

Editorials

Expanding the cross-species lens: Rodents in focus

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Cross-species functional neuroimaging is evolving from a niche pursuit to an emerging theme in systems neuroscience, with the potential to broaden the questions we can address about brain function through comparative work. Initially confined to studies of non-human primates, cross-species functional neuroimaging has in recent years — and in 2025 in particular — produced highly promising demonstrations of its potential when extended to rodents. In this short perspective, we highlight key achievements in this direction and discuss how the complementary insights afforded by this approach may prove useful for addressing long-standing questions in human neuroimaging.

INTRODUCTION

Human neuroimaging, notably functional magnetic resonance imaging (fMRI), has expanded enormously over the past few decades, with a progression from classical activation-based studies to detailed characterizations of intrinsic brain activity in the absence of explicit tasks, an approach known as resting-state fMRI (rsfMRI).¹⁻³ These investigations have significantly expanded our understanding of the brain's functional organization in both health and disease.^{4,5} However, despite these advances, the biological principles governing the dynamic organization of functional brain networks remain poorly understood. Addressing this gap increasingly calls for complementary studies in physiologically accessible species, such as non-human primates (NHPs) and rodents, where causal manipulations may provide direct access to underlying biology with unprecedented mechanistic specificity.

Owing to phylogenetic proximity to humans, most cross-species work has classically focused on NHPs.⁶⁻¹⁰ This line of research has been invaluable for uncovering core organizational principles of large-scale functional networks¹⁰⁻¹² and for elucidating the neurophysiological basis of the fMRI signal.¹³⁻¹⁵ However, there is now a compelling case to extend cross-species functional neuroimaging to rodents. First, rodents, and especially the mouse, are by far the most widely used mammalian model organisms in neuroscience, providing a vast experimental ecosystem that bridges molecular, circuit, and behavioral levels of investigation. Second, rodents offer an unparalleled set of shared resources and precise causal tools that can be leveraged to address

mechanistic questions currently beyond the reach of human neuroimaging.

Progress in this direction, however, has been constrained by both conceptual and practical hurdles. Given the substantial evolutionary distance between rodents and humans,¹⁶ a key conceptual challenge has been whether building a cross-species bridge between humans and rodents is meaningful in the first place. Debate persists over the neuroanatomical representation of higher cognitive processes in rodents compared to higher mammalian species,¹⁷ and differences in cortical organization,¹⁷⁻¹⁹ including the comparatively limited differentiation and expansion of higher-order cortical regions in rodents,²⁰ have put into question the interpretative value of this endeavor. From a more practical standpoint, the lack of well-defined rodent-human (and rodent-NHPs) anatomical correspondences has likewise posed a major obstacle to the extrapolation of network findings across species, limiting the possibility of morphing rodent anatomy to NHP and human brains.

BREAKING CONCEPTUAL AND TECHNICAL BARRIERS

In recent years, substantial progress has been made in overcoming these long-standing barriers. Conceptually, a growing body of work has shown that, despite evolutionary differences, it is both possible *and* meaningful to relate rodent brain networks to corresponding NHP and human systems. This shift has been enabled by initial evidence that large-

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scale functional networks such as the default-mode network,²¹⁻²³ salience network,^{21,24,25} and other distributed brain systems are evolutionarily conserved across the phylogenetic tree, spanning rodents, non-human primates and humans,²⁶⁻²⁸ and can reliably be mapped in rodents,²⁹ thus providing a common organizational scaffold that transcends regional anatomical differences. By focusing on networks rather than one-to-one regional correspondences, comparative network-based analyses can thus capture shared principles of large-scale network organization above and beyond finer-scale differences in cortical and subcortical organization.^{26,30} This framework has crucially benefited from large-scale, open-access initiatives that provide fine-grained anatomical and molecular characterization of the mouse brain, such as those spearheaded by the Allen Brain Institute.³¹ Leveraging these resources, seminal work has shown that mouse-human patterns of gene expression can be matched to obtain cross-species alignments of large anatomical regions.³² These approaches thus define a novel framework for relating network-level systems across the phylogenetic tree.

Equally important, a second conceptual leap has been the realization that rodent-human cross-species studies are not only viable, but also mechanistically informative. For example, early comparative fMRI work showed that humans and rodents harboring similar genetic mutations exhibit concordant fMRI network alterations.³³⁻³⁵ This line of inquiry underscores the possibility of using rodents to tackle mechanistic questions that at present cannot be investigated in humans.³⁶

Finally, significant technical advancements have been made towards the standardization of research procedures in rodent fMRI research.³⁷ This line of inquiry has encompassed both data acquisition,^{38,39} as well as image pre-processing and analysis.⁴⁰ These initiatives have crucially lowered barriers to entry into the field and promoted reproducibility across different research groups. Together, these advances have marked a turning point, laying the groundwork for a new phase of cross-species integration.

