Mini Review Article

Multiscale Phenotyping of the Mouse Brain: Insights into Neurological Health and Disease: A Mini Review

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Abstract | The mouse brain serves as a pivotal model in biomedical research, offering profound insights into the structural, functional, and molecular underpinnings of neurological health and disease. This mini review explores the integration of morphological, functional, and molecular phenotyping approaches to elucidate mechanisms of disorders such as Alzheimer's disease, Parkinson's disease, and autism spectrum disorders. Gross anatomical studies, bolstered by high-resolution imaging techniques like magnetic resonance imaging (MRI) and diffusion tensor imaging (DTI), reveal structural alterations, such as hippocampal atrophy and white matter degradation, critical to neurodegenerative processes. Histological analyses, including Nissl and Golgi staining, uncover cellular and synaptic changes, while advanced tools like two-photon microscopy and optogenetics enable dynamic observation of neuronal activity in vivo. Molecular phenotyping, through transcriptomics and proteomics, identifies key pathways and disease-associated proteins, enhancing therapeutic targeting. The review also highlights adult neurogenesis, cerebrovascular dynamics, and blood-brain barrier integrity as vital research avenues, supported by genetic tools like CRISPR-Cas9 in transgenic models. Multiscale connectivity mapping and electrophysiological studies further clarify neural circuit functions, with implications for addiction and metabolic disorders. Collectively, these integrated approaches underscore the translational value of mouse brain research, advancing our understanding of neurological conditions and guiding innovative therapeutic strategies.

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Introduction

One of the most complex and vital organs in biomedical research has been the mouse brain. It is an indispensable model for understanding human neurological conditions due to its structural, functional, and molecular complexities. This has resulted in a greatly enhanced understanding of how morphological phenotyping integrates across multiple domains to play a key role in health and

disease. In particular, mouse models are crucial to further understanding neurological disorders, such as Alzheimer's disease, Parkinson's disease, and autism spectrum disorders, which are also a major focus of global health initiatives (Esquerda-Canals *et al*., 2017; Ey *et al*., 2011; Taylor *et al*., 2010). Gross anatomical studies are used to establish baseline structural parameters of the mouse brain, starting the morphological phenotyping. Delineation of brain structures and subtle morphological change of various pathologic conditions has been made possible by high-resolution imaging techniques including magnetic resonance imaging (MRI). For example, hippocampal atrophy has been observed using MRI in mouse models of Alzheimer's disease (Helpern *et al*., 2004; Jullienne *et al*., 2022). Diffusion tensor imaging (DTI) complementary techniques are used for examining white matter integrity and providing clues to neurodegenerative processes (Massalimova *et al*., 2021; Müller *et al*., 2020). Mouse brain studies addressing human neurological conditions have translational value and such imaging modalities underscore this.

Histological analyses of mouse brain

Histological analyses further complement our knowledge of the mouse brain, by allowing us to view cellular architecture and synaptic connectivity. Neuronal density, dendritic morphology, and glial cell distribution have been studied by techniques including Nissl staining, Golgi staining, and immunohistochemistry. Martínez-Cerdeño (2017) for example, describe how dendritic spine alterations, seen in mouse models of autism, point to the importance of synaptic dysfunction in neurodevelopmental disorders (Phillips and Pozzo-Miller, 2015). Similar to neuroinflammation and traumatic brain injury models, have documented glial activation, as represented by astrocyte hypertrophy and microglial proliferation (Clark *et al*., 2019; Mira *et al*., 2021). The findings show how these dynamics underlie neurological health and disease. The integration of structural and functional phenotypic with advanced imaging technologies has been enabled. Two-photon microscopy and optogenetics have transformed our capacity to view neuronal activity *in vivo* and to do so in a dynamic way. For instance, calcium transients in cortical neurons have been tracked using two-photon imaging to uncover activity patterns in mouse models of epilepsy (Grienberger *et al*., 2022; Khan *et al*., 2021). However, in contrast to optogenetics, which allows the precise modulation of neuronal circuits to disentangle causal relationships between neural activity and behavior (Marton and Sohal, 2016), optochemical tools require the use of light or other perturbations to control neurons (Ankenbruck *et al*., 2018). These technologies have proved crucial in identifying the functional correlates of morphologic abnormalities in the mouse brain.

