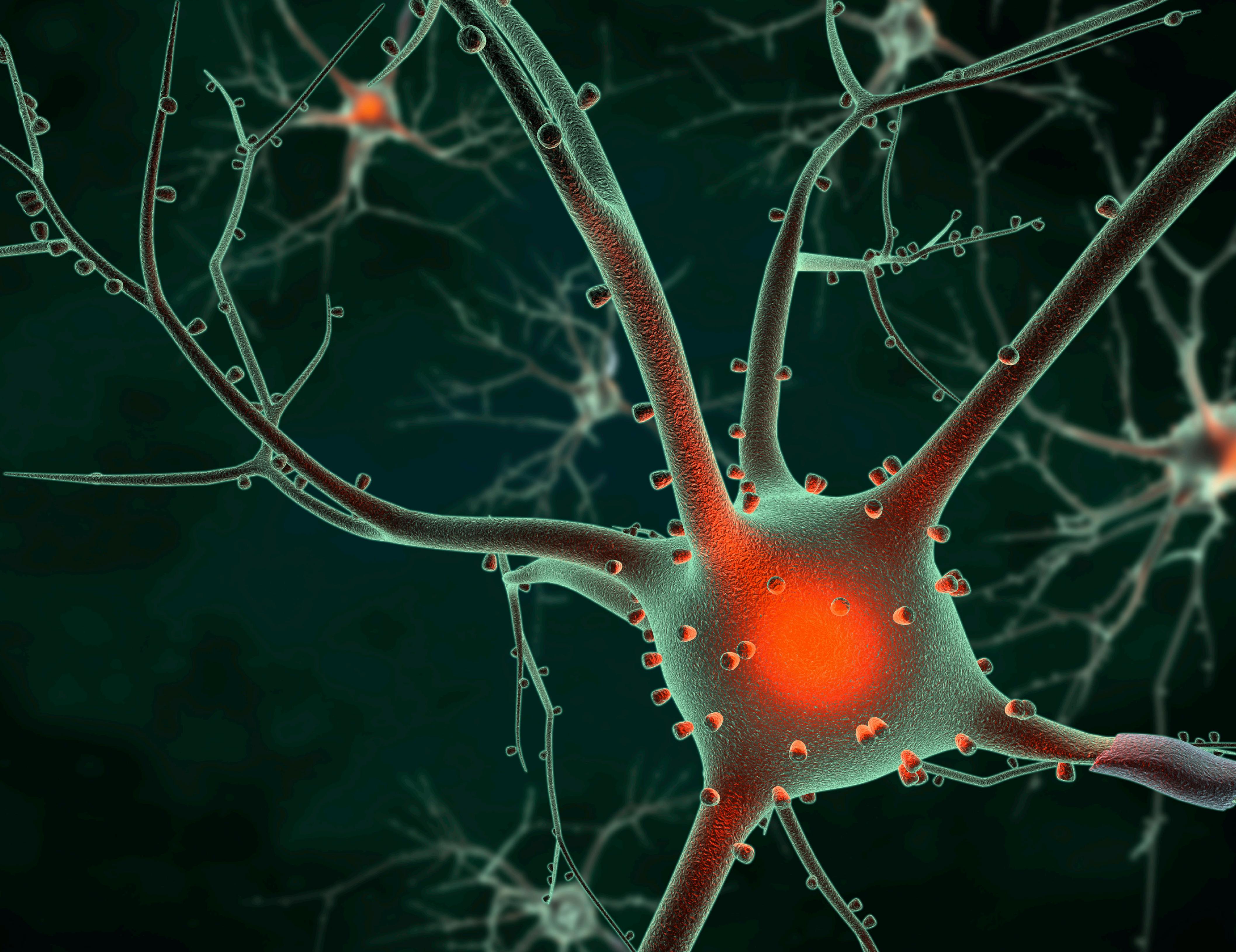
REPORT FROM THE WORKSHOP ON

SHIFTING PARADIGMS IN NEUROSCIENCE

What Can We Know by 2025?

COLUMBIA UNIVERSITY NEW YORK, NY MARCH 11–13, 2012

Neuroscience stands on the brink of developing an integrated understanding of how neuronal activity combines into circuits, which then produce behavior. Strategic investment now by the Department of Defense as recommended in this report could support substantial progress over the next two decades, with strong potential for translational impact.



EXECUTIVE SUMMARY

At a workshop sponsored by the Department of Defense, 22 distinguished neuroscientists (see Appendix I) met in New York City in March, 2012, to discuss research on the neural basis of behavior. In response to questions designed to spark discussion and debate (Appendix II), the participants identified recent strengths, opportunities over the next ten to twenty years, and roadblocks to neuroscience research. The workshop's purpose was to inform the strategic planning process as the Department of Defense seeks to maximize the payoff of investments in the field.

