence that new neurons are born in the adult songbird forebrain reignited the field (*23*, *28*, *29*). Development of technologies for labeling new cells in rodents and regulation of neurogenesis by factors such as stress, environmental complexity, and learning supported the existence of this phenomenon (*30*). Here, it was the complementary comparative approach between diverse model systems, technological development, and behavioral approaches that collectively gave rise to what is now one of the most prominent fields of research in neuroscience, with major implications for human health (*31*).

It is clear that the interplay between diverse species promotes scientific discovery and rigor of investigations, thus benefiting everyone involved. Often, the intensive study of a single standard model system is motivated by the belief of universal principles across species, and indeed, much success has come from this approach. Yet, as discussed above, it is important to consider that different nervous systems can reach different solutions to similar problems, and the comparative approach serves as an extremely powerful tool to assess the validity of universal principles on a case-by-case basis. In the absence of the comparative approach, many discoveries may not have occurred, would have reached the wrong conclusions, or would have taken far longer to be unveiled. None of these options is preferable for the continued and effective progression of the neuroscience field. Importantly, it makes one wonder, what else can we be missing? As will be discussed next, this question is not only applicable to basic science but also to the translational potential of neuroscience research.

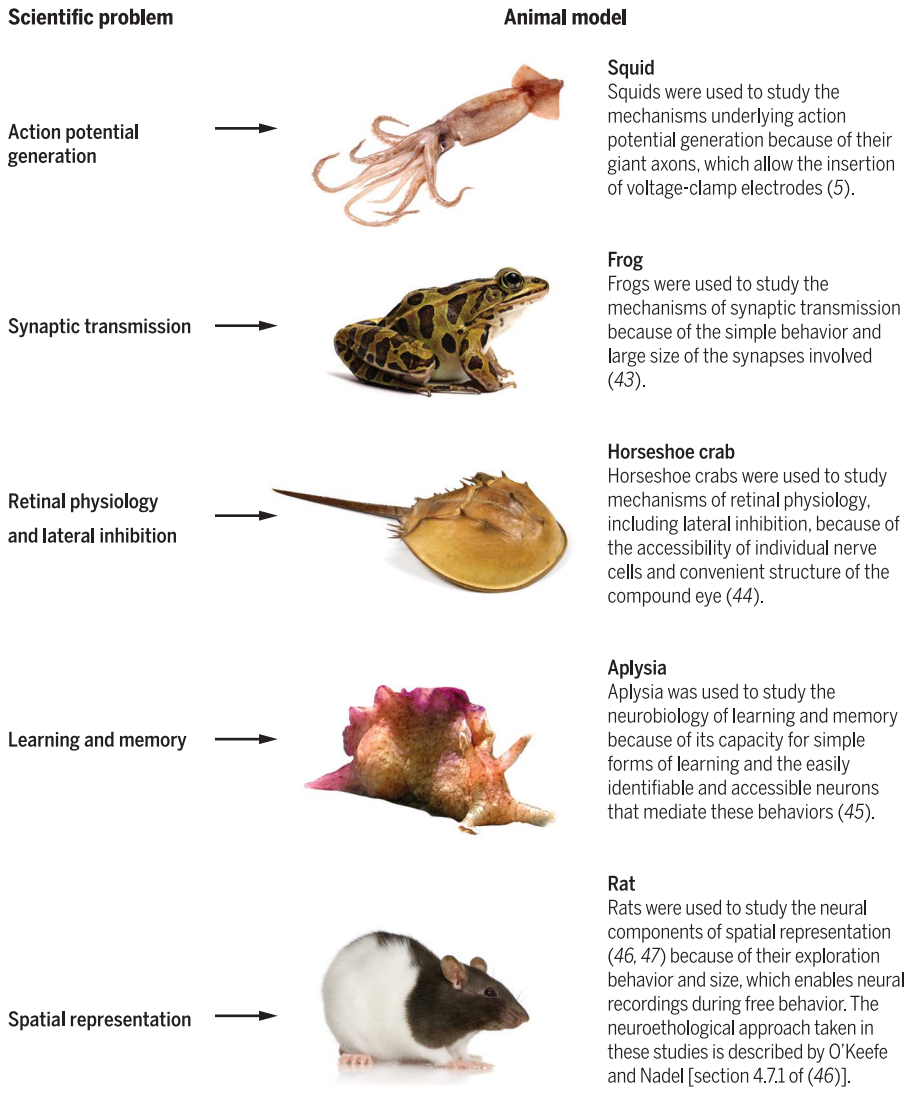

Fig. 1. Why were different animal models chosen to address different scientific problems in neuroscience? The selection process often followed a clear rationale for the advantages gained by using one model system over another and its particular appropriateness for the question at hand. A set of examples following this approach, that subsequently were awarded the Nobel Prize, are the squid, frog, horseshoe crab, aplysia, and rat. Additional foundational discoveries include (among many others) sensory processing in the weakly electric fish (*48*), odor codes in insects (*49*), reconfiguration of neural networks by neuromodulators in the lobster (*50*), nerve growth factors in chicks (*51*), γ-aminobutyric acid in the crab (*52*), channel rhodopsins in the algae (*53*), green fluorescent protein in the jellyfish (*54*), and the list goes on and on.

PHOTOS: [SQUID] JIANG HONGYAN/SHUTTERSTOCK.COM; [FROG] MICHIEL DE WIT/SHUTTERSTOCK.COM; [CRAB] ANDREW BURGESS/SHUTTERSTOCK.COM; [APLYSIA] GENEVIEVE ANDERSON; [RAT] ERIC ISSELEE/SHUTTERSTOCK.COM

Is diversity important for translational research?

