The Neural Exposome

Neuroscience has seen explosive growth over my career. Yet our knowledge of how the brain and nervous system work is probably just a percentage point of the total. Available tools primarily drove molecular advances until recently when after 2010 powerful tools became available to study neural networks. Of the 12 Nobel prizes in neuroscience before 2010, 11 were for primarily molecular discoveries, only one was awarded for studies of systems neuroscience, the study of how circuits lead to behavior or subserve sensory processing. The tables are turning. Advances in genomics played major roles in developing the tools currently available for research in both areas of neuroscience. The NIH Brain Research through Advancing Innovative Neurotechnologies (BRAIN Initiative) and allied research has revolutionized the ability to monitor, map and manipulate neural circuits putting this area of neuroscience on par with knowledge of the molecular mechanisms involved in brain function.

A third area of neuroscience that is less well-developed is the understanding of how the brain functions in the body. Indeed the preference is often to consider the brain as autonomous. Much of neuroscience is done *in vitro,* and findings are often over generalized with respect to their role in how the nervous system works. Much of the neuroscience is done in single strains of mouse and the finding are over generalized with respect to their role in how the human nervous system works. In truth, the brain is linked continuously to other body systems through the blood brain barrier, immune system, spinal fluid/blood, and sensory/motor/enteric/autonomic nervous systems. These also link to the outside world. Sometimes they link to the outside world directly as through the nerves to the nose, gut, skin; sometimes via the blood or immune system. In addition, maybe uniquely the brain is constantly changing in response to inputs—during development, learning, memory etc. The catch word is "neuroplasticity". The extent of the variables that can influence brain function is likely infinite depending upon how they (both brain functions and variable) are classified.

Exploring this broad field of how the environment influences the functioning of the nervous system is critically important but difficult. In our research on neurological disease the contribution due to genetics has been substantial. Genetic mutations have opened mechanistic insights for disease in rare disorders. Genetically determined subsets in common disorders like Parkinson's and Alzheimers have provided clues. But now we understand the limits of genetic influence and this leaves the majority of drivers of disease to the "neuralexposome". The expectation is that the greatest drivers of neurological diseases will be differentially weighted gene-environment influence. We hope to meet these challenges of what I term, "Brain in the World" in collaboration with NIEHS. The challenges are extreme. Much of the data so far remains epidemiologic in nature, and with the exception of specific toxins the mechanistic links to disease or brain function are thin. Epidemiologic data should motivate hypothesis-driven research that leads to biosignatures and molecular targets of exposure driven pathology. How to measure the important interactions between neural tissue and components in the environment? What among the many are the important environmental exposures or so called neural exposome? Do they act alone or in combination? What is the dose, duration or the factors that contribute to vulnerability or resilience? What are the critical periods in which exposures are impactful? How do they affect neurodevelopment, neural function or disease risk? As in most aspects of neuroscience the discoveries are likely determined by the available tools. We look forward with close interactions with NIEHS as we move along this common path.