The fundamental research aim of the participants is to determine the mechanisms by which activity in brain circuits produces sensory perception and behavior. Basic research on brain function is important to the Department of Defense because it has the potential to provide insight into many issues of concern to the military, including:

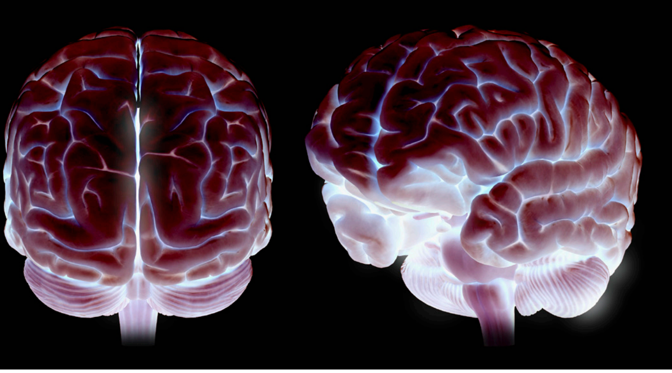
- **Optimization of training protocols**
- **Factors that influence memory performance**
- **Selective attention in combat**
- **Social behavior and group dynamics**
- **Post-traumatic stress disorder (PTSD) susceptibility and treatment**
- **Diagnosis and treatment of traumatic brain injury**

Important recent advances have resulted from cross-disciplinary collaborations between different subfields of neuroscience, as well as between neuroscientists and researchers in other fields, such as chemistry, mathematics, or genetics. The growing emphasis on dynamic properties of the brain, along with the availability of large datasets from techniques like multineuron recording, increasingly requires and rewards collaboration between experimental and theoretical researchers. As a relatively young field, neuroscience is particularly dependent on technical advances because the brain's complexity can be best investigated through sophisticated experimental methods targeted to particular brain areas and cell types in alert animals.

Work on artificial intelligence has led to relatively less progress in neuroscience than had been anticipated some years ago, mainly because computers and brains approach problems in different ways. Brains are optimized for solving poorly defined problems, while computers are best at solving well-defined ones. In addition, brains make a much more efficient use of energy than computers, though scientists do not yet understand why.

The workshop participants identified fifteen research areas that are promising for future advances and would benefit from additional funding.

- **Decision-making**
- **Ability to modify strategy and goals based on context**
- **Attention**
- **Face recognition**
- **Human behavioral studies**
- **Biomarkers to predict individual susceptibility to PTSD or traumatic brain injury**
- **Reward valuation and its plasticity**
- **Neural basis of functional imaging signals**



- Motor control and planning
- Plasticity in inhibitory neurons
- Acquisition, internal organization, and recall of memory
- How information is transformed between cortical layers and areas
- Population coding in groups of 100 to 10,000 neurons
- Relationship between high-level and low-level representations
- Functions of large-scale brain systems in behaving animals

Targeted investments in infrastructure present strong opportunities for impact on neuroscience research, which is often limited by the availability of specific technical advances, such as tools for stimulating, inhibiting, or recording activity in particular cells:

- Translate molecular techniques used in rodents to Rhesus monkeys
- Make voltage-sensitive dyes faster and less toxic
- Increase precision of genetic targeting for molecular tools
- Improve microscopy techniques used to visualize active neurons
- Record and perturb many neurons in multiple brain areas
- Measure true neural activity over millimeters of cortex, resolved in depth
- Provide computational tools for the analysis of large datasets
- Standardize methods for behavioral analysis across animal models
- Provide support and service contracts for major equipment
- Use Multidisciplinary University Research Initiative grants to encourage collaborations
    - between theoretical and experimental neuroscientists
    - between neuroscientists and researchers in other fields
    - between neuroscientists who work on different animal models

Neuroscience research has made great strides in the past twenty years. Although the brain is stunningly complex, there is enormous leverage in understanding how people think and act as a result of their innate biology, particular experiences, and environmental pressures. The field stands on the brink of developing an integrated understanding of how neuronal activity combines into circuits, which then produce behavior. Strategic investment now by the Department of Defense into the areas of research and infrastructure recommended in this report could support substantial progress over the next two decades, with strong potential for translational impact.

INTRODUCTION

A person's brain contains 86 billion *neurons* (italicized terms are defined in the Glossary), which connect to other neurons through an average of one thousand contacts each. **Thus, the total number of possible activity states within a single brain exceeds the number of particles in the known universe.** In addition, brain cells come in a variety of types, which have different functions. Neurons differ in their size and shape, in the chemical *neurotransmitters* released at their *synapses* to carry signals to other neurons, in their local and long-range *axon* connections, and in the sorts of information that they carry. *Glia,* another large class of brain cell types, also contribute to information processing, in addition to providing support for neural functions. This complex organization allows the brain to outperform the most advanced computers in solving certain classes of problems, while using only twelve watts of power, the same amount as the light inside a refrigerator.

Neuroscientists have made notable progress in understanding how the brain works, as 22 invited researchers discussed with eight Department of Defense repre-

Dr. Robert Desimone, Director of the McGovern Institute and Berkey Professor at MIT, summarizes results of a breakout group.

