Testimony

Of

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Mr. Chairman, Ranking Member Jordan, and distinguished Members of the Committee, thank you for inviting me to testify here today. Understanding and treating brain disorders is a topic I care deeply about, and pursue both in my own scientific research and in my public service. I am the Gardner Quarton Distinguished Professor of Neuroscience and Psychiatry at the University of Michigan and the co-Director of its Molecular and Behavioral Neuroscience Institute. I have served as President of the Society for Neuroscience (SfN) and currently serve on the Council of the Institute of Medicine of the National Academy of Sciences, and on the IOM Forum on Neuroscience and Nervous Systems Disorders. I also co-chair the Neuroscience Steering Committee of the Biomarkers Consortium at the Foundation for NIH.

I have had the good fortune of receiving continuous funding for my research from the National Institute of Health (NIH). I have held NSF grants and currently have a grant from the Office of Naval Research (ONR) focused on the biology of stress and PTSD. Our research group is part of the Pritzker Consortium, a large collaborative effort that aims to understand psychiatric diseases, supported by the Pritzker Philanthropic Fund. I enumerate these sources of funding not only to express my gratitude for the support, but to indicate my familiarity with funding mechanisms from federal and private sources.

Thanks to federal funding, our knowledge of neuroscience has advanced at a remarkable pace. We now know an immense amount about the brain relative to even a decade ago. This knowledge has fueled remarkable advances in the treatment of many brain diseases. Yet the challenge of understanding, predicting, preventing, treating or curing brain disorders is still largely before us. The burden of these brain disorders is staggering, with

neurological disorders affecting up to a billion people worldwide[1,4] and psychiatric and addictive disorders impacting comparable numbers.[2] Moreover, the disability burden of brain disease is huge, especially in low and middle-income countries where 80% of the mentally ill people live.[2] But beyond the health and economic costs[3] is the nature of these diseases, which are devastating to patients and their families, sometimes changing the affected person's very identity. Today, I outline what I believe to be the "Grand Challenge of Neuroscience" and suggest strategies for meeting it in order to advance our understanding of these disorders.

A- The Grand Challenge: Understanding "Neural Choreography"

Why "Neural Choreography"?
By the time a brain disorder is evident, it has typically affected not a single, uniform group of brain cells but a brain circuit, and it is the disruption of that circuit that leads to the symptoms of the illness. By analogy to a ballet performance, the problem may not be that a ballerina has stumbled, but that the choreography of the whole ensemble has fallen apart. Such a problem may be more subtle and harder to pinpoint, but it is no less disruptive. *I am using "neural choreography" to describe both our current scientific challenge and our path forward in attacking the problem of brain disorders.*

The brain contains approximately one hundred billion brain cells that communicate with each other via specialized connections or synapses. A typical adult brain has 100-500 trillion synapses.[5,6] *The point of all this communication is to orchestrate brain activity.* Each brain cell or neuron is a breathtaking piece of biological machinery that performs beautifully--genetically, biochemically and electrically. But no matter how accomplished, a single neuron can never perceive beauty, feel sadness or solve a mathematical problem. Through the magic of integration, completely new capabilities emerge when networks of neurons work together. Thus, ensembles of brain cells, sometimes quite far flung, form an integrated "neural circuit" and the activity of the network as a whole supports specific brain functions such as vision, hearing, hunger, sleep, learning or emotions.

We have made great progress in identifying the participants in these networks for some brain functions such as vision—the location of the relevant neurons, the chemicals they use to communicate with each other, the way they integrate information leading to the perception of a color, a form or a movement. For other brain functions, we may still be missing some important actors—for example the brain circuit that mediates mania in a person suffering from Bipolar Disorder is not nearly as well identified as that which mediates Parkinson's Disease.

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[1] Neurological disorders affect millions globally: WHO report (Feb. 2007)
[2] W.H.O. Report: Mental health and development: targeting people with mental health conditions as a vulnerable group (released September 2010)
[3] http://www.bocyf.org/benefit_cost_workshop_highlights.pdf
[4] http://www.sfn.org/index.aspx?pagename=brainfacts
[5] http://www.sfn.org/index.aspx?pagename=core_concepts
[6] Drachman D (2005). "Do we have brain to spare?". *Neurology* **64** (12): 2004–5. doi:10.1212/01.WNL.0000166914.38327.BB. PMID 15985565.

But aside from identifying the participants, *our main challenge is to understand the workings of the circuit as a whole, its dynamics and how it controls itself. We need to watch these circuits as they perform in real time, and watch how their choreography fails in each disease.* This is important because these dynamic features are the very basis of what goes right, and wrong, in our brain. Whether we are talking about a smooth walking gait that is disrupted in Parkinson's disease, the capacity to deal with a threat signal that is damaged in a soldier with PTSD, the ability to resist a drug that is lost in an addict, or the discrimination between reality and fantasy that is erratic in a psychotic patient, we have to think about disrupted brain circuits- neural choreography gone awry.

