

## EDITORIAL

# The Power of Diversity in Neuroscience Research Models

Abhishek Banerjee<sup>1,2</sup>  | Emmanouil Froudarakis<sup>2,3,4</sup>  | Georgia Rapti<sup>2,5,6</sup> | Lisa Genzel<sup>2,7</sup> | Nikolaos Konstantinides<sup>2,8</sup> 

<sup>1</sup>Adaptive Decisions Lab, Barts and Queen Mary University of London and the University of Oxford, London, UK | <sup>2</sup>Scholar FENS-KAVLI Network of Excellence, Brussels, Belgium | <sup>3</sup>Foundation for Research and Technology Hellas, Institute of Molecular Biology and Biotechnology, Heraklion, Greece | <sup>4</sup>Faculty of Medicine, University of Crete, Heraklion, Greece | <sup>5</sup>Developmental Biology Unit, European Molecular Biology Laboratory, Heidelberg, Germany | <sup>6</sup>ULB Neuroscience Institute (UNI), Université Libre Bruxelles (ULB), Brussels, Belgium | <sup>7</sup>Donders Institute, Radboud University, Nijmegen, the Netherlands | <sup>8</sup>Institut Jacques Monod, Université Paris Cité, CNRS, Paris, France

**Correspondence:** Nikolaos Konstantinides ([nikos.konstantinides@ijm.fr](mailto:nikos.konstantinides@ijm.fr))

**Received:** 10 July 2025 | **Revised:** 12 December 2025 | **Accepted:** 23 December 2025

**Associate Editor:** Yoland Smith

## ABSTRACT

Neuroscience thrives on diversity—not only in the questions it asks but also in the models it uses to explore them. Across the field, different animal models have played pivotal roles in uncovering the principles governing brain function, development, and disease. Yet, the choice of model organisms remains a subject of debate. This editorial highlights the importance of embracing a wide range of animal models in neuroscience research. Each model offers unique strengths aligned with particular experimental approaches and scientific questions, contributing complementary insights that no single species alone can provide. By leveraging this diversity, we can achieve a more comprehensive understanding of the brain across levels of organization, from molecular pathways to behavioral outputs at the organismal level. Beyond the scientific advantages, we also discuss ethical and practical considerations: A diverse approach can promote responsible animal use by tailoring species choice to specific research goals. It can also foster environmental sustainability by avoiding unnecessary duplication of effort and resources. We call on neuroscientists to reflect on the value of integrating insights across species and experimental approaches. By moving beyond entrenched preferences and disciplinary silos, the field can unlock new opportunities for discovery. In championing the use of diverse animal models, we aim to inspire a more inclusive, efficient, and impactful neuroscience that rises to the complexity of its subject.

## 1 | Introduction

Neuroscience thrives on diversity—not only in the questions it asks but also in the models it uses to explore them. Across the field, different animal models have played pivotal roles in uncovering the principles governing brain function, development, and disease. Yet, the choice of model organisms remains a subject of debate. This editorial highlights the importance of embracing a wide range of animal models in neuroscience research. Each model offers unique strengths aligned with particular experimental approaches and scientific questions, contributing complementary insights that no single species alone can provide. By

leveraging this diversity, we can achieve a more comprehensive understanding of the brain across levels of organization, from molecular pathways to behavioral outputs at the organismal level. Beyond the scientific advantages, we also discuss ethical and practical considerations: A diverse approach can promote responsible animal use by tailoring species choice to specific research goals. It can also foster environmental sustainability by avoiding unnecessary duplication of effort and resources. We call on neuroscientists to reflect on the value of integrating insights across species and experimental approaches. By moving beyond entrenched preferences and disciplinary silos, the field can unlock new opportunities for discovery. In championing the

**Abbreviations:** iPSCs, induced pluripotent stem cells.

Abhishek Banerjee, Emmanouil Froudarakis, Georgia Rapti, and Nikolaos Konstantinides contributed equally to this study.

use of diverse animal models, we aim to inspire a more inclusive, efficient, and impactful neuroscience that rises to the complexity of its subject.

## 2 | Contribution of Diverse Animals in Different Areas of Neuroscience

### 2.1 | Cellular and Developmental Neuroscience

Cellular and developmental neuroscience, which flourished in the 20th century, has been shaped by a variety of model organisms. The development of neural circuits—segmentation, patterning, neurogenesis, differentiation, guidance, connectivity, and plasticity—has been elucidated by complementary contributions from various models. Examining key discoveries can illuminate how diverse models enable a comprehensive understanding of neuroscience.

Neurulation and segmentation, early neural patterning steps, are regulated by Hedgehog, Wnt, and Notch pathways, discovered in *Drosophila* (Nüsslein-Volhard and Wieschaus 1980), and further studied in *Caenorhabditis elegans* and mice (Whangbo and Kenyon 1999; Aguirre et al. 2010; Conlon et al. 1995; McMahon and Bradley 1990; Echelard et al. 1993). Hox transcription factors, key in patterning, were found in *Drosophila* (1995 Nobel Prize) and further explored in the zebrafish nervous system (Akimenko et al. 1994; Lewis 1978). *Xenopus* research advanced knowledge on neural tube formation by BMP signaling, previously discovered in mice (Sasai et al. 1995; Urist 1965).

Neural cell birth relies on asymmetric cell division via neuroblast stem cells and proneural genes discovered in *Drosophila* (Doe and Bowerman 2001) and on the roles of nerve growth factor which was discovered in mouse studies (Cohen and Levi-Montalcini 1956) (1986 Nobel Prize). Otherwise, neural crest cell migration contributing to neural cell differentiation benefited from studies in *Gallus* chick embryos (Nakagawa and Takeichi 1995). Recent studies uncovered how radial glial cells control neuronal birth in the mouse while they were first suggested as neural precursors in songbirds. Moreover, current studies in human iPSCs and organoids model early neurogenesis for studying disorders and drug discovery (Pasca et al. 2015). Adding to embryonic neurogenesis, adult neurogenesis was identified in songbirds (zebra finches) (Nottebohm 2002) and then examined across vertebrates (Kuhn et al. 2018). Programmed cell death, also essential for neurodevelopment, was genetically dissected in *C. elegans* (2002 Nobel Prize) to then prove conserved across models (Ellis and Horvitz 1986).