Photo credit: Keith Mulet, Office of the Executive Vice President for Research, Columbia University

sentatives (Appendix I) at a meeting in New York City from March 11 to March 13. Dr. Michael Goldberg, David Mahoney Professor of Brain and Behavior at Columbia University, organized the conference at the request of Dr. G. Michael Purdy, Executive Vice President, Columbia University. The workshop was supported by the Office of the Assistant Secretary of Defense for Research and Engineering (Basic Research). The discussion, which focused on *cognition* and the neural basis of behavior, opened with a brief presentation by each scientist on the key questions in the field today and how the Department of Defense might help to address them. In discussions over the next two days, the participants explored these issues more deeply and developed a set of recommendations based on questions distributed before the meeting (Appendix II).

The field's main aim is to determine the mechanisms by which activity in brain circuits produces sensory perception and behavior. A deeper understanding of basic neuroscience could lead to significant progress in areas of concern to the Department of Defense, including predicting and reducing vulnerability to PTSD, which is a disorder of unwanted memories, diagnosing and treating brain trauma, increasing training effectiveness, and augmenting selective attention and judgment under challenging conditions. Single neurons are relatively well understood, the researchers agreed, but much remains to be discovered about how their interactions enable the brain to process information effectively. The Nobel Prize–winning model of Hodgkin and Huxley, published in 1952, described how voltage-sensitive proteins control the flow of ions into and out of neurons to produce regenerative electrical signals called action potentials that travel down axons to activate synapses. This activation causes the synapse to release neurotransmitters, which bind receptors on a second, recipient neuron to produce a chemical or electrical signal. If enough synapses on the recipient neuron are activated at once, then it produces an action potential of its own.

Over time, these activity patterns modify the strength of synapses, so that frequently used connections are reinforced and rarely used connections are weakened or lost. This process, known as ***synaptic plasticity,* allows the brain to learn and adapt to its environment.** Synaptic plasticity is particularly powerful early in life, and recent work has identified ways to increase it during adulthood as well. The biochemical pathways that mediate synaptic plasticity in excitatory neurons are extensive and redundant. The brain must regulate synaptic plasticity to balance the need for learning with the need for stability, as runaway synaptic strengthening can produce disorders such as epilepsy. Maladaptive synaptic plasticity can lead to many problems, for example addiction or PTSD.

Action potentials function as a pulse code, carrying information that varies with a neuron's location in the brain and its connections to other neurons. For example, neurons in the primary visual *cortex* combine incoming information about light and dark spots in the world to calculate the locations of lines and edges, which later visual areas then assemble into object representations. Individual brain regions specialize in making particular computations, from localizing sounds in space to recognizing faces to assigning values to stimuli in the environment. **Because**

86
billion neurons
(in a person's brain)

glia
Cells of the nervous system that are not neurons and that support brain function.

cortex
The largest part of the human brain

Brains are good at solving poorly defined problems, such as motor control, visual perception, or problems requiring new, creative solutions. In contrast, computers are good at solving well-defined problems, in which the steps can be specified exactly.

many neurons are involved in producing any perception or behavior, the questions that are possible to ask in experimental neuroscience research depend on technical advances in the ability to record signals or manipulate chemical or electrical activity simultaneously in many neurons distributed across multiple brain areas.

Most brain processes occur beneath conscious awareness. Vision feels effortless, though it takes roughly a third of the human cortex to process data from this sense, because the calculations involved are not accessible to awareness. For this reason, introspection is a poor guide to brain function, though researchers are beginning to study the neural basis of subjective experience rigorously. For example, researchers have combined visual illusions that can be perceived in two ways with *functional magnetic resonance imaging* (fMRI) to determine how brain activity changes as the subject's perception of the same stimulus switches back and forth.

Throughout history, the brain has been compared to the most advanced technology of its time, from Greek writing tablets to telephone switchboards, and most recently to computers. The computer analogy is inexact, however. **Because humans must respond rapidly to ambiguous signals and events, the brain must make many calculations in approximate ways, good enough to lead to adaptive behavior most of the time.** Brains are good at solving poorly defined problems, such as motor control, visual perception or problems requiring new, creative solutions. In contrast, computers are good at solving well-defined problems, in which the steps can be specified exactly. Most artificial intelligence research demonstrates how a function might be accomplished in theory rather than providing insight into how the brain actually processes information in practice. In addition, computers, designed for a particular function, tend to calculate exactly the values needed for the task and to deal poorly with ambiguity.

Furthermore, there is a huge structural difference between computers and the brain. Computers process data at gigahertz speeds (1 billion cycles per second), but even the most sophisticated supercomputer arrays have only a few thousand nodes. Each neuron in the brain processes information at kilohertz speeds (1,000 cycles per second), but there are billions of them, and often a single neuron can be connected to hundreds or thousands of other neurons. Together, these properties make brains more flexible and more variable in their responses than computers.