Neural Choreography and the Search for Causes of Brain Disorders

The view that the majority of brain disorders result from disrupted neural circuits has profound implications for the way we search for the causes of brain disorders. Even for illnesses such as Bipolar Disorder or Autism that are clearly familial and highly heritable, the quest for clear genetic causes has been more difficult than anticipated. Why? Because what we diagnose is the result of a disrupted brain circuit and there are countless ways to bring about this disruption--any given dancer in the troupe can fail in the fine-tuning of a dance movement and disrupt the overall choreography.

Indeed, this is the basis of an opinion piece that we have recently published in Science entitled: *"The Future of Psychiatric Research: Genomes and Neural Circuits"*.[7] While this article was focused on psychiatric diseases, the same logic can be applied broadly to other complex brain disorders including neurological and addictive disorders. The rationale is based on the view that *different families can suffer from completely different genetic problems and still share the same medical diagnosis*. This is because the disruptions caused by these genetic problems converge on a common brain circuit, which in turn results in shared symptoms and a shared diagnosis. Thus, beyond genetic "complexity" which refers to the existence of multiple genes each of which contributes to vulnerability to the illness, we need to consider the possibility of "heterogeneity" where non-overlapping genetic causes can lead to a common disease. This recalls the opening sentence of Leo Tolstoy's Anna Karenina: "*Happy families are all alike; every unhappy family is unhappy in its own way".*

Beyond the heterogeneity in genetic causes, we need to recall that the brain is in the business of remodeling itself based on *experience.* This is not a minor feature of brain function but rather represents the essence of how the brain operates in order to cope with a complicated and unpredictable world. *Therefore, environment matters and interacts closely with genetics in either increasing or buffering the risk for disease.* This is particularly true in early childhood when our brains are most adaptable, but is certainly true during adolescence when the brain is undergoing dramatic remodeling, and continues into adulthood and old age. Thus, two people could carry the same genetic load but have

[7] Akil H, Brenner S, Kandel E, Kendler KS, King MC, Scolnick E, Watson JD, Zoghbi HY. The future of psychiatric research: genomes and neural circuits. ***Science.*** 2010 Mar 26;327(5973):1580-1. PMID: 2033905

a very different outcome in terms of disease due to their environment. *Brain is where nature and nurture most clearly meet*. This is both a complication and a source of hope.

The central role of brain circuits, the heterogeneous nature of the genetics and the role of the environment in brain diseases might also speak to the challenges of developing treatments, since patients can share a common diagnosis but have a differing underlying cause of their illness. But the circuit idea means that we do not need a different medication for each family. There can be multiple ways to repair the problem by adjusting the choreography—we can help other dancers alter their movement or tempo and produce a new smooth balance.

B. Meeting the Challenge: Choreographing Research Teams of the Future

General Considerations: President John F. Kennedy said: "*I'm an idealist without illusions*". Similarly, we need to strive to conquer our grand challenge while being grounded in some hard earned realities:

1) Understanding the brain and mind, and using this knowledge to cure brain disease may well be *the hardest scientific problem that humans have attempted*.
2) *We need to rely on every conceivable approach to probe the brain—no holds barred.* We need help— not only from each other, but from chemists, physicists, mathematicians and engineers. Moreover, since we are embedded in a social environment that literally shapes and reshapes our brain, we need to seriously engage our colleagues across the social sciences in this quest.
3) *Nevertheless, partial understanding can lead to new treatments*. We have, in fact, made immense progress, which indicates that deeper understanding of the brain is doable. And this has resulted in better treatments, which shows that we do not need to fully solve a problem before we make an impact on people's lives.
4) *Knowledge in neuroscience is a two-way street*- Studying the normal brain is essential for understanding what goes wrong with it. Conversely, studying the diseased brain reveals a great deal about the normal workings of healthy brains.
5) *Fundamental principles of brain function and dysfunction are shared*. While the circuit involved in each function is unique, and while the molecular culprits for each disease vary, dramatic advances in one area clearly advance the entire field.

A Proposed Approach:

The inspiration for tackling the complexity of the brain comes from the brain itself- *the creation of well-orchestrated networks of scientists who work together to achieve what can never be achieved separately.* Just as new capabilities emerge in the brain when networks of neurons work together in a well-oiled manner, so do dramatically different insights emerge if we bring together researchers who have differing specialties and vantage points. The process can be transformative and the discoveries unimaginable.