Neural cell fate specification ensures circuit complexity. *C. elegans* studies revealed that diversification is driven by transcription factor codes (Hobert 2008) and microRNAs (2024 Nobel Prize) (Lee and Ambros 2001). Powerful lineage-tracing methods in chick-quail interspecies chimeras revolutionized our understanding of neural crest development and cell fate in the nervous system (Le Douarin 1973). Sea urchins contributed to understanding gene regulatory networks, with mouse studies integrating these insights into stem cell division and cortical layering (Cui et al. 2014; Molyneaux et al. 2007). Recent work also uncovered diversification mechanisms in glial cells (Kriegstein

and Götz 2003), the often-overlooked half of the nervous system, nowadays an emerging frontier.

Neural morphogenesis and formation, driven by axon guidance and synaptogenesis, are essential for circuit functionality. Guidance cues like Netrin and *Robo/Roundabout* were first identified and mechanistically dissected in invertebrates *C. elegans* and *Drosophila* and mouse studies for their pathfinding roles (Kidd et al. 1999; Hedgecock et al. 1990; Kolodkin and Tessier-Lavigne 2011). *Xenopus* and *Gallus* helped characterize additional guidance factors (Ephrin and Semaphorin) (Frisén et al. 1998; Weigl et al. 2003). Studies also revealed synaptogenic roles for the guidance cues Netrin and Ephrin in *C. elegans*, *Xenopus*, *Danio* (Manitt et al. 2009). Synaptic architecture is also dependent on Neurexins and SynCAMs—discovered in rodents and studied across species. Other molecules driving synaptic architecture—LRRTMs, (proto)cadherins, neuroligins, and neuropilins—were first studied in vertebrates (De Wit and Ghosh 2015; Yamagata et al. 2003). Nervous system development culminates in connectome assembly. *C. elegans* produced the first mapped connectome (White et al. 1986). This complements recent connectomes that reveal neural network organization, individuality, plasticity, and sex-dimorphic features (Cook et al. 2019; Witvliet et al. 2021). Ongoing connectomics studies in *Drosophila*, zebrafish, and mice aim to map complex networks and enable cross-species comparisons (Kasthuri et al. 2015; Hildebrand et al. 2017; Zheng et al. 2018; Dorkenwald et al. 2024; Schlegel et al. 2024).

Synaptic function and plasticity rely on neurotransmitter receptors. While most were discovered in rodents (e.g., receptors for acetylcholine, dopamine, histamine, GABA, glutamate, glycine, adrenergic, and purinergic signaling), serotonin receptors were first identified in *Drosophila* (Saudou et al. 1992) and nicotinic acetylcholine receptors in the electric ray Torpedo (Changeux et al. 1970). Studies in frontier models also deepened our understanding of synaptic function in vivo, including the discovery of how neurotransmitter release modulates synaptic efficacy and affects learning habituation and sensitization by research in the sea slug *Aplysia* (2000 Nobel Prize) (Kandel 2001).

The continued use of diverse models advances frontier research areas, including neural regeneration and glial biology. Regeneration studies in *Danio* and planarians provide insights into stem cell proliferation and repair. Glial studies in *Drosophila* (in synaptic development and whole-organism behavior circadian rhythms), *C. elegans* (glia-neuron signaling), *Xenopus* and *Danio* (glial roles in neurogenesis/myelination), and rodents (glial contributions to plasticity and psychiatric disorders) further highlight the value of comparative models (Fields and Stevens-Graham 2002; Rapti 2023; Singhvi et al. 2024). Together, these organisms remain essential for unravelling how neural circuits form, function, and adapt.

### 2.2 | Evolutionary Neuroscience

Research across a wide array of animal species has been pivotal in advancing *evolutionary neurobiology* and *ecology*. By comparing the nervous systems and behaviors of diverse organisms, we can uncover how ecological pressures shape the

evolution of brain structure, function, and plasticity—and how these adaptations support survival and reproduction in distinct environments.

Insects like *Drosophila melanogaster* have been central to understanding the evolutionary conservation and divergence of neural circuits (Perry et al. 2017). For example, comparative studies between *D. melanogaster* and other drosophilids have shown how ancestral neural circuits can be co-opted to produce novel behaviors in different species (Seeholzer et al. 2018; Ding et al. 2016; Sato et al. 2020). Work in nematodes, such as *C. elegans* and *Pristionchus pacificus*, has allowed researchers to trace the evolution of neural circuits by comparing connectomes across species (Cook et al. 2024). This approach reveals how small modifications in wiring patterns or neuron types correspond to behavioral innovations, shedding light on how neural complexity scales with ecological specialization. From a more evolutionarily distant perspective, cephalopods represent an independent experiment in large-brained, behaviorally complex animals. Their radically different body plans and neural architectures allow us to test which aspects of cognition and brain organization are convergent—offering rare comparative leverage on the evolution of intelligence outside the vertebrate lineage (Albertin and Katz 2023).