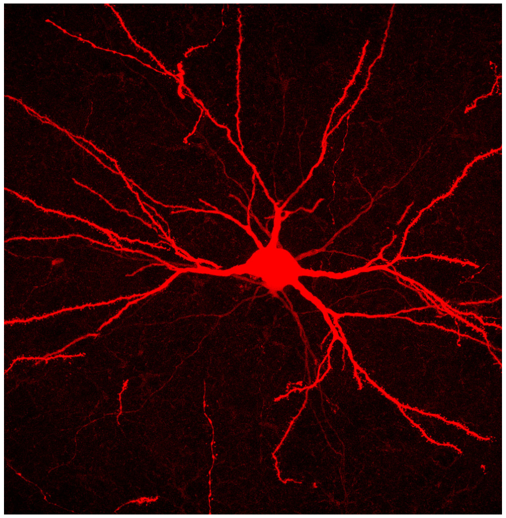
RELEVANCE TO DEPARTMENT OF DEFENSE NEEDS

The field of neuroscience can offer insight into many issues of concern to the military. Effective training of personnel depends on understanding the brain's learning and memory systems. Cognitive neuroscience and learning research can inform the design of better training strategies, including computer-aided instruction and game-based simulations. A variety of brain and environmental conditions influence memory, which is important not only for training but also for learning to respond correctly to changing conditions.

In a fast-moving situation like combat, it becomes crucial to deploy attention correctly, resisting distractions while remaining alert for important events. Research on attention can help determine how to present and scan for information in ways that work with the brain's predispositions. In particular, neuroscience can inform the design of better human–system interfaces, especially human-autonomous system interfaces. Pattern recognition and control systems design can also be aided by neuroscience research.

Team performance depends on appropriate interpersonal interactions. Research into the brain basis of social behavior can lead to training and selection procedures to improve group dynamics. Social neuroscience can also provide insight into the causes and treatment of disruptive social behavior.

Combat-related injuries often affect the brain. Susceptibility to traumatic brain injury and PTSD varies across people, and so does the response to treatment. Research into these areas can help predict individual risks and the effectiveness of different treatments for a particular person.



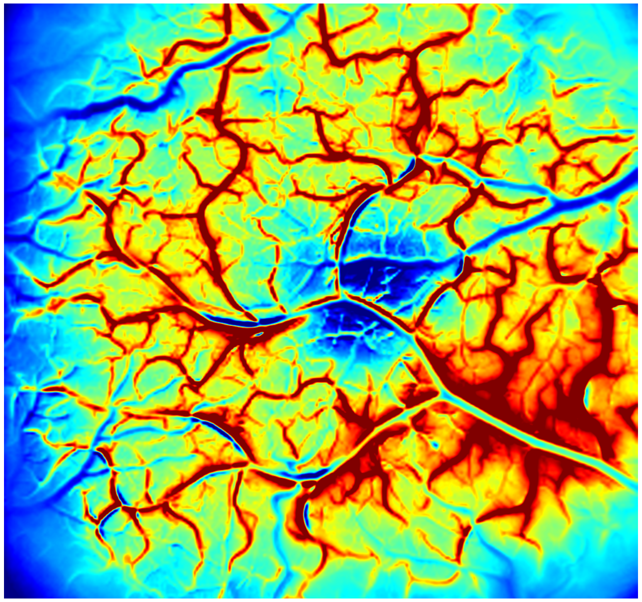
A confocal microscope image of the dendrites of a cortical layer 5 neuron labeled in a living rat. Not visible here are the thousands of its entangled, neighboring neurons. Each of the tiny "spines" along the dendrites are the site of a synaptic input from another neuron.

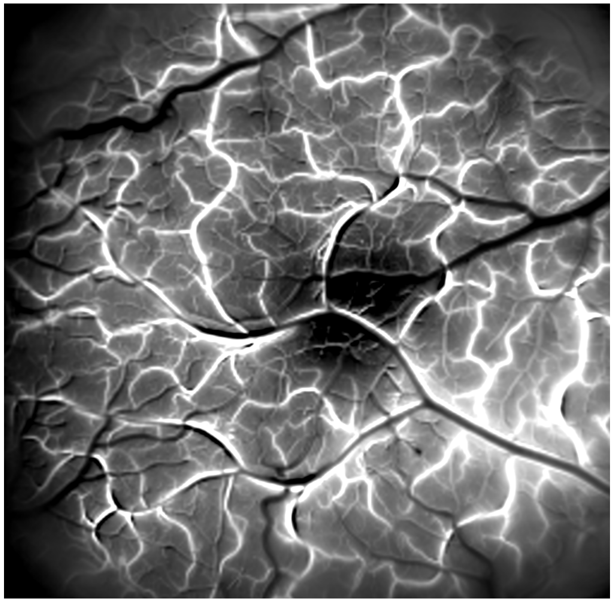
Photo credit: Carl Schoonover, Marissa Ilardi, and Randy Bruno, Department of Neuroscience, Columbia University

RECENT ADVANCES IN NEUROSCIENCE

Many exciting accomplishments of the past two decades have resulted from the integration of previously separate areas of inquiry. The increasing emphasis on dynamic properties of the brain, along with the availability of large datasets from techniques like multineuron recording and fMRI, has led experimental neuroscientists to work more closely with theorists. Quantitative analysis of the brain's dynamic properties can help make sense of the data through *computational models.* **The most productive partnerships involve close collaboration between experimentalists and theorists through all phases from experimental design through data interpretation.**

One example of the value of this approach is the concept of balanced *excitation* and *inhibition,* identified through an iterative process between theoretical and experimental research. Cortical neurons prevent runaway excitation by adjusting the strength of inhibition to precisely equal the strength of their excitatory inputs. In computational models, such balance is important both for stability of neural responses and for information processing. The strong excitation makes the circuit respond quickly to any input; inhibition then kicks in rapidly to reestablish balance and ensure that the circuit remains stable. Balanced models explain several characteristics of cortical neuron firing





Brain imaging signal from primary visual cortex of a monkey playing a periodic video game. The small patch at the center is the response to the stimulus that animal sees; the larger surround is a signal in anticipation of the start of the game.