Molecular phenotyping of mouse brain

Our understanding of the mouse brain is further complicated by the inclusion of molecular phenotyping. Key molecular pathways of brain development and disease have been identified through transcriptomic and proteomic analyses. For instance, single-cell RNA sequencing has uncovered transcriptional heterogeneity of neuronal and glial populations to give insights into cell type-specific vulnerabilities in neurodegenerative diseases (Ahmadi *et al*., 2021; He *et al*., 2024). These findings have been complemented by proteomic studies that identify disease-associated proteins, like amyloid beta in Alzheimer's disease, and alpha synuclein in Parkinson's disease (Demartini *et al*., 2014; Kasap *et al*., 2017). These molecular signatures not only provide insight into pathophysiology but also provide insight into the rational design of targeted therapeutics. Much work has been done in the study of neurogenesis that has involved integrating morphological and molecular phenotyping. The discovery of adult neurogenesis in the hippocampus of mice has challenged traditional notions of brain plasticity and suggests that the adult brain is capable of neural repair (Fares *et al*., 2019; Lledo *et al*., 2006). The proliferation and differentiation of neural progenitor cells have been studied morphologically, and molecular analyses have identified such pathways as the Wnt and Notch pathways that regulate this process (Cardozo *et al*., 2011). This research is clinically relevant because dysregulation of these pathways has been linked to psychiatric disorders such as depression (Ramachandran *et al*., 2021). Studies of cerebrovascular dynamics and blood-brain barrier (BBB) integrity have also been facilitated by mouse models. Electron microscopy-based morphological phenotyping has delineated the ultrastructural organization of the BBB and molecular studies have identified key regulators of barrier function, such as tight junction proteins and transporters (Krueger *et al*., 2019). The importance of this research for the development of targeted therapies is underscored by the disruption of BBB integrity in several neurological

disorders, including multiple sclerosis and stroke (Anwarkhan *et al*., 2024; Schreiner *et al*., 2022).

Use of advanced genetic tools

The application of advanced genetic tools in mouse brain research is one of the most promising areas. The precise manipulation of genes associated with neurological diseases has been possible with the development of transgenic and knockout mouse models. For instance, the HTT gene has been mutated using CRISPR Cas9 technology to generate mouse models of Huntington's disease as a platform to study disease progression and therapeutic intervention (Ekman *et al*., 2019; Kolli *et al*., 2017). These models demonstrate how genetic engineering can help us understand brain disorders. Our understanding of neural circuits has also been informed by the integration of multiple-scale phenotyping approaches. Connectivity patterns between brain regions have been mapped with tract tracing studies and the functional properties of these circuits have been characterized with electrophysiological recordings. For example, studies in the mesolimbic dopamine pathway in mice have helped elucidate its function in reward processing and addiction, and have provided a basis for developing treatments for substance use disorders (Sagheddu *et al*., 2015; Volkow *et al*., 2019). These results indicate the translational potential of understanding mouse brain behavior. Beyond neuroscience, mouse brain research is important for fields including immunology and endocrinology. As a critical area of study, the brain's interaction with the immune system, mediated by microglia and peripheral immune cells, has come to the fore. They offer insight into potential therapeutic targets for example, using mouse models of multiple sclerosis it has been shown that pro-inflammatory cytokines can mediate neurodegeneration (Smith *et al*., 2012). Brain function and systemic health are so interrelated that the hypothalamic regulation of metabolic processes, as studied in mouse models, has helped us understand what can happen with obesity and diabetes (Jais and Brüning, 2017; Stranahan, 2015).

Mouse brain is the foundation of biomedical research, providing exceptional insights into the structural, functional, and molecular basis of neurological health and disease. In addition to enhancing our understanding of brain disorders, this integration of multiple phenotyping approaches has provided critical guidance on therapeutic strategies, underscoring their translational value.

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Author's Contribution

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