I hasten to add that I am not recommending, by any stretch, the dissolution of the classical small team of scientists that makes up the majority of current neurobiological research. This model has served neuroscience extremely well, specifically because we have so much to discover. The diversity of minds, strategies, tools and interpretations that come from having a large number of independent scientists thinking originally about the myriad facets of brain function is critical for our continued success. There also exists another layer of science where research groups are larger, or where projects rely on collaborations between multiple small labs, using funding mechanisms such as NIH Program Project Grants or Center Grants, and those should be preserved as well.

What I am suggesting is: a) supporting new mechanisms for greater integration within the NIH, between funding agencies, and between government and industry; b) defining integration in more than one way; and c) creating a partnership between the funders and the scientists to identify the questions and strategies that might be most fruitful.

Horizontal Integration: With this approach, one gains power by bringing together a significant number of investigators with the same general class of expertise focused on solving a given aspect of a problem, for example the validation of biomarkers for a brain disease. A highly successful example of such an effort is the Alzheimer's Disease Neuroimaging Initiative (ADNI), a public-private collaboration which aims to discover biomarkers for AD. Results from ADNI promise to transform the diagnosis and development of drugs for AD and other types of age-related cognitive disorders.

Vertical Integration: involves focusing on a core scientific question by bringing together expertise from within and outside of neuroscience. The initial question can be basic or clinical in nature, but the vertical integration should erase these boundaries, allowing the team to follow the most promising leads and move bi-directionally from the most fundamental to the most clinical and back. For example, in our search for genes of psychiatric diseases, we need the expertise of clinicians, geneticists, neuroscientists, and computational biologists. But the identification of one or more gene that contribute to the vulnerability to, say, bipolar disorder is only the start of the journey. "Reverse translation" work is needed to understand the basic functions of that gene and its role in particular brain circuits both in animal models and in humans. Such work can lead to the validation of biomarkers for the illness and the identification of new targets for drug development that can be pursued in collaboration with industry. Ongoing work in the Pritzker Neuropsychiatric Disorders Research Consortium[8] exemplifies this model. A similar project focusing on PTSD would be highly feasible.

Two Dimensional Integration: represents special large-scale projects that combine both vertical and horizontal integration. The goal of such an effort is to *address a fundamental question in neuroscience and study its implications across a range of brain disorders*. For example, we can ask how a normal brain circuit achieves optimal control of its functioning, and what can cause brain circuits to become unstable. This is relevant to many disorders such as epilepsy, bipolar illness and chronic pain. By focusing on a

[8] http://www.pritzkerneuropsych.org/about/overview.htm

shared central problem—unstable circuit dynamics, regardless of disorder, we can use the convergence of information to extract the central features of a stable versus unstable brain circuit- the well choreographed versus the badly choreographed networks.

This approach has the potential to move from molecule to mind and back to molecule. Discoveries may well inform many other disorders than those initially investigated. This understanding can help us devise ways to reset the balance of that circuit either by directly replacing the defect, or more likely by retuning it elsewhere. And we can set the stage for partnerships with industry that lead to new treatment modalities, be they drugs or other types of interventions that help overcome the disease.

Creating a partnership between the funders and the scientists These proposed teams of the future may require integration not only across agencies, but also across laboratories, universities and disciplines. I believe neuroscientists can be comfortable with such efforts, as the discipline is intrinsically highly multidisciplinary—we exemplify E.O Wilson's view: "Complexity is what interests scientists in the end, not simplicity".[9]

But whatever the model, it is critical that the scientific community have a strong voice in helping define the parameters of the scientific questions and the strategies for attacking them. Researchers in the field typically perceive the funding process as binary-- either *investigator-driven research* (e.g. RO-1 or Program Project Grants), whereby scientists generate ideas for evaluation through peer review, or *agency-generated programs,* whereby agencies issue a program announcement and investigators attempt to adapt their research to the parameters of the program in order to compete for funding. It is the case that many agencies seek extensive expert input as they define the programs that they plan to announce. But this is not a highly visible aspect of the process, and many investigators are wary of what they perceive to be agency-driven "big science". *If we were to undertake large scale, inter-disciplinary efforts in neuroscience that may involve multiple funding agencies, it would be very important to devise a highly visible, iterative process that requires collaboration between the funding agencies and the scientific community in defining the scope and the nature of these projects.* Any program announcement would be informed by this input but kept sufficiently flexible to allow for ideas that had not surfaced in previous discussions. In many ways, this would be a hybrid between the investigator-driven and the agency driven mechanisms. Such a partnership between the funding agencies and the scientific community is essential for getting broad buy-in from the scientific community, identifying the areas that are most ripe for in depth analysis, and educating the peer review system in evaluating such projects.

C. Conclusions

Understanding the brain and healing it when it is sick may well be the most difficult challenge that humanity has ever undertaken. We need to give this amazing organ its due, by bringing together every tool we have at our disposal and finding new ways of working together to probe its mysteries.

[9] E.O. Wilson, "Consilience: The Unity of Knowledge", 1998, Knopf.