Photo credit: Yevgeniy Sirotin, Shelby White, and Leon Levy Center for Mind, Brain and Behavior, Rockefeller University, and Aniruddha Das, Department of Neuroscience, Columbia University that are observed experimentally, such as temporal precision and tuned responses to environmental stimuli.

Another area where theory and experiment have combined productively is in understanding the circuit that animals use to map their location within the environment. In the rodent *hippocampus,* a brain region important for memory and spatial processing, most principal neurons are place cells, which fire action potentials only when the animal is at a specific location. Computational models show that such responses can be constructed from three other cell types that experimental neuroscientists have found in the entorhinal cortex, which provides a major input to the hippocampus. Grid cells fire in a series of locations forming a triangular grid, thus representing the environment in a context-independent way. Head-direction cells signal the angle of the animal's head relative to its surroundings. Border cells, which were predicted by theorists before they were identified experimentally, signal the animal's location relative to environmental boundaries. The recent development of new experimental techniques, discussed below, makes it possible to begin testing the detailed predictions of various models of this system.

Neurobiological studies of decision-making represent another area where circuit neurobiology and cognitive science come together to determine the brain mechanisms of how we make choices. Experimental and theoretical work has uncovered some basic neural computations underlying decision-making, such as slow time integration of evidence for or against choice options, winner-take-all competition leading to a categorical choice, valuation of choice outcomes, and reinforcement learning for adaptive economic choice behavior. Working out the mechanisms of such neural computations promises to provide a neuroscientific understanding of decision-making.

Major technical innovations have resulted from cross-pollination between neuroscience and other fields, particularly chemistry. Neuroscientist Roger Tsien and geneticist Martin Chalfie won a Nobel Prize in chemistry in 2008 for modifying the jellyfish-derived green fluorescent protein to allow molecular biologists to label neurons based on their protein expression or other characteristics. Such labels are also used to track lineages across many rounds of cell division during neural development. Tsien also developed a set of calcium indicator molecules, which permit spatially specific measurement of this ion, important for synaptic plasticity and other biochemical functions, in a large group of cells simultaneously. Voltage-sensitive dyes, an older technology, allow similar large-scale measurements of neural activity.

The participants agreed that **the most important recent technical advance in neuroscience is the development of *optogenetics*** in the laboratory of Karl Deisseroth. This technique allows neuroscientists to ask previously unapproachable questions by using light to activate or inhibit specific neurons with precise timing in living animals. The key to this technique is the insertion of microbial opsin genes, which code for proteins that pump ions across cell membranes in response to light, into particular neurons under genetic control. More advanced tools are now available that use different colors of light to control multiple cell populations in the same brain region.

Such approaches can be used to dissect the behavioral function of neural circuits. Two groups recently expressed

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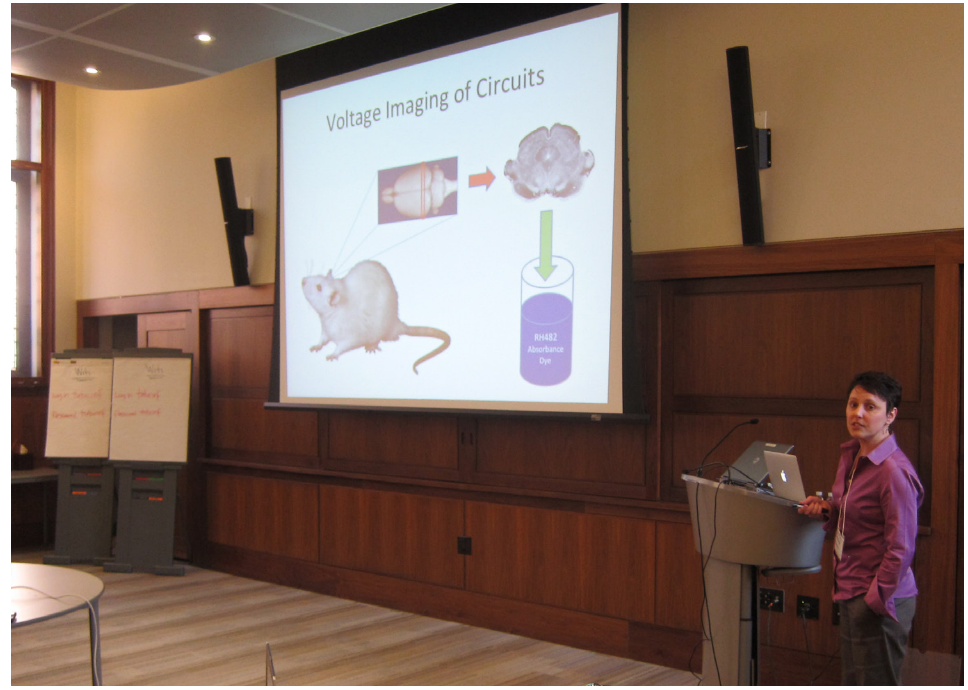

Above left: Dr. Dayu Lin from New York University Medical Center describing her research on neural circuits underlying aggression using mice as an animal model.