Among vertebrates, *D. rerio* (zebrafish) and related teleost species provide a powerful platform to examine how gene duplications—such as those resulting from whole-genome duplication events—can lead to the diversification of brain regions and functions. Avian models have also been key to evolutionary neuroscience. In migratory birds, the hippocampus is expanded as a product of enhanced neurogenesis that is associated with long-distance navigation (Pravosudov et al. 2006). Hence, comparative analyses across species with different ecological niches (e.g., migratory vs. resident birds) provide insights into how spatial memory and navigation circuits evolve in response to life-history demands. Similarly, songbirds offer another evolutionary window: Vocal learning, a rare trait in animals, has evolved independently in different lineages of birds and mammals (Nowicki and Searcy 2014). Neuroanatomical and genetic comparisons across vocal and nonvocal learners allow us to trace convergent evolution in brain regions and gene expression underlying complex communicative behavior (Johnson and Whitney 2005). More recently, single-cell transcriptomics has provided insights into the evolution of different brain structures in amniotes (Tosches et al. 2018; Hain et al. 2022). In mammals, studies of the evolution of neocortex development help us understand the molecular and cellular mechanisms underlying the emergence of the mammalian brain with its salient sensory, motor, and cognitive capacities (Franchini 2021). Finally, nonhuman primates have also provided critical insights into the neural basis of vocal communication, with comparative studies across species shedding light on the evolution of vocal learning, voice perception, and the circuits underlying these complex behaviors (Petkov and Jarvis 2012).

By drawing on these diverse models, evolutionary neuroscience reveals how ecological, genetic, and behavioral pressures shape the nervous system across deep evolutionary time (Konstantinides and Desplan 2025; Roberts et al. 2022). These studies not only highlight the adaptive diversity of brains and behaviors but also clarify the conserved principles that underpin neural function across the animal kingdom.

## 2.3 | Systems Neuroscience

Understanding how neurons organize into networks that allow them to perform different functions is a difficult challenge. For example, the human brain is an extraordinarily complex system. With about 100 billion neurons and over 100 trillion synapses, it outcompetes even the known universe in complexity (Vazza and Feletti 2020). Exploring the function of such a system has been of interest to humans for thousands of years, and yet we are still far from even estimating how close we are to a comprehensive understanding. Along our journey in understanding the brain, we have come to appreciate the evolutionary advantage of any nervous system, giving organisms the ability to interact with their environment in an adaptive manner. One of the key aspects is that the fundamental principles of the functionality of neural networks are conserved across species (Barron et al. 2021; Banerjee et al. 2023). Simpler neural circuits provide a far more manageable system to study, allowing researchers to focus on specific interactions and processes without the overwhelming complexity of the human brain. By studying these basic mechanisms, we can then identify and understand similar processes in the more complex human brain.

Each model has its own strengths and limitations. Model organisms such as fruit flies, zebrafish, and worms offer well-characterized systems for behavioral, genetic, and genomic research that can be applied to humans. These animals allow for robust genetic modifications, helping us to determine the roles of genes and proteins in brain function, as well as offering evolutionary perspectives that can illuminate neurological mechanisms pertinent to human brain development. Simpler circuits can also be more easily linked to specific behaviors, aiding in understanding neural control of behavior and improving the development of therapeutic strategies by accounting for genetic and environmental variability. Animals with faster generational turnover and maturation also allow researchers to study long-term neurobiological and evolutionary processes that otherwise would be hard or impossible to investigate.

Meanwhile, perception and cognition remain at the forefront of scientific inquiry and pose questions that cannot be addressed with species that have very different neural systems compared to humans. While noninvasive techniques allow the study of these brain functions directly in humans, they still lack the power of invasive methods such as electrophysiology, calcium imaging, and manipulation methods, such as optogenetics or gene therapy. Mice have been at the forefront of behavioral and systems neuroscience research due to these techniques, which are now increasingly being applied to other rodents and non-human primates. Studying species that are closely related evolutionarily allows researchers to examine how small differences in brain structure and function lead to distinct cognitive and behavioral abilities, providing insights into the neural basis of complex traits. Other than the apparent relationship between humans and nonhuman primates, small animals such as rodents can also, in many cases, serve as effective models for studying such processes. While they are generally thought to be far from the cognitive capabilities of humans, they present similarities in cognitive processing that should be systematically investigated and harnessed. In the face of their distance to human cognition, nonhuman primates remain indispensable for understanding complex brain functions, offering unique insights

into human physiology, particularly in areas like perception, cognition, and communication (Janssen et al. 2023).

Therefore, utilizing a diverse array of models enables cross-species validation that ensures a more robust and comprehensive understanding of brain function in health and disease. This facilitates technological and methodological advances that can then be applied to more complex systems and ultimately allows us to better serve humanity.

## 2.4 | Preclinical Neuroscience

Animal models have been fundamental in advancing neuroscience research for the last half century, including for understanding brain function and developing preclinical strategies for treating neurological disorders. From neurodevelopmental to neurocognitive disorders, studies primarily using rodents and, to a lesser extent, primates and other species have provided valuable insights into disease mechanisms. These insights, at multiple scales and granularity, from individual neurons to micro- and meso-scale circuits, are crucial in developing strategies for potential therapies. However, despite their contributions, the use of animal models in preclinical neuroscience remains a topic of debate due to issues of translational failure, ethical concerns, and the emergence of New Approach Methodologies that are proposed to better reflect human neurobiology.

Research using animal models has been crucial in identifying neurobiological mechanisms underlying altered neural circuit function. Many fundamental discoveries, such as the role of neurotransmitters in mood regulation and the neural circuits involved in learning and memory, were made possible through animal studies. The biological similarities between humans and certain animals, particularly in brain structure and genetic pathways, have allowed researchers to model diseases and test interventions under controlled conditions. Some aspects of the diseases can even be studied in simpler organisms (while others may not), that is, many genes for axonal development, circuit formation, or glial biology that are linked to neurological and neuropsychiatric disorders are conserved and function mechanistically similarly—even in invertebrates (Rapti 2023).

