



The National Academies Keck Futures Initiative: Complex Systems: Task Group Summaries

The National Academies Keck Futures Initiatives
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Task Group Summary 6

The brain is the epitome of complexity. How will understanding the complex, linked interactions among the many types of neurons in the brain lead to knowing how the brain contributes to normal function and susceptibility to neuropsychiatric disease?

CHALLENGE SUMMARY

The human brain, especially our cerebral cortex, is responsible for the sophisticated thoughts, memories, perceptions, and language that distinguish our species from all others. These functional abilities are the result of a complex, prolonged developmental history that involves expression of about half of the genes in our genome and proliferation, migration, and differentiation of scores of different cell types. This is especially evident in the human cerebral cortex, a multilayered structure that is roughly 3 times larger than that of our nearest primate ancestors. Correspondingly, molecular analysis suggests that these human-specific characteristics are associated with accelerated rates of evolution of the protein products of the genes implicated in the development of the human central nervous system that are higher in primates than in other organisms

These complex developmental programs and processes not only are responsible for the enhanced functional abilities of the human brain but are also error prone and likely to contribute to common complex disorders of the central nervous system (CNS) such as schizophrenia, bipolar disease and obsessive-compulsive disorder, conditions that in aggregate affect 2-3% of adults. Understanding the etiology of these multi-factorial diseases, each of which appears to be the result of both genetic and environmental variables, and developing effective strategies for their treatment and/or prevention is a major contemporary challenge for medicine and biomedical research.

Key Questions

- What are the evolutionary forces driving the rapid evolution of the human brain and what are their consequences for the sources and frequencies of neuropsychiatric disease?
 - Can genetics and genomics identify all the genes involved in the development and function of the central nervous system?
 - Can we understand how the protein products of these genes integrate into biological systems essential for CNS development and function?
 - What are the components, structure, and behavior of the biological systems that underlie complex CNS functions such as memory, reasoning, and language?
 - How do combinations of variants in a subset of these genes and proteins perturb the function of the biological systems characteristic of the CNS and increase risk for neuropsychiatric disease?
 - What technologies and resources, existing and yet to be developed, would improve our abilities to understand normal and abnormal brain development and function?

Required Reading

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Due to the popularity of this topic, two groups explored this subject. Please be sure to review the second write-up, which immediately follows this one.

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TASK GROUP SUMMARY – GROUP A

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The Problem

The philosopher John Stuart Mill once marveled at the combustion of methane: What went in—a violently flammable fuel—bore no resemblance to what came out—innocuous water and carbon dioxide. The scientific understanding of the 1800s could not account for this seemingly miraculous transformation.

Likewise, most people are stupefied when pressed to explain the mind: What goes in—the electrical and chemical interactions of 100 billion cells, agglomerated into three pounds of fatty flesh—seems to have no relation to the phenomena that emerge—emotions, imagination, abstract reasoning, physical dexterity.

Today, the subject of Mill's wonder is far less mysterious; developments in chemistry and physics explain chemical reactions as the predictable movements of electrons between atoms.

Neuroscientists hope for a similar outcome—that a more thorough comprehension of the brain's components and their interactions will explain its remarkable output.

In recent years, our understanding of the brain has burgeoned. We are learning how currents flash through neurons, how neurons are born and how they die, how connections between them develop, strengthen, and fade

away, and how different regions of the brain interact. We can even replicate small portions of the brain *in silico*—as IBM’s Blue Gene supercomputer did with a cubic millimeter of the cortex in 2006. And yet, we seem no closer to understanding how all this neuronal chattering manifests as the mind. It is clear that an approach that might work for the brain will be different from the reductionist one, where general properties of the grand structure are indispensable.

At the 2008 National Academies Keck *Futures Initiative* Conference on Complex Systems, a group of scientists charged with designing a protocol for ‘the brain as the epitome of complexity,’ decided to develop a strategy for teasing out the principles that govern this metamorphosis. The team was composed of engineers, neuroscientists, epidemiologists, computer scientists, physicists and psychologists.

Neural Complexity

The group viewed the brain as a quintessential complex system: it consists of fairly simple components (neurons) that engage in coordinated interactions, which are somehow bound or integrated to produce complex emergent phenomena (thoughts). “Complexity” in the brain refers to the structure and behavior of these interactions—the physical connections traveling forward, backward, and laterally between various regions of the brain, as well as the timing of the communications.

“If you have all your neurons firing randomly, with only short-range connections, that’s not very complex,” Larry Yaeger of Indiana University observed. “But if you have them all synchronized, all firing in lockstep, that’s not complex either. The good stuff is in the middle.”

“The good stuff”—a highly complex brain—has a balance between these extremes of organization: neurons that are coordinated mostly with their close neighbors, but also communicate with other neuronal neighborhoods. A brain with specialized but interconnected regions—such as a region that processes vision connected to a region that generates movements—is necessary for complex behaviors, like stopping at a red light.

