Cell

Building a Better Brain

Maps of Mechanisms

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What would it take to engineer a brain circuit to perform a new kind of computation or to augment an existing brain computation with additional information? Perhaps you could augment a memory circuit (starting with, say, a mouse) so that it could tap into digital data, boost the capacity of working memory so that dozens of things could be held in mind at once, or enable algorithms from computer science to be run on in-brain wetware. A key difference between neural circuits and computers, of course, is that computers were designed by humans, so the principles of how to program them are well-defined. However, the principles of controlling neural circuits, to make them do exactly what you want them to do, are not fully understood. Perhaps you activate neurons in a certain pattern, and as-yet-unknown homeostatic mechanisms kick in and cancel out the effect you just created. Perhaps you drive one kind of signal at a synapse, and a chemical cascade is triggered that sends a novel signal in a retrograde fashion. We don't have a full list of the cell types of any mammalian brain, so perhaps you perturb one kind of cell, and an as-yet-undescribed cell type, equipped with unknown mechanisms, rebels against the changes you were trying to induce. Right now, there are many ongoing attempts to make maps of the brain's wiring, or connectomics. That is a necessary step toward understanding brain networks. But if we want the brain to become a predictably engineerable system, we will likely need to go further and map out the molecular and cellular mechanisms throughout the wiring.

Aim Big, Start Small

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The human brain has long captured our fascination. It is touted as the most mysterious, where imagination, curiosity, and creativity brew. It is the origin of emotions including happiness, sorrow, fear, and courage. As genetic and environmental factors make each brain unique, a multitude of functions display a spectrum, at the end of which often lies disease states. Understanding the brain becomes not just a fascination but also a mission to make the blind see, the forgetful remember, the sad happier, and the addicted sober. While our ultimate goal is to understand the human brain, this two-fist-sized organ of 100 billion neurons is dauntingly complex and not readily accessible for research. Could we start elsewhere? Indeed, it is a recurring theme in biology that model organisms teach us fundamental principles applicable to humans. The zebrafish, a "see-through" vertebrate, has orthologs to 85% of human disease genes. Compared to ours, the brains of zebrafish are tiny. The larval zebrafish brain, the size of a human eyelash, has 100,000 neurons. This number is already incredible. By deconstructing this tiny brain at systems levels and with exquisite cellular and molecular clarity, through applying and advancing a combination of imaging, chemical, genetic, and computational tools, we could uncover new concepts and principles of the brain. Having experienced the discovery of RNAi in *C. elegans* and witnessed recent FDA approval of the first RNAi-based drug, I am a true believer of the power of model organism research for an ultimate understanding of the human brain.

Making New Connections

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In the pre-optogenetics era, molecular genetics defined the concepts of neural circuit development, providing mechanistic insights into axon guidance and synapse assembly. Since 2005, optogenetics has furthered our understanding of how specific cell types, their afferent inputs, and efferent outputs contribute to specific behaviors. In some brain areas, our understanding of how microcircuits drive specific behaviors is amazing, but how they assemble during development is often unknown. Today, single-cell RNA sequencing provides us with candidate connectivity cues, giving us entry points to define the principles of circuit assembly of our favorite microcircuits. In addition, this information will give us the opportunity to generate artificial or "neomorphic" circuits in which the connectivity is altered in a predictable fashion, resulting in alternative behavioral outputs. Such a strategy has advantages over loss-of-function approaches, by telling us whether the altered microcircuit, when light activated, is sufficient to drive a new behavior. Exposing the animal to multiple sensory cues in a naturalistic behavioral setting will also give us insights into how the altered microcircuit promotes scaled outputs to control flexible behaviors. Moreover, since circuit assembly happens during development, we could ask whether neuronal plasticity subsequently changes the impact of the altered circuit and corrects the animal's new behavior. With the rapid progress in circuit neuroscience and single-cell transcriptomics, we are only limited by our own imagination where in the brain it would make most sense to make new functional connections.

Shape Circuitries

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The extraordinary diversity of animal behaviors relies on the precise assembly and fine-tuning of synapses in neuronal circuits. We are just beginning to uncover how connectivity and function emerge in the developing brain through novel tools to modify animal models. For example, RNA sequencing analysis is becoming increasingly critical to identify the molecular signatures of different neurons. Genetic manipulations (e.g., shRNA and, more recently, CRISPR/Cas9) allow engineering new strategies to sculpture the brain. Can we manipulate human brains using some of these approaches? And if so, in addition to its possible therapeutic benefit, would it have any impact for the organism? For example, we know that inhibition sharpens the tuning of cortical neurons to preferred stimuli. We could perhaps modify gene expression using viral or non-viral vectors, such as lipid-based or polymer-based carriers, to target specific populations of interneurons. A further thrilling ambitious idea would be to remodel specific populations of synapses using our knowledge of their signatures and, by doing that, enhance particular networks to improve cognition. We are getting close to identifying the means necessary to build bridges on specific synapses, increasing their density or strength. Could we genuinely improve humanity, for example, by enhancing learning? Could we upgrade the human being and boost cognition? I recognize that it is a provocative idea, but this is something we may well see in just a few decades.

Look to the Past

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For inspiration into how to wire novel behavioral circuits into the brain in the future, we may wish to look to the past. Evolution has been tinkering with nervous systems for hundreds of millions of years, ultimately giving rise to the incredible diversity of behaviors apparent within the animal kingdom. Yet we are only just beginning to glean how evolution alters circuit wiring and function. Recent technical advances in genome editing, single-cell sequencing, and connectomics have ushered in a new era in comparative neurobiology. We are now poised to be able to directly compare the homologous sensory circuits in closely related species and identify the specific changes that produce behavioral innovations. As Francois Jacob noted, evolution does not engineer optimal structures from scratch but rather tweaks pre-existing components to create novel forms. Viewing brain circuits through the lens of evolution will provide deeper insight into this tinkering process and shed light on the neural mechanisms that contribute to natural behavioral diversity. What are the developmental and functional constraints that limit neural circuit evolution? Where are the flexible nodes within neural pathways that are amenable to change? Are there predictable ways in which neural circuits evolve to generate different behaviors? By taking a broader comparative approach, we may one day be able to tease apart the conserved and core features of behavioral circuits from the idiosyncratic adaptations tailored to any single species.