While animal models have provided invaluable insights into neuroscience and remain essential for understanding physiology and pathophysiology, the translation of these findings to effective human treatments remains a major challenge. This should not be viewed as a failure of animal research but rather as a reflection of the immense complexity involved in modelling human brain disorders. One prominent success example is the development of deep-brain stimulation (DBS) for Parkinson's disease (PD), which was developed based on decades of basic electrophysiology and anatomy studies of basal ganglia circuits in NHP, showing that lesions of the STN mitigate the core motor symptoms of PD (Bergman et al. 1990). Neurological and psychiatric disorders in humans are influenced by a complex interplay of genetics, environment, and individual experiences—factors that are difficult to replicate in animal models. While rodent models can display behaviors resembling human disease symptoms (e.g., anxiety-like or depression-like behaviors), and there are some prominent recent examples of success in translating basic

scientific research into drug discovery (Banerjee et al. 2019; Neul et al. 2023), in many cases, they fail to capture the full spectrum of complex human cognitive and emotional experiences. This complexity is especially apparent in areas like Alzheimer's disease, where many drugs that successfully reduce amyloid plaques in rodent models failed to demonstrate clinical benefit in humans. However, this discrepancy may reflect not just interspecies differences but also early assumptions about amyloid pathology as a therapeutic target—assumptions that, in hindsight, may have been overly simplistic, even within the preclinical context. Likewise, disorders such as schizophrenia involve uniquely human social and cognitive dimensions that are difficult to replicate in animals, despite useful mechanistic insights.

The high attrition rate in neurological drug development—often cited as exceeding 90%—must therefore be interpreted with caution. It reflects not only species differences but also the broader difficulties in disease modelling, biomarker identification, and outcome measure alignment across preclinical and clinical research. Drugs may fail for many different reasons at different stages of the drug development process, but often thanks to preclinical testing using animals, many potentially harmful or ineffective drug candidates are rejected. In fact, the majority of drugs that make it to human clinical trials fail not on the grounds of safety concerns but because the effect of the new drug is not as good as was hoped—or are only marginally better than existing drugs (Ineichen et al. 2024).

Recognizing these limitations, coupled with ethical concerns, should not be viewed as undermining animal research but rather as an opportunity: Integrating emerging technologies with traditional models may allow for a more nuanced understanding of neurological disorders and, therefore, offer a more effective and humane path for preclinical neuroscience research while leveraging the advantages of each model organism in a complementary manner. For example, human iPSC-derived brain organoids and assembloids now enable researchers to model disease-relevant developmental trajectories and circuit dysfunction in vitro, capturing human-specific features. These simplified neural circuits provide a powerful platform for pinpointing key disruptions and identifying potential therapeutic targets. Crucially, such findings can then be validated in living animal models, where full body–brain interactions, complex behaviors, and systemic responses can be studied, including the rescue of behavioral phenotypes. In this way, organoid-based approaches and animal research form a complementary pipeline: Organoids generate initial mechanistic insights with direct human relevance, while animal studies provide the integrative context necessary to assess functional outcomes and translational potential.

## 3 | The Complementary Nature of Diverse Models

Scientific discoveries in neuroscience necessitate a wide-ranging approach, leveraging the strengths of diverse model organisms. Each species offers unique conceptual and technical opportunities to address specific scientific questions, with its own advantages and limitations. Integrating insights from multiple models is not only complementary but also essential for constructing a holistic understanding of the nervous system across scales, from molecules to behavior.

Certain models have short life cycles, simple genomes with human homologs, and advanced genetic tools, providing unparalleled tools for high-throughput genetic manipulation and the study of conserved neural mechanisms. Their simplicity allows researchers to dissect fundamental processes, such as neural development, synaptic function, and plasticity, in ways that are often impractical in more complex organisms. These discoveries frequently inform and guide studies in vertebrates. Transparency and externally developing embryos are also key advantages of certain models (e.g., *C. elegans* and *Danio rerio*), enabling single-cell resolution studies and producing large numbers of offspring for statistical power.

Invertebrate organisms also provide genetic and physiological insights with broader impact without the ethical and regulatory burdens associated with vertebrate research (Box 1). They offer a powerful alternative to vertebrate models while aligning with the principles of Replacement, Reduction, and Refinement (3Rs). Their use reduces reliance on vertebrates (**Replacement**), minimizes animal numbers needed due to their high-throughput potential

#### BOX 1 | Ethical considerations.

The use of animals in neuroscience research provides invaluable insights into brain function that cannot be ethically or effectively obtained from human studies alone. As researchers, we rely on animal models to study complex neural mechanisms, disease processes, and potential therapies, contributing essential knowledge that informs treatments for neurological and psychiatric disorders. However, to justify the use of animals, we must demonstrate that no viable alternatives exist and that the scientific benefits of the research are significant and outweigh the ethical cost of animal use. This justification involves rigorous ethical review, adherence to the 3Rs principles (Replacement, Reduction, and Refinement), and a commitment to minimizing animal distress. To that end, using a diverse set of animals can further align with these ethical considerations to an even greater extent; excluding specific mammalian models, such as non-human primates, would itself be ethically problematic, as their unique closeness to humans makes them indispensable for probing the highly complex neural mechanisms with maximal translational relevance.

Moreover, alternative methods are gaining traction, which include some of the approaches described in detail in other sections of this review. Advances in human cell line-based research, such as induced pluripotent stem cells (iPSCs), 3D brain organoids, and computational modelling, offer promising avenues for studying neurological disorders without the ethical and translational limitations of animal models. iPSC-derived neurons allow researchers to study human-specific disease mechanisms at the cellular level, while brain organoids provide a more accurate representation of human brain development. Additionally, artificial intelligence and machine learning are revolutionizing neuroscience by analyzing large-scale patient data to identify new therapeutic targets. We believe that while some of these *ex vivo* approaches can be suitable and even preferred depending on the questions being studied, mammalian models are still indispensable in preclinical studies to investigate intact *in vivo* neural circuit function probed using neurotechnology tools, findings from which can be faithfully compared to cross-species human studies.