Complexity, in this formal sense, is a way to quantify how the brain is organized, and so is directly correlated with how the brain works. The group thinks differences in neural complexity is likely to account for differences in intelligence. For example, animals capable of abstract reasoning will exhibit greater complexity than less intellectually capable animals. By dissecting this complexity measurement, one can understand what organizational

principles make the region complex—how many connections the neurons make, what type of connections they make, how each neuron behaves. This may enlighten understanding of how the brain achieves abstract reasoning.

An important control when measuring complexity is size—an elephant's brain has about four times as many neurons as a human's, yet we assume it is less complex. Although more neurons may result in more connections and potentially more behaviors, the connections may be irrelevant or even detrimental to functioning. It is the organization—not sheer number—of the brain's connections that result in intelligence; complexity captures this organization.

The Approach: Focus on Impulse Control

To use neural complexity as a probe for understanding how the brain produces intelligence, the group found it helpful to focus on a microcosm of intelligent behavior: impulse control. The human ability to voluntarily postpone gratification for the sake of later outcomes vastly exceeds that observed elsewhere in the animal kingdom—humans have the ability to abstain from drugs and sex, they diet, they save money, some even go to college and professional schools.

Primates, too, can delay gratification, picking large delayed rewards over smaller immediate rewards—but only if the delay is on the order of minutes. Mice can only delay gratification for a few seconds, and this ability differs between different strains.

A chief reason for selecting impulse control is its relevance to psychiatric disease. People with schizophrenia, bipolar disorder, and obsessive compulsive disorder have poor impulse control—as do “normal” individuals if they have had a bit too much to drink.

Impulse control is also related to more subtle differences in human behavior. A striking 1989 study demonstrated that impulse control in 4-year-olds is predictive of their later success in life.

In the experiment, a researcher placed a marshmallow in front of a child and told him he would return in 20 minutes with a second marshmallow—but would only give it to the child if he had not eaten the first before the researcher's return.

The study showed that children who delayed gratification and waited for the second marshmallow developed into more cognitively and socially competent adolescents. They were more likely to go to college, less likely

to be arrested, and less likely to develop eating disorders. The measure of impulsivity was more predictive of their success in life than IQ.

Impulse control, then, is a specific, measurable behavior that is relevant to intelligence, making it ideal for probing the relevance of neural complexity. The group hypothesized that specific aspects of the brain's organization, quantified as complexity, will be predictive of impulse control.

The Plan of Attack

1. For a detailed measurement of neural complexity, it is essential to gather data: the connections, communications, and firing patterns of as many neurons as possible. This requires great advancements in technology—implanting tens of thousands of recording electrodes, for example, and imaging anatomy with much improved resolution in both space and time. In high numbers, these data points would provide insight into higher levels of cognitive processing.

2. The group proposes to process the data by calculating neural complexity. There are a number of equations and models that quantify complexity, each looking at different aspects of the brain's organization—timing of communications, number and type of connections, etc.

3. The group would compare these different complexity measurements between organisms with different abilities to control their impulses—different strains of mice, different species, humans with certain diseases, and humans with different skills, such as artists and scientists. This will reveal which aspects of the brain's organization are related to impulse control.

If this strategy is effective, the group will apply it to other intelligent behaviors, such as language. The group hopes to understand which aspects of the brain's organization are linked with intelligent behaviors—developing a complexity “signature.” This knowledge will enlighten our understanding of the relationship between the brain's complicated form and phenomenal function.

Applications

A key ambition of the group is to use its strategy to benefit society. The presumption is that understanding impulse control is important to many psychiatric diseases—not only for diagnosis but also for therapy. For example, if it is possible to use measures of complexity to pinpoint

the precise mis-wiring or mis-firing that leads to impulsivity in obsessive-compulsive disorder, it might be possible to use this measure to evaluate potential interventions.

The brain is a daunting enigma for today's neuroscientists, but the group is confident that an understanding of its underlying principles is in the foreseeable future. The inevitable advances in neuroscience technology will give researchers a real-time view of neuronal interactions across the entire brain; by analyzing the complexity of these interactions, the group hopes to unravel how the phenomenal mind emerges from the physical brain.

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TASK GROUP SUMMARY – GROUP B

*By Jennifer Lauren Lee, Graduate Science Writing Student,
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Every year, new and more sophisticated methods of investigation bring the workings of the human brain into sharper relief. Yet the more details we gather, the less clear it is where the journey to a complete understanding of the brain will end; each new rise in knowledge reveals a horizon still out of reach. The brain is composed of complex systems (cells) with highly diverse and plastic connections that distinguishes it, and in turn its properties, from

many other types of complex networks. A full understanding of the brain could provide innumerable boons to the field of medicine, granting physicians the ability to diagnose neurological diseases more quickly and treat them more effectively. At the 2008 meeting of the National Academies Keck Futures Initiative Conference on Complex Systems, one multidisciplinary Task Group (6B) was determined to see whether treating the brain as a *complex* system might spark ideas for new tools to help scientists understand the brain as a *complete* system.

