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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Hill RS, Walsh CA. Molecular insights into human brain evolution. *Nature* 2005;437:64.

Pollard KS, Salama SR, Lambert N, Lambot M-A, Coppens S, Pedersen JS, Katzman S, King B, Onodera C, Siepel A, Kern AD, Dehay C, Igel H, Ares M, Vanderhaeghen P, Haussler D. An RNA gene expressed during cortical development evolved rapidly in humans. *Nature* 2006;443:167-172.

Sawa A, Snyder SH. Schizophrenia: Diverse approaches to a complex disease. *Science* 2002;296:692-695.

Ross CA, Margolis RL, Reading S, Pletnikov M, Coyle JT. The neurobiology of Schizophrenia. *Neuron* 2006;52:139-153.

Due to the popularity of this topic, two groups explored this subject. Please be sure to review the other write-up.

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TASK GROUP SUMMARY – GROUP B

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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 collect 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.