#### BOX 2 | An emerging need to establish more frontier organisms.

As neuroscience progresses, researchers are looking beyond traditional models into frontier species for unique insights into brain function, plasticity, and evolution. Models like mice, *Drosophila*, and *C. elegans* have driven fundamental discoveries and still do. Yet, some nonmodel organisms can reveal different evolutionary perspectives or neural adaptations inaccessible to conventional systems. For example, the large neurons of *Aplysia californica* were pivotal in discovering synaptic plasticity and memory formation (Kandel 2001). The distributed nervous system and RNA editing of *Octopus vulgaris* reshaped our understanding of intelligence and plasticity (Garrett and Rosenthal 2012). Social insects (ants, honeybees, termites) serve as models for collective cognition and social behavior (Frank and Kronauer 2024), while naked mole rats, resistant to pain and hypoxia, offer insights into neuroprotection and aging (Hadj-Moussa et al. 2021). In neuroregeneration research, *Ambystoma mexicanum* axolotls can regrow brain regions (Amamoto et al. 2016), informing stroke recovery studies. *Hydra* and tardigrades demonstrate stem-cell-based nervous system regeneration (Holstein 2023). *Ciona* tunicates and ctenophores provide different views to brain evolution (Burkhardt et al. 2023); (Mazet et al. 2005), while sea anemones *Nematostella vectensis* with their simple but plastic nerve nets advance our understanding of neuronal evolution and neuropeptide signaling (Thiel et al. 2023). Organisms from extreme environments also offer new perspectives; the blind cavefish *Astyanax mexicanus* models sensory compensation and sleep regulation, while crustaceans like mantis shrimp, with their advanced vision, offer insights into color perception and visual processing (Marshall 1988). *Torpedo* electric rays helped isolate nicotinic acetylcholine receptors (Changeux et al. 1970), laying the groundwork for modern neuropharmacology. Aging and neurodegeneration studies also benefit from frontier models. The African killifish *Nothobranchius furzeri*, with its short lifespan, aids brain aging and neurogenesis research (Tozzini et al. 2012), while the sea urchins *Strongylocentrotus purpuratus* contribute to understanding neural gene regulatory networks (Paganos et al. 2021). As neuroscience expands beyond conventional species, these organisms offer evolutionary and ecological insights that in the long-term future may uncover novel mechanisms with environmental or therapeutic potential. Importantly, new frontier organisms cannot replace established model organisms, due to the lack of standardization, background knowledge, established tools, and resources of anatomy, genome, and physiology annotations. Moreover, caution is needed to avoid fragmentation. While championing model diversity, relying solely on distinct, single, or distant frontier organisms without cross-species investigations that include organisms with widely characterized physiology presents the risk to increase result variability and hinder our ability to identify broadly applicable principles of nervous system biology. Science thrives on replication and the cumulative building of knowledge, which depends on the integration of findings across organisms. Therefore, while frontier species enrich our perspectives and reveal unique biological mechanisms, they should complement—rather than replace—the foundational role of established model organisms. Striking this balance is crucial to maintaining both innovation and cohesion within the neuroscience community.

(**Reduction**), and eliminates concerns about invasive procedures (**Refinement**). Embracing invertebrates as complementary to vertebrate models can advance biomedical discovery while aligning with ethical and sustainable research.

On the other hand, rodents and other mammals produce fewer offspring and are less accessible for large-scale genetics and imaging studies but have greater genetic and physiological similarity to humans, making them more suitable for disease studies and modelling. Rodents, particularly mice and rats, have been instrumental in uncovering the cellular and circuit-level dynamics of the brain. With their well-characterized genomes and advanced tools for imaging and genetic modification, they serve as a bridge between basic molecular insights and more complex, translational questions.

Furthermore, integrating frontier organism research (see Box 2) with established model organism research may reveal new principles of nervous system biology in diverse ecological and evolutionary levels, while providing the tools to dissect mechanisms in detail. These nontraditional models, such as songbirds for vocal learning or bats for spatial navigation, show how species-specific adaptations illuminate broader principles of neural function and evolution. Marine species like zebrafish and octopuses, as well as unique mammals such as naked mole rats, further exemplify the breadth of questions that can be addressed by exploring animals adapted to diverse environments. Frontier species may inspire hypotheses, but model organisms are still required to validate, dissect, and mechanistically expand upon them. By combining biological diversity, from *C. elegans* to nonhuman primates and humans, with established experimental systems, neuroscience can move toward an integrative and comprehensive view of the nervous system.

The complementarity of diverse animal models lies in their ability to bridge the gap between findings across different species, each contributing critical pieces to the puzzle describing how neural circuits form, function, and adapt. Neuroscience stands to gain the most when researchers move beyond disciplinary silos and adopt a truly integrative perspective, recognizing that understanding the brain's complexity requires insights drawn from the full spectrum of life.

#### Author Contributions

**Abhishek Banerjee:** writing – original draft, writing – review and editing. **Emmanouil Froudarakis:** writing – original draft, writing – review and editing. **Georgia Rapti:** writing – original draft, writing – review and editing. **Lisa Genzel:** writing – review and editing. **Nikolaos Konstantinides:** writing – original draft, writing – review and editing.

#### Conflicts of Interest

The authors declare no conflicts of interest.

#### Data Availability Statement

No datasets were generated during the current study.

#### Peer Review

The peer review history for this article is available at <https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.70384>.

