Neuron
Voices
30 THREE DECADES OF EXCITING NEUROSCIENCE SINCE 1988

Visions for the Future of Neuroscience

Neuroscience is a broad discipline that embraces technology at multiple scales to understand the brain and to develop potential therapies. Scientists share their perspectives on the evolution of neuroscience research and what excites them about the future prospects for the field.

A Basis for Mental Processes

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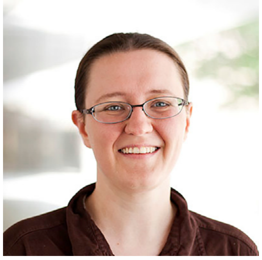
One major factor motivating neuroscience investigators is the prospect of a mechanistic basis of our own mental capacities, perceptions, and actions, both normal and dysfunctional. An abundance of transformational tools has enriched and enlarged experimental datasets, and a wealth of computational tools has emerged to help understand those datasets. Yet, how best to deploy this growing experimental and analytic arsenal toward a mechanistic understanding of the forms of mental functions we possess is an important question. It remains unclear how to optimize the choice of model species in which to pursue those mechanisms given the usual tradeoff between the availability of novel experimental tools in a given model and the relevance of that model to human behavior and mental health. Likely, too little weight is placed on the latter, as demonstrated by the low rate at which discoveries are translated into more effective treatments of mental illness. While behavioral phenotypes homologous (or analogous) to human mental functions are clearly present in simpler, evolutionarily distant species, we can be certain that the circuitry underlying those functions differs in crucial ways, a fact that is already evident in other functions (e.g., vision). But those differences need not be viewed as an inconvenience. Rather, they should be a focus of inquiry, as they are instructive about the evolution of brain circuitry.

The Fast-Moving Field of Neural Interfaces



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To quote Bill Gates, “we always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten.” This has been particularly true in the field of neural interfaces, which involves forming stable, high-density connections to a living nervous system for recording and stimulation. This field has advanced rapidly in the past 50 years. Several decades ago, we had medical devices barely more complicated than pacemakers. About one decade ago, proof-of-concept experiments established the future vision but were still low performance. In experimental brain-machine interfaces, computer cursors jumped all over the computer screen, we would have hesitated to give the animal a robot to control, and signals sometimes only lasted a few months. Then things happened unexpectedly quickly. Algorithmic advances led to stable control and, ultimately, human experiments with activities of daily living. Electrodes became small or soft enough to fly below the radar of the immune system. Problems still remain, for example, in materials’ longevity. But as the list of show-stopping problems is dwindling, it’s worth asking whether the next 10–20 years will see them solved. And like accessing the electrical control system of a building or a car, these tools may one day be the primary tools that doctors use to diagnose and cure disease.

CNS Repair: Look Within

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Each issue of *Neuron* leads us deeper into the intricacies of neural circuit connectivity and closer to understanding a neural basis of behavior. These exciting discoveries are offset by the sobering realization that conventional therapies cannot achieve the spatial and molecular precision needed to overwrite fundamental pathologies in these circuits. As biotech companies shutter CNS divisions and mental health care systems strain under the weight of new challenges, fresh perspectives are needed. Could the means for functional circuit reprogramming lay right under (or behind) our noses? The small, neurochemically diverse clusters of long-range neuromodulatory nuclei buried deep in the brainstem, midbrain, and basal forebrain have evolved the means to modify processing and plasticity in local circuits with a precision that easily surpasses the latest CNS devices and pharmaceutical interventions. We know little about their specific social, sensory, and cognitive activators; nor do we have satisfying taxonomies to understand differences in form, spatial specificity, and temporal endurance of local circuit changes imparted by each system. Future efforts may distill the activators for these nuclei in controlled, immersive virtual realities and deliver corrective stimuli once the brakes that limit physiological plasticity in adult brains are temporarily released. Exogenous drug and device remedies developed in the 20th century have their place, but we would be wise to look within for 21st century solutions.

Stress and Psychopathologies

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When a situation is perceived as stressful, the brain activates many neuronal circuits, involved in sensory, motor, autonomic, neuroendocrine, cognitive, and emotional functions, to adapt to the demand. However, the pathways by which the brain translates stressful stimuli into an integrated biological response are not completely understood. Nevertheless, the dysregulation of these physiological responses to stress can have severe psychological and physiological consequences, and inappropriate regulation of the stress response is linked to the etiology and pathophysiology of multiple disorders including anxiety, depression, and metabolic disorders.

Though many of us are exposed to stressful events or experience chronic exposure to a stressful lifestyle, we do not necessarily develop stress-linked diseases. So, why are some of us more resilient than others? Why are some of us more susceptible to develop a disease when exposed to stress? The answer may lie in the complex interaction between genetic predisposition and psychological or physiological stressors. Stressors, through different epigenetic mechanisms, induce changes in gene expression levels that might mediate the onset of disease by affecting the relevant brain circuit activity. Elucidating the role of specific epigenetic processes in mediating brain functions may promote a better understanding of the pathophysiology and neurobiology of stress-induced psychiatric disorders and could promote the much-needed breakthroughs in the development of new drug targets and biomarkers for these illnesses.

Technology (R)evolution

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What makes a conscious human brain? This fundamental question intrigues not only neuroscientists but also inspires major interdisciplinary research efforts more than ever. The contemporary explosion of new technology combined with global efforts to push its broad dissemination enables new discovery at a stunning pace. Undoubtedly, this is a most exciting time to decipher the general principles instructing the assembly and function of neural circuitry—bottom up and top down. Only about 100 years ago, Ramon y Cajal postulated the neuron as independent element. Today, we experience a technical revolution enabling us to decode the physiological and genetic properties of all cell types in the brain at unprecedented single-cell resolution. The wealth of global data-gathering initiatives offers exciting opportunities at the interface of biology and computer science. These efforts, in combination with blue-sky research by individual investigators who are enabled to pursue curiosity-driven basic research, hold an enormous potential for breakthrough discovery. In such exciting times, neuroscience research, in combination with human genetics, has an increasing societal impact. It will be important to communicate with the general public and to integrate new advances with ethical frameworks. Future ever-evolving technology and revolutionizing research avenues will guide us to the fascinating prospect of understanding the complexity of human brain development and function in health and disease.

Embracing Complexity

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Connected by trillions of synapses and gap junctions, neurons and glia in the brain exchange (bio)chemical, electrical, and mechanical cues. This symphony of signals originates at the nanoscale, where molecular machinery coordinates chemical reactions and conformation changes, e.g., ion channel opening. Combined, these events govern cellular function at the microscale, e.g., action potential firing. Coordination on the microscale then translates into emergence of macroscale neural circuits, which drive behavior. Creating tools capable of recording and manipulating this signaling diversity across scales ranging from nanometers (biomolecules) to centimeters (entire organisms) requires seamless integration of many functional features within neurobiological probes. Such integration, in turn, relies on a continuous dialog between the biological and physical scientists and cannot be simply limited to the sequential attachment of engineering modules designed to "service" molecular or electrophysiological tools. The physical properties of the neural tissue and its adverse response to the external hardware further impart design constraints onto synthetic sensors and actuators of brain signaling. To deterministically link naturally occurring behaviors to a series of molecular events within the brain, it may be necessary to pivot away from existing engineering infrastructures toward biologically inspired design of materials and devices that can transduce signals to and from molecular machines within behaving organisms.