Above right: Dr. Michele A. Basso from University of California, Los Angeles, describing her work on voltage imaging of neuronal circuits underlying cognitive behavior and decision-making.

Photo credit: Keith Mulet, Office of the Executive Vice President for Research, Columbia University

opsin genes selectively in the neurons that were active during the formation of a specific spatial memory in mice and then used light activation to replay this memory in the animal's brain. Optogenetic techniques work reliably in rodents, but it has proven more challenging to translate them to other experimental animals. In particular, the development of optogenetic techniques for Rhesus monkeys would allow researchers to extend the power of rodent studies to our close primate relatives.

Another set of technical advances that has led to important experimental progress is the ability to study the role of molecules in behavior by genetically modifying mice. Molecular biologists can insert or delete a single gene in a certain cell type in a particular brain area and then regulate the timing of its expression by using drugs to turn regulatory elements on or off. Researchers have used this technique to dissect the function of the memory system in the hippocampus. For example, memory is enhanced by adult expression in the forebrain of a subtype of the N-methyl-D-aspartate glutamate receptor that is common in early development. As a practical application of this research, **neuroscientists have had some initial success in attempts to suppress unwanted memories as a treatment for PTSD.**

This line of inquiry raises an important conceptual issue: if changes in the expression of single genes can improve learning and memory, why would evolutionary pressures on intelligence not have caused these changes to occur already? It appears that cognitive enhancement is not simply advantageous, but involves trade-offs. For example, people with unusually good memory often have difficulties in sorting through large quantities of stored facts. That is, they could equally well be described as people with a deficiency in forgetting unimportant information. Similarly, children are more susceptible to epilepsy than adults, presumably because their synaptic connections are more easily strengthened.

The investigation of simple model systems has provided important insights into brain function. By studying the brain circuits active when baby songbirds learn their songs and adult birds sing, neuroscientists have reached a detailed understanding of how individual neurons interact to produce a complex motor behavior and modify it based on experience. Scientists studying the nematode worm *Caenorhabditis elegans* have used genetics, anatomy, physiology, and computational modeling to work out the mechanisms underlying a variety of behaviors, from spatial navigation to social interaction. The fruit fly *Drosophila melanogaster* has also been a productive model system for studying the molecular basis of behavior. Finally, in monkeys, the well-understood circuitry of the eye movement system has been used to probe cognitive questions like memory, motivation, attention, decision-making and spatial perception

The study of human subjects has also made significant contributions to neuroscience, particularly for abilities that are not well developed in other animals, such as language and future planning. Researchers can collect more data from people because they are easier to train and test than other animals, which is useful for the study of complex tasks and individual variation. Some areas of neuroscience were first studied in humans, including color vision, many visual illusions, attention, and aspects of motor control, and this work was then extended to other animals, where it is possible to investigate neural mechanisms in more detail.

In general, neuroscientists have progressively moved from investigating concrete sensory and motor signals to more abstract neural signals, such as those involved in planning, attention, or decision-making. An example of a productive experimental approach is the study of motion processing in the visual cortex of macaques. Researchers use a mathematical measure called *choice probability,* which compares behavioral accuracy with neural responses on a trial-by-trial basis, to determine whether the neural signals in a particular cortical area are sufficient to explain the behavior. If so, they use electrical stimulation to activate the same neurons to determine if the stimulation can evoke the behavior or inhibit neural function to determine if the behavior is disrupted. This approach has since been extended to the study of decision-making in the prefrontal cortex, using variants of the same motion task to facilitate comparison with the earlier work.

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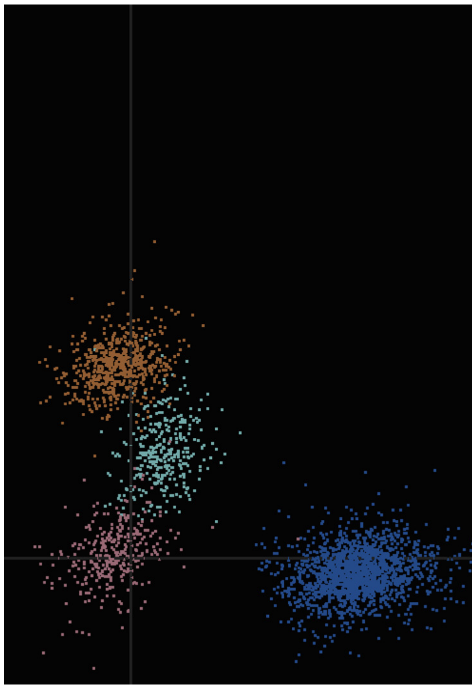
CONCEPTUAL CHALLENGES



This image reflects experiments observing how newly born neurons influence neural activity in the hippocampus, a center for learning and memory, as they are integrated into a circuit, a phenomenon that has potential implications for the action of antidepressants. The four distinct clusters suggest the neurophysiologist was observing four different neurons.