#### References

- Aguirre, A., M. E. Rubio, and V. Gallo. 2010. “Notch and EGFR Pathway Interaction Regulates Neural Stem Cell Number and Self-Renewal.” *Nature* 467, no. 7313: 323–327.
- Akimenko, M. A., M. Ekker, J. Wegner, W. Lin, and M. Westerfield. 1994. “Combinatorial Expression of Three Zebrafish Genes Related to Distal-Less: Part of a Homeobox Gene Code for the Head.” *Journal of Neuroscience* 14: 3475–3486.
- Albertin, C. B., and P. S. Katz. 2023. “Evolution of Cephalopod Nervous Systems.” *Current Biology* 33: R1087–R1091.
- Amamoto, R., V. G. L. Huerta, E. Takahashi, et al. 2016. “Adult Axolotls Can Regenerate Original Neuronal Diversity in Response to Brain Injury.” *eLife* 5: e13998.
- Banerjee, A., M. T. Miller, K. Li, M. Sur, and W. E. Kaufmann. 2019. “Towards a Better Diagnosis and Treatment of Rett Syndrome: A Model Synaptic Disorder.” *Brain* 142: 239–248.
- Banerjee, A., B. A. Wang, J. Teutsch, F. Helmchen, and B. Pleger. 2023. “Analogous Cognitive Strategies for Tactile Learning in the Rodent and Human Brain.” *Progress in Neurobiology* 222: 102401.
- Barron, H. C., R. B. Mars, D. Dupret, J. P. Lerch, and C. Sampaio-Baptista. 2021. “Cross-Species Neuroscience: Closing the Explanatory Gap.” *Philosophical Transactions of the Royal Society B* 376: 20190633.
- Bergman, H., T. Wichmann, and M. R. DeLong. 1990. “Reversal of Experimental Parkinsonism by Lesions of the Subthalamic Nucleus.” *Science* 1979, no. 249: 1436–1438.
- Burkhardt, P., J. Colgren, A. Medhus, et al. 2023. “Syncytial Nerve Net in a Ctenophore Adds Insights on the Evolution of Nervous Systems.” *Science* 1979, no. 380: 293–297.
- Changeux, J. P., M. Kasai, and C. Y. Lee. 1970. “Use of a Snake Venom Toxin to Characterize the Cholinergic Receptor Protein\*.” *Proceedings of the National Academy of Sciences* 67: 1241–1247.
- Cohen, S., and R. Levi-Montalcini. 1956. “A Nerve Growth-Stimulating Factor Isolated From Snake Venom.” *Proceedings of the National Academy of Sciences* 42: 571–574.
- Conlon, R. A., A. G. Reaume, and J. Rossant. 1995. “Notch1 Is Required for the Coordinate Segmentation of Somites.” *Development* 121: 1533–1545.
- Cook, S. J., T. A. Jarrell, C. A. Brittin, et al. 2019. “Whole-Animal Connectomes of Both *Caenorhabditis elegans* Sexes.” *Nature* 571, no. 7763: 63–71.
- Cook, S. J., C. A. Kalinski, C. M. Loer, et al. 2024. Comparative Connectomics of Two Distantly Related Nematode Species Reveals Patterns of Nervous System Evolution. bioRxiv 2024.06.13.598904. <https://doi.org/10.1101/2024.06.13.598904>.
- Cui, M., N. Siriwon, E. Li, E. H. Davidson, and I. S. Peter. 2014. “Specific Functions of the Wnt Signaling System in Gene Regulatory Networks Throughout the Early Sea Urchin Embryo.” *Proceedings of the National Academy of Sciences of the United States of America* 111: E5029–E5038.
- De Wit, J., and A. Ghosh. 2015. “Specification of Synaptic Connectivity by Cell Surface Interactions.” *Nature Reviews Neuroscience* 17, no. 1: 4.
- Ding, Y., A. Berrocal, T. Morita, K. D. Longden, and D. L. Stern. 2016. “Natural Courtship Song Variation Caused by an Intronic Retroelement in an Ion Channel Gene.” *Nature* 536: 329–332.
- Doe, C. Q., and B. Bowerman. 2001. “Asymmetric Cell Division: Fly Neuroblast Meets Worm Zygote.” *Current Opinion in Cell Biology* 13: 68–75.
- Dorckenwald, S., A. Matsliah, A. R. Sterling, et al. 2024. “Neuronal Wiring Diagram of an Adult Brain.” *Nature* 634: 124–138.
- Echelard, Y., D. J. Epstein, B. St-Jacques, et al. 1993. “Sonic Hedgehog, a Member of a Family of Putative Signaling Molecules, Is Implicated in the Regulation of CNS Polarity.” *Cell* 75: 1417–1430.

