Minding the Gaps in Neuroscience: Enabling Great Science to Become Great Medicine

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The Brain -
This Three Pound Gem Is
The Most Powerful Information Tool
In The Known Universe
The Brain - Functions to Receive, Process and Act Upon Information

Receive → Process → Send
Brains Share Information in Context

Receive  Process  Send

Send  Process  Receive
To Understand the Brain Is The Most Important Human Undertaking

We Can Transform Our World If We Can: Decipher How The Brain Receives, Processes and Acts Upon Information
Receive: in spite of sensory loss or distraction.  
Process: even during stress or in old age.  
Send/Act: even when power is diminished.
Brain function is written in the structure and function of neural circuits.
NEURONAL CIRCUITS MEDIATE ALL BRAIN FUNCTIONS

INFORMATION

DENDRITE → SYNAPSE → AXON

CELL BODY

MYELIN FORMING CELL

CHANGE IN FUNCTION

NEURON 1 ← NEURON 2 ← NEURON 3

RECEIVE → PROCESS → SEND
Deciphering The Brain Requires That We Learn:

- how neural circuits assemble and operate,
- how learning modifies circuits,
- how circuits create behavior,
- how circuit disorders impact the brain.
Deciphering Neural Circuits: Working Across Scales To Understand Brain Function
Playing the Brain Scales

- **Length** – nanometers to meters ($10^9$)
- **Time** – milliseconds to decades ($10^9$)
- **Complexity** – the structure and function of single molecules to higher order processing of brain signals
- **Development** – conception to old age
- **Health Status** – well to ill
- **Disease profile** – from development to dysfunction to degeneration
- **Context** – discovery to delivery
For success, we need to:

- create *new technologies* to decipher the basis of circuit dysfunction,
- establish *strong collaborations* between physicians and colleagues in the physical sciences, engineering, behavioral sciences and education,
- discover new ways to *repair/replace circuits*,
- create a *culture that speeds translation* of great science into great medicine.
Basic Science Advances Are Key to Success in Helping People

• In the last 20 years we have gone from:
  – Biochemical studies on crude homogenates to precise definition of molecular and synaptic complexes
  – Imaging fixed tissue to live-imaging of neurons
  – Recording single neurons to watching entire circuits
  – Surgical lesions to precise genetic control of circuits
  – Observing function to real-time modulation of function
  – Few tools for studying people to a wealth of methods
Basic Science Advances: Enable A 100-fold Increase in Signal Detection
Theory

Structure

- Molecular/Cellular

Function

- Neurons/Synapses

Cognition/Behavior

- Function-Circuits

Dynamic Modeling of Circuits Across Scales

Function-Circuit

Structure-Circuit

Function-Neurons/Synapses

Structure-Molecular/Cellular
Signaling Endosomes Carry Trophic Signals
Tracing Endosomal Traffic: Quantum Dot Labeled NGF

\[ \text{Biotin-NGF} + \text{Streptavidin-Qdot} = \text{Qdot-NGF} \]
Separting Axons from Cell Bodies

Watching Traffic in Real-Time
Qdot-BDNF Transport in Hippocampal Neurons

Retrograde
Disrupted Trafficking of Signaling Endosomes May Contribute to Dementia
Array Tomography: A Means to Image the Molecular Basis of Circuits

Embed Specimen in Acrylic Resin

Cut & Place

Serial Section Ribbons

Glass Microscope Slide

Immunostain & Image

Synapsin I  Tubulin
Kristina Micheva
Stephen Smith
Automated Synapse Classification in Cortex of a Mouse Model of Down Syndrome

80K-150K Synapses Classified by a Machine Learning Algorithm
Imaging Circuits In Vivo

Two-photon microscopy

Confocal microscopy

Hippocampus

Caudate

Substantia Nigra

Fluorescence microendoscopy

Mark Schnitzer and Colleagues
Two-Photon Imaging Device

Cost: $50,000
A Microscope That Weighs Less Than 2 gm And Fits In Your Wallet

And costs ~$5.00

Mark Schnitzer and Colleagues
Imaging Function of Neurons in Circuits in Behaving Mice