Photo credit: Clay Lacefield, Postdoctoral Research Fellow, Department of Neuroscience, Columbia University

Much of the discussion at the workshop centered on large-scale conceptual questions in the field. **The collection of data in neuroscience has outpaced the elucidation of general principles of brain function, participants agreed.** However, some researchers also felt that new theories were most likely to emerge from the analysis of larger datasets. It is even possible that neural computation depends on some variable that experimental neuroscientists are not yet recording reliably. A related problem is that many past studies of neural function have been correlational and might therefore be misleading. Optogenetic tools for manipulating brain function should be valuable in distinguishing causal relationships from correlations in the near future.

The new technologies should also help address another big question in neuroscience, the role of cell types, which is poorly understood at the moment. Part of the problem is that the electrodes used for physiological recording are most likely to pick up signals from the largest neurons in a brain region. Genetically targeted approaches should allow more balanced study of cell types of all shapes and sizes.

Another open question is how the nervous system maintains stability, preventing the runaway excitation that would be possible at many levels, from cells to circuits, while retaining the ability to react dynamically to events in the environment. Participants also agreed that the fundamental unit of computation in the nervous system is not yet clear, with possibilities ranging from single dendrites to individual neurons to neural circuits. Another puzzle is to what extent information is coded in neural firing rates versus synchronous firing among neurons. Solving this puzzle might give insight into another major question, how the brain manages to require so much less energy than electronic computers.

Whereas much effort has been devoted to studies of local circuits, very little is known about the operation and computational principles of a large-scale brain systems composed of many interacting subsystems or modules. Cognitive functions like decision-making or selective attention involve many processes and brain regions. Participants agreed that a major challenge today is to develop experimental tools and theoretical models for studying the organization, dynamical operation, and computational principles of large-scale brain circuits.

A long-standing aim of neuroscientists has been to apply principles across levels of brain organization, building progressively from molecules to cells to circuits to behaviors. **The field now has a realistic chance of developing an integrated understanding of how behavior emerges from the combined activity of neurons.** All the themes and recommendations discussed in this report will contribute to this aim. It is not yet clear which will be most valuable in the long run, but support for any subset of the promising areas discussed below, scientific or technical, will contribute toward the achievement of this overarching goal.

PROMISING RESEARCH AREAS

The Department of Defense requested specific recommendations of areas where additional funding could lead to substantial progress in the field. The goal is to gain insight into why individuals think, react, and make the decisions that they do. The phrase "s/he's only human" is a direct recognition of how often people make the wrong decision, react the wrong way, or generally do not act in their own best, long-term interest. Whether it is a third helping of pie at the dinner table or a foolhardy move on the battlefield, a deeper understanding of how our brains work cannot help but provide important insights on multiple fronts. The recommendations are presented in two groups: particular lines of research that are likely to reward investment and areas where research progress is being held back by infrastructure or technical limitations that could be overcome by strategic funding decisions.

The workshop participants identified fifteen areas of research that appear poised to achieve major results in the next two decades. In some cases, technical advances have opened up new areas of inquiry, while in others recent theoretical insights are likely to lead to further progress.

Theoreticians discuss the future of computational neuroscience. Clockwise from bottom left: Barry Richmond (NIH), Stefano Fusi (Columbia), Sandra Aamodt (science writer), Larry Abbott (Columbia), Mulugeta Semework (Columbia), Ken Miller (Columbia), John Cunningham (Washington), Thomas McKenna (Office of Naval Research), Xiao-Jing Wang (Yale), Robert Wurtz (NIH).

Photo credit: Keith Mulet, Office of the Executive Vice President for Research, Columbia University

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A particular strength of the human brain is flexibility, the ability to modify strategy and goals based on environmental and internal context. This abstract ability, based in the latest-developing parts of the brain, is the foundation of strategic planning and is linked to intelligence and success in work and life. Neuroeconomics researchers, among others, have begun to understand this capacity and how it develops, and continued progress in this area is likely.

Decision-making has been a major recent area of research because of its importance for adaptive behavior and because it is an experimentally tractable model of higher brain function. The next decade should extend these findings to more complex decisions, decision-making under time pressure, and a better understanding of how multiple brain areas interact to produce decisions. One promising approach would be to fund collaboration with theoretical neuroscientists who have experience at working with large datasets from multielectrode recordings.

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Because the external environment contains far more information than even the human brain can deal with simultaneously, the brain must select what objects in the world or what internal plans to concentrate on. This selection process is attention, which must balance internal goals and external distraction. **A unifying understanding of this attentional bottleneck would have major practical implications for the design of head-up displays and other information systems that need to provide information in a way that effectively drives action in a distracting environment**. Recent work has focused on filtering and gaining control of sensory inputs, and future work will address learning, adaptation, voluntary attention, and how goals modify attention.

Face recognition, which is difficult even for advanced computer systems, is a specialized skill of the brain. In general, object recognition depends on a combination of physical features and internal models that interact across brain regions. **Some participants believe that over the next twenty years it should be possible to use neural principles to build an artificial face-recognition system as accurate as the brain, which could be used to address security concerns.** The massively parallel processing available from modern computers, in conjunction with computational models, should drive progress on this aim.