- Ellis, H. M., and H. R. Horvitz. 1986. "Genetic Control of Programmed Cell Death in the Nematode *C. elegans*." *Cell* 44: 817–829.
- Fields, R. D., and B. Stevens-Graham. 2002. "New Insights Into Neuron-Glia Communication." *Science* 298: 556–562.
- Franchini, L. F. 2021. "Genetic Mechanisms Underlying Cortical Evolution in Mammals." *Frontiers in Cell and Development Biology* 9: 591017.
- Frank, D. D., and D. J. C. Kronauer. 2024. "The Budding Neuroscience of Ant Social Behavior." *Annual Review of Neuroscience* 47: 167–185.
- Frisén, J., P. A. Yates, T. McLaughlin, G. C. Friedman, D. D. M. O'Leary, and M. Barbacid. 1998. "Ephrin-A5 (AL-1/RAGS) Is Essential for Proper Retinal Axon Guidance and Topographic Mapping in the Mammalian Visual System." *Neuron* 20: 235–243.
- Garrett, S., and J. J. C. Rosenthal. 2012. "RNA Editing Underlies Temperature Adaptation in K<sup>+</sup> Channels From Polar Octopuses." *Science* 1979, no. 335: 848–851.
- Hadj-Moussa, H., M. E. Pamerter, and K. B. Storey. 2021. "Hypoxic Naked Mole-Rat Brains Use microRNA to Coordinate Hypometabolic Fuels and Neuroprotective Defenses." *Journal of Cellular Physiology* 236: 5080–5097.
- Hain, D., T. Gallego-Flores, M. Klinkmann, et al. 2022. "Molecular Diversity and Evolution of Neuron Types in the Amniote Brain." *Science* 377: eabp8202.
- Hedgecock, E. M., J. G. Culotti, and D. H. Hall. 1990. "The unc-5, unc-6, and unc-40 Genes Guide Circumferential Migrations of Pioneer Axons and Mesodermal Cells on the Epidermis in *C. elegans*." *Neuron* 4: 61–85.
- Hildebrand, D. G. C., M. Cicconet, R. M. Torres, et al. 2017. "Whole-Brain Serial-Section Electron Microscopy in Larval Zebrafish." *Nature* 545, no. 7654: 345–349.
- Hobert, O. 2008. "Regulatory Logic of Neuronal Diversity: Terminal Selector Genes and Selector Motifs." *Proceedings of the National Academy of Sciences of the United States of America* 105: 20067–20071.
- Holstein, T. W. 2023. "The Hydra Stem Cell System – Revisited." *Cells and Development* 174: 203846.
- Ineichen, B. V., E. Furrer, S. L. Grüniger, W. E. Zürrer, and M. R. Macleod. 2024. "Analysis of Animal-to-Human Translation Shows That Only 5% of Animal-Tested Therapeutic Interventions Obtain Regulatory Approval for Human Applications." *PLoS Biology* 22: e3002667.
- Janssen, P., T. Isa, J. Lanciego, et al. 2023. "Visualizing Advances in the Future of Primate Neuroscience Research." *Current Research in Neurobiology* 4: 100064.
- Johnson, F., and O. Whitney. 2005. "Singing-Driven Gene Expression in the Developing Songbird Brain." *Physiology & Behavior* 86, no. 390: 398.
- Kandel, E. R. 2001. "The Molecular Biology of Memory Storage: A Dialogue Between Genes and Synapses." *Science* 1979, no. 294: 1030–1038.
- Kasthuri, N., K. J. Hayworth, D. R. Berger, et al. 2015. "Saturated Reconstruction of a Volume of Neocortex." *Cell* 162: 648–661.
- Kidd, T., K. S. Bland, and C. S. Goodman. 1999. "Slit Is the Midline Repellent for the Robo Receptor in *Drosophila*." *Cell* 96: 785–794.
- Kolodkin, A. L., and M. Tessier-Lavigne. 2011. "Mechanisms and Molecules of Neuronal Wiring: A Primer." *Cold Spring Harbor Perspectives in Biology* 3: 1–14.
- Konstantinides, N., and C. Desplan. 2025. "Neuronal Circuit Evolution: From Development to Structure and Adaptive Significance." *Cold Spring Harbor Perspectives in Biology* 17, no. 5: a041493. <https://doi.org/10.1101/cshperspect.a041493>.
- Kriegstein, A. R., and M. Götz. 2003. "Radial Glia Diversity: A Matter of Cell Fate." *Glia* 43: 37–43.
- Kuhn, H. G., T. Toda, and F. H. Gage. 2018. "Adult Hippocampal Neurogenesis: A Coming-of-Age Story." *Journal of Neuroscience* 38: 10401–10410.
- Le Douarin, N. 1973. "A Biological Cell Labeling Technique and Its Use in Experimental Embryology." *Developmental Biology* 30: 217–222.
- Lee, R. C., and V. Ambros. 2001. "An Extensive Class of Small RNAs in *Caenorhabditis elegans*." *Science* 1979, no. 294: 862–864.
- Lewis, E. B. 1978. "A Gene Complex Controlling Segmentation in *Drosophila*." *Nature* 276, no. 5688: 565–570.
- Manitt, C., A. M. Nikolakopoulou, D. R. Almarino, S. A. Nguyen, and S. Cohen-Cory. 2009. "Netrin Participates in the Development of Retinotectal Synaptic Connectivity by Modulating Axon Arborization and Synapse Formation in the Developing Brain." *Journal of Neuroscience* 29: 11065–11077.
- Marshall, N. J. 1988. "A Unique Colour and Polarization Vision System in Mantis Shrimps." *Nature* 333, no. 6173: 557–560.
- Mazet, F., J. A. Hutt, J. Milloz, J. Millard, A. Graham, and S. M. Shimeld. 2005. "Molecular Evidence From *Ciona intestinalis* for the Evolutionary Origin of Vertebrate Sensory Placodes." *Developmental Biology* 282: 494–508.
- McMahon, A. P., and A. Bradley. 1990. "The Wnt-1 (Int-1) Proto-Oncogene Is Required for Development of a Large Region of the Mouse Brain." *Cell* 62: 1073–1085.
- Molyneaux, B. J., P. Arlotta, J. R. L. Menezes, and J. D. Macklis. 2007. "Neuronal Subtype Specification in the Cerebral Cortex." *Nature Reviews Neuroscience* 8: 427–437.
- Nakagawa, S., and M. Takeichi. 1995. "Neural Crest Cell-Cell Adhesion Controlled by Sequential and Subpopulationspecific Expression of Novel Cadherins." *Development* 121: 1321–1332.
- Neul, J. L., A. K. Percy, T. A. Benke, et al. 2023. "Trofinetide for the Treatment of Rett Syndrome: A Randomized Phase 3 Study." *Nature Medicine* 29, no. 6: 1468–1475.
- Nottebohm, F. 2002. "Neuronal Replacement in Adult Brain." *Brain Research Bulletin* 57: 737–749.
- Nowicki, S., and W. A. Searcy. 2014. "The Evolution of Vocal Learning." *Current Opinion in Neurobiology* 28: 48–53.
- Nüsslein-Volhard, C., and E. Wieschaus. 1980. "Mutations Affecting Segment Number and Polarity in *Drosophila*." *Nature* 287, no. 5785: 795–801.
- Paganos, P., D. Voronov, J. Musser, D. Arendt, and M. I. Arnone. 2021. "Single Cell rna Sequencing of the Strongylocentrotus Purpuratus Larva Reveals the Blueprint of Major Cell Types and Nervous System of a Nonchordate Deuterostome." *eLife* 10: e70416.
- Pasca, A. M., S. A. Sloan, L. E. Clarke, et al. 2015. "Functional Cortical Neurons and Astrocytes From Human Pluripotent Stem Cells in 3D Culture." *Nature Methods* 12, no. 7: 671–678.
- Perry, M., N. Konstantinides, F. Pinto-Teixeira, and C. Desplan. 2017. "Generation and Evolution of Neural Cell Types and Circuits: Insights From the *Drosophila* Visual System." *Annual Review of Genetics* 51: 501–527.
- Petkov, C. I., and E. D. Jarvis. 2012. "Birds, Primates, and Spoken Language Origins: Behavioral Phenotypes and Neurobiological Substrates." *Frontiers in Evolutionary Neuroscience* 4: 20259.
- Pravosudov, V. V., A. S. Kitaysky, and A. Omanska. 2006. "The Relationship Between Migratory Behaviour, Memory and the Hippocampus: An Intraspecific Comparison." *Proceedings of the Royal Society B: Biological Sciences* 273: 2641–2649.
- Rapti, G. 2023. "Regulation of Axon Pathfinding by Astroglia Across Genetic Model Organisms." *Frontiers in Cellular Neuroscience* 17: 1241957.