(Real time)

(10x real time)
• Activity of hundreds of neurons can be visualized simultaneously in awake, behaving animals
Recording of Ensemble Activity During Behavior

Longitudinal imaging allows identification of changes in ensemble activity during learning.
Imaging Circuits In Vivo

Two-photon microscopy

Confocal microscopy

Hippocampus

Cerebellum

Mark Schnitzer and Colleagues
Looking Deeply Into the Brain

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Looking Deeply Into the Brain

Diagram:
- Micro-optical probe
- Imaging guide tubes
- Mouse brain
- Experimental tissue
- Control tissue
- Dorsal
- Rostral

Label:
- Objective
- Skull
- Micro-optical probe

Measure:
- 0.02 Inch Dia.
Imaging Circuit Structure Over Time

Mark Schnitzer and Colleagues
Real Time Measures of Blood Flow in Hippocampus

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Imaging the Hippocampus Live
Imaging Circuit Function Over Time

Schnitzer and Colleagues
Exploring the Neuro-Vascular Link

Neuronal excitation - *vasodilatation*,
Neuronal inhibition - *vasoconstriction*

Devor et al., JNeurosci 2007, 2008
Stimulus-Induced Vasodilation: Fast, Propagates Upstream along Trunks, Invades Lateral Branches

B. cortical depth <150 μm

D. onset time

Surface arteriole

Deep arteriole

Tian et al., PNAS 2010
Modulating Circuit Activation

**Optogenetics** – Allows millisecond-timescale, genetically targeted optical control of activity.

This tool enables light-driven control of neuronal firing within circuits with precise temporal and spatial resolution.

Karl Deisseroth and Colleagues
A Growing Toolbox for Optogenetics
Selectively Stimulating Circuits

Karl Deisseroth and Colleagues
Deciphering Circuits in Humans: Toward a World Without Human Brain Disorders

Basic Science Research Promises to:

• Help understand normal human brain function
• Inform us about human brain disorders
• Teach us how to diagnose brain disorders
• Provide insights needed to treat them, and
• Ultimately, allow us to prevent them

But What About Tools for Human Studies?
Speech Processing in Humans

- What is the locus of speech processing?
- Role of anterior superior temporal lobe?
- What features do single units encode?
- Do phonemes exist as constructs?
Single Units Fire to Specific Words

Chan et al. (2012) in preparation
Single Units Fire to Specific Phonemes and its Associated Letter

Chan et al. (2012) in preparation
Single Units Fire to Specific Phonemes and its Associated Letter

Chan et al. (2012) in preparation
Brainwave controllers

Put your thinking cap on

Consumer electronics: Once the stuff of fables, hoaxes and science fiction, controlling things via thought alone is fast becoming a reality

Sep 3rd 2011 | from the print edition
Brainwave controllers

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Watching Brain Connectivity - Live
Brainwave controllers

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Consumer electronics: Once the stuff of fables, hoaxes and science fiction, controlling things via thought alone is fast becoming a reality
Ultra-thin, Ultra-light, Flexible Electronics

‘electronic temporary disposable tattoo’
A Sensor with Many Capabilities

Kim et al., Science, 2011
New Directions: Beyond Skin and Beyond Sensing

Directly Applied to the Brain Surface

Integration of LEDs of multiple colors

Todd Coleman and Colleagues
Future Use of Sensors to Modify Neurons and Circuits?

Recent Results in Culture: Todd Coleman and Colleagues
A Tool to Modify Brain Function?

Start/stop delivery

protein not produced

protein produced
Basic Science Advances Are Key to Success in Helping People

• In the next 20 years we could:
  – Define the genes responsible for normal brain function
  – Detail the many circuits responsible for most aspects of brain function
  – Define the molecules that mediate essential aspects of brain function
  – Create tools that allow us to understand the fundamental causes of neurological disorders, and
  – Apply these insights to alleviate or prevent suffering in millions of Americans
Exploring the Neural Basis of Empathy

Hein and Singer, Curr Opin N’biol, 2008
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