One of the biggest and most heavily funded enterprises in neuroscience is the establishment of animal models, nearly exclusively transgenic mice (*Mus musculus*), for human disease. The guiding hope is that discoveries in animals will translate to successful therapeutic solutions in humans (*32*). In reality, this has not been the case, with the majority of preclinical animal studies rarely translating into successful treatment of major disorders in humans—such as neuropsychiatric disorders, neurodegenerative diseases, and others—despite vast investments of both time and money (*32*–*34*). Although this enterprise is relatively new and improved tools are continuously being incorporated, this translational gap represents one of the biggest challenges in neuroscience research (*32*). A potential major limitation of this endeavor has been the notable dissociation between laboratory animal models and humans with respect to diversity.

Effectively all laboratory mouse strains are genetically uniform, emerging from a small founder population (*20*, *35*). Deliberate human intervention has further constrained the phenotypic variability of breeders to those that would promote reproductive success in socially and environmentally deprived laboratory conditions (*35*). Yet in humans, it is precisely the diverse genetic background, individual variability, and environmental complexity that have been identified as core factors in a person's resilience or susceptibility to most Mendelian and complex diseases (*33*, *36*). This major limitation has also been explicitly recognized by the National Institute of Mental Health and is described in their strategic objectives: "While...individual variation is a source of risk and resilience for illnesses, the study of brain circuits is still focused more on group averages than on individual differences."

How can this translational gap be bridged? One avenue might be to consider that studies leveraging diversity rather than uniformity are a crucial component of translational research, as they more closely reflect the conditions in the human population, which are inherently diverse. This necessitates expanding the portfolio of utilized animal models while carefully considering their origin as well as the environmental conditions under which they are raised and tested

(*33*, *35*, *37*). Further, the full complexity of human neurological disorders is unlikely to be recapitulated by any single model system for such diseases (*32*). This suggests that different animal models are going to offer distinct advantages for studying specific aspects of complex human disorders. Ideally, such model systems should be selected after careful consideration of the etiological homologies to humans and would also likely require venturing outside of the standard laboratory mammalian domain. For example, certain types of mice [such as the white-footed mouse (*Peromyscus leucopus*)] are photoperiodic specialists and can thus very accurately estimate seasonal variations on the basis of environmental cues indicating day length. Interestingly, they exhibit several behavioral and neural phenotypes that mirror some of the etiology of human posttraumatic stress disorders (*37*) and other forms of depression linked to seasonal variations (*38*). Although these mice certainly do not recapitulate the full suite of phenotypes exhibited by human patients, they could potentially provide important insight into some specific aspects of such disorders (*37*). Thus, although lab-reared, transgenic model systems of diseases are considered the gold standard for translational research and indeed provide a wealth of knowledge, it is likely the case that diverse model systems can also provide important and etiologically relevant translational insight for understanding and curing human diseases.

"...leveraging diversity rather than uniformity..."

Is it time for rebalancing the scales, and, if so, what will it take?

The tremendous progress in genome sequencing and DNA-editing methods over the past several decades has been a major driving force in the convergence of neuroscience research on a handful of model organisms. Interestingly, the modern-day genetic revolution might just enable the field to reverse its course. The costs associated with genome sequencing are decreasing (*39*), and revolutionary DNA-editing methods that can be applied to any animal are being developed (*40*–*42*). These methods allow scientists to bypass the need to engineer germline-modified mutant strains and facilitate robust genetic access that is fast, is independent of genetic background, does not require massive inbreeding, and can thus be applied in a wide range of species (*41*, *42*).

Despite this exciting potential, in the absence of substantial support from the neuroscience community, society, and funding sources, diversifying may not be feasible because of the large overhead associated with establishing nonstandard model systems in the current landscape of neuroscience research. There is increasing pressure from society through governmental regulation and funding agencies to limit research to a handful of model organisms. In parallel, neuroscience has entered an industrialized era where animal facilities are largely equipped to handle standard model systems, scientists are expected to rapidly obtain data (often of a translational nature) to compete for limited funding resources, and academic promotion is tightly coupled to a rapid, high-impact publication rate. This operational model is not compatible with the considerable time and financial investment that is often required for establishing an innovative research program utilizing a nontraditional model system for which an immediate return cannot be promised. The specific details of such efforts can vary from one case to another but can be composed of difficulties in obtaining animal subjects, establishing appropriate custom facilities and operational procedures, meeting governmental regulation, performing a careful and detailed analysis of the new model organism, establishing necessary technologies for executing the research, and dealing with other challenges that one does not commonly need to overcome when utilizing a standard model system. As discussed above, in many cases the benefits of this process can outweigh the costs, but such efforts will likely require dedicated funding and academic support to encourage scientists willing to undertake this challenge.

To conclude, we ask one last question, which is perhaps the most difficult one: What should a scientist looking 30 years into the future do? There are probably many answers to this question, but most will likely agree that there are no easy shortcuts for scientific discovery, and in many cases, the long path inevitably passes through a junction where an appropriate model system needs to be carefully selected. Assessing both the feasibility of the model system as well as the evidence supporting its relevance are likely excellent filters for assigning a particular organism to the scientific question at hand. What is important to realize (and what might not be entirely evident in the eyes of young neuroscientists these days) is that there is a choice. One can, and should, be given the option to think carefully and select the model system for the scientific question rather than feeling compelled to select the scientific question for the model system. As discussed here, stepping outside of the box is of great importance for the successful progression of neuroscience research, at the levels of both basic and translational science. Well-thought-out and carefully assessed diversification in animal models can provide exceptional insight into core scientific problems that are more difficult or less appropriate to study using standard model systems, and the two approaches can complement each other well. From the perspective of a junior professor navigating these issues, I propose that the emperor would greatly benefit from adding more appropriate clothes to its wardrobe for the overall benefit of the neuroscience research community.

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