CROSS-SPECIES NEUROIMAGING COMES OF AGE

The last couple of years have witnessed the emergence of remarkable examples of cross-species research involving rodents. We discuss below some of this recent work (most of which is still in preprint form) that demonstrates the added value of extending functional neuroimaging to rodents.

One potentially transformative study describes an updated computational framework for matching patterns of fMRI connectivity and/or network activation between mice and humans at the whole-brain level.⁴¹ The approach described in this study compellingly integrates transcriptomic and connectome-based features of brain organization to construct a latent space that enables a seamless, bidirectional mapping of brain patterns across species. The versatility of this method was tested in three case studies (spanning resting-state organization, circuit-to-cognition inference, and translational modeling of autism), under-

scoring its utility, and the potential to serve as a next-generation platform for relating rodent and human networks within a unified framework.

Another series of remarkable cross-species neuroimaging studies have revealed a set of species-specific organizational principles of brain activity in mammals. For instance, using resting state recordings in awake humans, macaques and rodents, Griffa et al.⁴² found that humans exhibit more complex interareal information processing patterns than macaques and mice, involving parallel (rather than sequential) stream of neuronal communication. More recently, Deco et al.⁴³ used whole-brain modelling grounded in stochastic thermodynamics combined with empirical fMRI data to quantify the energetic cost of information processing across species. The authors reported that the human brain is markedly more energy efficient than that of macaques or mice. These studies are of great interest for their ability to underscore the distinctive nature of human brain activity within the broader context of mammalian evolution. In this regard, the inclusion of rodent models has been essential to generalize species-specific principles beyond the evolutionary proximity of NHPs.

While these studies revealed species-specific differences in brain organization across the phylogenetic tree, other recent studies have instead described shared features. For instance, anesthesia-induced changes in brain activity measured with resting-state fMRI revealed an evolutionarily conserved signature shared by multiple mammalian species, including mice, marmosets, macaques and humans.⁴⁴ Likewise, computational whole-brain modelling based on empirical fMRI data from humans, macaques, and mice has shown that, across all species, brain activity is best reproduced when network architectures combine modular cooperative interactions (where areas activate together) with diffuse, long-range competitive interactions (where the activation of one region coincides with the suppression of another).⁴⁵ Altogether, these studies pave the way for the use of cross-species and rodent fMRI to identify foundational principles of brain organization across the phylogenetic tree, as well as to pinpoint patterns of activity and functional motifs underlying the specificity of human brain function.

Finally, major progress has also been made in the application of cross-species fMRI to biologically decode patterns of fMRI network disruption associated with psychiatric and developmental disorders.⁴⁶ For example, using fMRI recordings in mice and people harboring comparable mutations, we recently found that, in a prevalent genetic syndrome associated with autism and schizophrenia, developmental changes in synaptic density tracked with a major reconfiguration of connectivity across puberty.⁴⁷ This study adds to earlier parallel mouse and human investigations linking fMRI hyperconnectivity to overabundant excitatory synapse density.³⁵ More recently, in a multi-site study encompassing fMRI mapping in 549 individual mice and 1,976 human participants, we showed that heterogeneous connectivity alterations observed in autism can be subdivided into distinct hypo- and hyperconnectivity subtypes, each mapping onto specific etiopathological path-

ways involving synaptic, transcriptional, and immune-related mechanisms.⁴⁸ Together, these initial studies provide proof-of-concept evidence that biologically grounded rodent imaging can be used to mechanistically decode patterns of dysconnectivity observed in humans. Combined with large-scale cross-species neuroanatomical imaging (e.g.,⁴⁹) this powerful approach may pave the way for novel strategies to stratify complex disorders, opening new avenues for future diagnostic and clinical applications.

CONCLUSION

The convergence of systems neuroscience approaches spanning basic research, neuroimaging, and clinical neurosciences is transforming how we study the brain. In this context, recent studies have brought rodents into focus as a powerful bridge that can expand cross-species investigation to lower mammalian species, and link observational findings in human neuroimaging to specific (patho)biological mechanisms. These advances highlight the potential of rodent neuroimaging as a robust translational tool, but also

as a platform poised to advance our understanding of human brain function in health and disease.

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CONFLICTS OF INTEREST

Authors declare no conflict of interest.

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