





The field of neurogenetics: where it stands and where it is going

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Introduction

The field of Neurogenetics lies at the intersection of Neuroscience and Genetics, two rapidly advancing fields in terms of novel technology and knowledge over the last couple of decades. Neurogenetics spans the gamut of a wide range of topics and questions with the primary focus of understanding how genes control the development of the nervous system and the wide range of behavioral repertoires observed throughout the animal kingdom. The two founders of the field of Neurogenetics, Seymour Benzer and Sydney Brenner recognized more than half a century ago the power to use the tools of the microbial genetics trade, in which Benzer and Brenner were so well versed, to the question of how the nervous system develops and functions. Forward genetic screens and later reverse genetic approaches have firmly established the power of genetics in revealing fundamental insights into the brain. With the advancement of technological tools, we are able to understand with increased resolution the composition of the nervous system and construct atlases from comprehensive molecular composition of diverse neuronal and glial types, to activity maps of single neurons/ensembles, to complete connectomes of the nervous system. Genetically encoded reporters of neuronal activity are now allowing us to see the brain at work, in some organisms already with single-cell resolution on a whole nervous system angle. The cataloging of cell types and neuronal activity patterns are defining novel phenotypic spaces that can be subjected to incisive mutant analysis. Another monumental break-through has been the introduction of CRISPR-Cas9-mediated gene editing, which has started to permit non-classic model organisms to join the fray of genetic analysis.

In recognition of the prominence of this field, *GENETICS/G3* has called for submissions to a Neurogenetics Series which are published in the August issue of *GENETICS* and *G3*. We have received a large number of papers that address a number of exciting questions in the field of Neurogenetics, using a range of different model systems. The papers published in the Series touch on a wide array of problems, from nervous system

development to function. As a reflection of the overall interest in Neurogenetics, *GENETICS* has decided to launch a new, permanent section in the journal, called "Neurogenetics and Behavior". This section will publish papers that explore the genetic basis of nervous system development, function, plasticity, and animal behavior. Such studies include mechanistic genetic loss and gain of function approaches, but also the description of molecular maps of the nervous system, and employ a wide range of biological systems, from conventional invertebrate and vertebrate model systems to novel, non-conventional models.

In this introductory editorial, the section editors asked their post-doctoral trainees to discuss their vision of the field and to solicit opinions from other trainees in the field. A diverse group of over 50 students, post-docs and new PIs working on four continents and on a wide range of model systems, responded to a questionnaire asking about the most pressing questions in the field as well as the challenges that lie ahead. Below we summarize how the practitioners, the real drivers in the field who are on the experimental forefront, view the field, its potential and promises.

What is Neurogenetics?

Like the rest of the animal, the brain develops through the unfurling of genetic programs. Thus, the brain and the innate behaviors it generates can be understood through genetic approaches. As a synthesis of disciplines, the field of neurogenetics brings together geneticists and neuroscientists in pursuit of the common goal of understanding the nervous system. Within that broad definition, though, lies a wealth of diversity that reflects the richness of the broad interests and goals of the field. Many neurogeneticists are fascinated by the many mysteries of the brain and want to understand their molecular basis of nervous system development and function. Other neurogeneticists are driven to understand how the genome encodes the complexity of the nervous system and the behaviors it controls. Increasingly, the field is focused on using neurogenetic tools to understand the brain at circuit and systems levels, with much attention on defining the connected neurons

that regulate perception and behavior. Still, others are motivated by a desire to understand how changes to genes and their expression can lead to neurological disorders and, through this understanding, how they might be treated.

Current research and future challenges in Neurogenetics?

We have significantly advanced our knowledge about the contribution of genes, genetic networks, and underlying pathways in development, function, and maintenance of the nervous system. The development of new genomics technologies such as single-cell transcriptomics combined with 4D and super-resolution imaging technologies has vastly expanded the resolution with which we can visualize nervous system development and organization. In parallel, genetic approaches for visualizing neural connectivity and activity in live, behaving animals is yielding unprecedented insight into neural circuitry and function. All of these rapidly evolving approaches can, in principle, be leveraged in designing next-generation genetic screens that capture more complex and sophisticated phenotypes than has ever been possible before. A major challenge for the field will be to automate the acquisition of these phenotypic features to allow for unbiased screens. Another challenge will be to develop more precise tools to dynamically and reversibly regulate and monitor both gene expression and neuronal activity in specific neurons. Ultimately, studies at the level of genes, development, nervous system function, behavior, and aging are all fundamental to our understanding of the brain. Integrating these levels of analysis to inform one other and move the field toward a more comprehensive understanding of the nervous system is a key challenge going forward.

Understanding the function of the nervous system holistically will require the continuing development of computational tools to analyze and integrate content-rich molecular and functional atlases and connectivity maps. Novel theoretical and experimental approaches will also be necessary to translate the knowledge resulting from these large datasets into how we think about and experimentally validate the ways in which gene regulation and function translate to neuronal properties, to the establishment of circuitry, and ultimately to behavior and consciousness. The utilization of diverse model organisms has always been important in the field of genetics and neurogenetics to understand both the conserved mechanisms of neural development and function, as is evident by the demographic of our respondents, but to also to understand how evolution has resulted in the elegant mechanisms underlying the diverse behavioral outputs necessary for the individual organisms to respond to different environments. With recent advances in high-throughput sequencing and in gene editing technologies enabling the genomes of non-model and wild organisms to be easily manipulated, developing tools and technologies that can be used across systems has become a challenging task to conquer. We believe that strong research outputs from all existing model organisms and the development of

novel model organisms to explore the complexity of the animal kingdom, will be an important part in advancing our understanding of the nervous system.

Diversity in perspective comes not only from studying a range of questions about the nervous system in a range of model systems but equally from the diversity of scientists who are applying their minds to these questions. Building on the scientific and technological diversity of the field to increase demographic diversity, equity and inclusion also represents a critical imperative for the field that will deepen the impact of neurogenetics.

Many of the neurogeneticists we heard from highlighted the challenge going forward of bridging gaps: the gap between genes and behaviors; the gap between single neurons and the whole brain; and the gap between model systems, including non-traditional models. As early career researchers, the questions they plan to pursue reflect their interest in bridging these gaps, with many planning to study basic mechanisms of how the brain forms and functions, from circuit formation to neuronal cell biology to control of behavioral repertoires. A number of respondents are focused on understanding how brain function is disrupted in neurological disorders in the hope of therapeutic development while, as one respondent put it, maintaining a humanist perspective that values neural diversity and takes care to avoid stereotypes about neuro-typical versus abnormal conditions in the context of human genetics.

Concluding perspectives

Neurogenetics is a broad field employing an ever-growing repertoire of genetic tools to understand the nervous system from genes to behavior. From the conceptual beauty of genetic screens to our newfound power to manipulate genomes with ease to the depth of information arising from large scale studies to molecularly, structurally, and functionally map the nervous system, the field of neurogenetics is at the threshold of boundless discovery into how the brain is built and how it functions in health and disease. We are eager to see what this future brings!

Acknowledgments

To present a fuller picture of the field, as it is today and its aspirations for the future, we incorporated the perspectives of a diverse group of over 50 students, post-docs and new PIs, working on four continents and on a wide range of model systems. We thank them for generously sharing their thoughts on the field of neurogenetics.

Conflicts of interest

None declared.