- Roberts, R. J. V., S. Pop, and L. L. Prieto-Godino. 2022. "Evolution of Central Neural Circuits: State of the Art and Perspectives." *Nature Reviews Neuroscience* 23: 725–743. <https://doi.org/10.1038/s41583-022-00644-y>.
- Sasai, Y., B. Lu, H. Steinbeisser, and E. M. De Robertis. 1995. "Regulation of Neural Induction by the Chd and Bmp-4 Antagonistic Patterning Signals in *Xenopus*." *Nature* 376, no. 6538: 333–336.
- Sato, K., R. Tanaka, Y. Ishikawa, and D. Yamamoto. 2020. "Behavioral Evolution of *Drosophila*: Unraveling the Circuit Basis." *Genes* 11, no. 2: 157. <https://doi.org/10.3390/genes11020157>.
- Saudou, F., U. Boschert, N. Amlaiky, J. L. Plassat, and R. Hen. 1992. "A Family of *Drosophila* Serotonin Receptors With Distinct Intracellular Signalling Properties and Expression Patterns." *EMBO Journal* 11: 7–17.
- Schlegel, P., Y. Yin, A. S. Bates, et al. 2024. "Whole-Brain Annotation and Multi-Connectome Cell Typing of *Drosophila*." *Nature* 634: 139–152.
- Seeholzer, L. F., M. Seppo, D. L. Stern, and V. Ruta. 2018. "Evolution of a Central Neural Circuit Underlies *Drosophila* Mate Preferences." *Nature* 559: 564–569.
- Singhvi, A., S. Shaham, and G. Rapti. 2024. "Glia Development and Function in the Nematode *Caenorhabditis elegans*." *Cold Spring Harbor Perspectives in Biology* 16: a041346.
- Thiel, D., L. A. Yañez Guerra, A. Kieswetter, et al. 2023. "Large-Scale Deorphanization of *Nematostella Vectensis* Neuropeptide G Protein-Coupled Receptors Supports the Independent Expansion of Bilaterian and Cnidarian Peptidergic Systems." *eLife* 12: RP90674.
- Tosches, M. A., T. M. Yamawaki, R. K. Naumann, A. A. Jacobi, G. Tushev, and G. Laurent. 2018. "Evolution of Pallium, hippocampus, and Cortical Cell Types Revealed by Single-Cell Transcriptomics in Reptiles." *Science* 360: 881–888.
- Tozzini, E. T., M. Baumgart, G. Battistoni, and A. Cellerino. 2012. "Adult Neurogenesis in the Short-Lived Teleost *Nothobranchius Furzeri*: Localization of Neurogenic Niches, Molecular Characterization and Effects of Aging." *Aging Cell* 11: 241–251.
- Urist, M. 1965. "R. Bone: Formation by Autoinduction." *Science* 1979, no. 150: 893–899.
- Vazza, F., and A. Feletti. 2020. "The Quantitative Comparison Between the Neuronal Network and the Cosmic Web." *Frontiers of Physics* 8: 525731.
- Weinl, C., U. Drescher, S. Lang, F. Bonhoeffer, and J. Löschinger. 2003. "On the Turning of *Xenopus* Retinal Axons Induced by Ephrin-A5." *Development* 130: 1635–1643.
- Whangbo, J., and C. Kenyon. 1999. "A Wnt Signaling System That Specifies Two Patterns of Cell Migration in *C. Elegans*." *Molecular Cell* 4: 851–858.
- White, J. G., E. Southgate, J. N. Thomson, and S. Brenner. 1986. "The Structure of the Nervous System of the Nematode *Caenorhabditis elegans*." *Philosophical Transactions of the Royal Society of London. B, Biological Sciences* 314: 1–340.
- Witvliet, D., B. Mulcahy, J. K. Mitchell, et al. 2021. "Connectomes Across Development Reveal Principles of Brain Maturation." *Nature* 596, no. 7871: 257–261.
- Yamagata, M., J. R. Sanes, and J. A. Weiner. 2003. "Synaptic Adhesion Molecules." *Current Opinion in Cell Biology* 15: 621–632.
- Zheng, Z., J. S. Lauritzen, E. Perlman, et al. 2018. "A Complete Electron Microscopy Volume of the Brain of Adult *Drosophila Melanogaster*." *Cell* 174: 730–743.e22.