The Opportunities of Neuroscience

Early in the discussions, the members of this task group were concerned with the problem of scale. Each year brings improvements in the techniques that allow scientists to probe the brain at many levels—that of protein structure, for example, or single neurons interacting with one another, or entire sections of the brain that each consist of millions of neurons working together as a unit. But what these technological improvements do not do is improve scientists' ability to see how the various levels connect with one another. The "rules" for neuron-to-neuron interaction, as compared to those governing the relationship between two zones or areas in the brain, for example, are so different that a person can spend an entire career studying a single level of interactions without ever looking beyond. In a sense, each scale in the brain is a separate field of study, with its own jargon and techniques for collecting data—an island in the ocean of brain science.

These gaps between the scales are unknown territories in studies of the brain—what one member of the group called the "wastelands of neuroscience." And it was these lacunae that became this group's focus.

One of the first orders of business was defining terms, so that researchers with different areas of expertise could be sure their words meant the same thing to everyone at the table. The brain is always active—"till you're dead," as one participant put it. But it can exhibit what could be called different "states" depending on what it is doing. Taking a snapshot of the complete activity on every scale of the brain in a given state would yield what could be called a "signature" for that state. A healthy brain would have the healthy signature for juggling, or sleeping, or looking at the color blue, while doing each of those tasks. A diseased brain—one with the earliest signs of epilepsy or Alzheimer's disease, for example—might have an abnormal signature; its pattern of activity for a given task would be different, in theory, on at least

one scale. The size of the difference would determine when and how the disease manifests itself, and how quickly it progresses.

The team also considered the possibility that neurological diseases might affect the level of complexity itself, possibly lowering the brain's complexity and reducing its ability to respond to problems. The challenge, then, would be to make a model that shows the relationship between the various scales, using the tools of complexity to analyze data at each level simultaneously. In this way, one could determine the characteristic "disease state" for a particular activity.

Brave New Methods

In order to "see" the connections between the scales, the group decided it would need to study various levels of the brain *at the same time* in response to some stimulus. Getting a sense of how the various levels interact with one another would give the team a signature for that particular brain state. The first step would be finding the complexity signature of the resting state of a healthy brain. Then researchers would perturb the system, and see how those perturbations affected the other scales. They could make changes at the smallest scale—that of genes and proteins—then track those changes through the higher levels, up through the largest networks of neurons in the brain. They could also use a top-down approach, perturbing the whole system (through sleep deprivation or a behavioral change, for example) and observing what happens at the smaller scales. Researchers would start by using existing techniques, such as probing individual neurons with fluorescent imaging or assessing the activity of larger areas with functional magnetic resonance imaging (fMRI). But the scientific community would also need to develop "Brave New Methods," new tools to "see" changes at each scale and map those changes together.

Also necessary would be a method of connecting the different scales, to catch the changes in the brain's activity signature at each level in response to the task being performed. Here the group ran into some hypothetical problems. How would they know whether they had matched up the scales correctly, given the different methods (each with its own types of errors) they had used to collect the information at each scale? How would they decide how many scales to consider, and how to break them up? And how could they know when they were finally looking at a complete system—that, as one task group member put it, they had the whole system in their scopes?

Without brave new methods, the immediate answer would be to col-

lect data—a lot of data—and compare the results with models that would reconstruct the missing points between the layers in space and time. The only way to validate a model is to test how well it predicts the results of the next data collection. The more data, the more sophisticated (and, presumably, reliable) the models.

Waiting for Symptoms

Although the techniques for conducting this research need to be refined, the benefits could revolutionize humanity's understanding of the brain and also the facility with which brain diseases such as epilepsy are treated. It could take ten years after an injury for the first symptoms of epilepsy to present themselves as a seizure; and by then, perhaps, the damage is done. If measuring the changes in the complexity of the system could allow scientists to catch the earliest signs of a disease, regardless of the scale on which it presents itself, patients might have a better chance of recovery.

This new way of mapping the brain using complexity may also provide researchers with a short-cut to a functional understanding of the brain. One member of the group compared the practice of studying the brain on a neuron-to-neuron level to that of trying to understand the economy by following all the shoppers in a supermarket: although these details may give the viewer insight into one level of the system, they do not give much useful information about the system as a whole. A method of studying the brain that makes use of complexity theory might allow us to get a full picture of how the brain “works” before we have finished defining the roles of every gene and protein in the body. With any luck, this new view could yield incalculable benefits to medicine. In the meantime, it would provide a brave new way of thinking about the brain—a way that might inspire people to create new models and tools for tackling a new problem.