Detailed research on neural mechanisms of behavior are mainly done in nonhuman animals because they require invasive techniques. However, **quantitative behavioral studies in humans can be an inexpensive way to test ideas about neuronal circuitry derived from other animal models.** Such studies could determine the human relevance of large areas of research done on other animals.

Previous research suggests that genetics and childhood experience interact to determine the varying capacities and vulnerabilities of individuals. Researchers may soon be able to develop biomarkers that predict such individual differences, in terms of brain structure or behavioral testing. For example, recent work suggests that people who have a small hippocampus may be especially susceptible to future PTSD. The outcome of traumatic brain injury also varies across individuals, and it may be possible to predict the appropriate strategies and monitoring of therapy for such brain disorders in particular individuals.

Dr. Michael Goldberg (Department of Neuroscience, Columbia University), the organizer of the workshop, introducing Dr. Robert Wurtz (National Eye Institute), the keynote speaker at the opening dinner.

Photo credit: Keith Mulet, Office of the Executive Vice President for Research, Columbia University

An important role of the brain's emotional system is to assign values to environmental features and potential actions, based in part on the history of reward and punishment associated with these features in the past. This capacity is an important basis for adaptive behavior, as it helps to determine which goals an individual will pursue. Its dysfunction is a potential source of behavior disorders, for instance in addiction. **Determining how the brain assigns value and how these values vary with experience is an important near-term aim.**

The detailed neural basis of functional imaging signals, especially fMRI scanners, remains obscure. The widespread use of this fascinating tool may have outstripped researchers' understanding of what they are measuring, and continued efforts need to be directed at improving the tool itself. In particular, the relationships among blood oxygenation, subthreshold neural signaling, action potentials, and local control of blood flow are likely to be complex but contribute importantly to the interpretation of fMRI signals.

The motor system, which plans and executes movements, is notably vulnerable to brain trauma and neurological diseases. Research on motor planning and execution investigates how the brain initiates and coordinates the complex set of muscle actions involved in, for instance, reaching out for a cup of coffee and taking a sip. Researchers do not yet know why motor performance improves with practice, what underlies interindividual differences in ability, or how training interacts with endogenous plasticity.

Synaptic learning rules in excitatory neurons are relatively well understood, from both experimental and computational perspectives. **Researchers expect similar progress in the near future in describing the properties of plasticity in inhibitory neurons. This process is important for the maintenance of stability in brain circuits,** and its failure may underlie disorders like epilepsy.

Plasticity in both excitatory and inhibitory neurons is a key component of the brain's memory system, but higher-level aspects of memory are also a promising area of study. The acquisition, internal organization, and recall of memory depend on interactions between different brain areas, including the hippocampus, entorhinal cortex, and other cortical areas. **Determining how memories are transferred between these areas and permanently stored is important for learning and the design of effective training programs.**

Understanding how information is transformed between cortical layers and areas is another promising area of future research. Techniques for measuring activity in local circuits will be valuable in this effort. A related question is the basic computation performed by neurons in brain regions with different basic patterns of connectivity, such as the cortex versus the *cerebellum.* **One hypothesis, for example, is that the cortex is specialized for unsupervised learning and the cerebellum is specialized for supervised learning.**

Recent progress in determining how individual neurons code information should be extended to *population coding* in groups of 100 to 10,000 neurons. This work will need to take into account neural cell types, dynamics, and connection patterns, as well as synaptic plasticity and signaling on different time scales. **Advances in this area are likely because of improved recording techniques, new strategies for managing large datasets, and collaboration between theoretical and experimental neuroscientists.**

High-level representations in the brain, such as recognition of a particular object, are maintained despite considerable variation in low-level features, for example due to changes in lighting, tilt of the object, or distance from the observer. **Achieving such invariance presents a substantial challenge for artificial intelligence systems, but the brain is extremely good at this type of calculation. Understanding the relationship between high-level and low-level representations is a promising area of research.** The solution is likely to rely on feedback loops between the two representations, which are flexibly gated by higher brain areas depending on context.

Much work has been done describing the activity of neurons in awake, behaving animals. **The visual and oculomotor systems of nonhuman primates have been particularly productive for the study of cognitive problems like attention, motivation, memory, deficient decision-making, or spatial perception.** However, it remains unclear how networks within the brain create that activity. Future progress will depend on studies of neural interactions, both within a particular brain area and between brain areas, to reveal the functions of large-scale brain systems in behaving animals.

INVESTMENTS IN INFRASTRUCTURE

The Department of Defense could advance progress in neuroscience by funding new tools for examining brain function. Participants identified ten infrastructure needs that would substantially improve researchers' ability to investigate key questions in the field. It should be practical to develop these techniques as extensions of existing approaches over the next decade or so. This line of investment presents a unique opportunity to advance neuroscience research because the conservatism of study sections at the National Institutes of Health often makes it difficult to get support for technique development, which is viewed as risky despite its obvious importance.

Rhesus macaques are the most common primate models in neuroscience, as their brain function is highly similar to that of humans. But molecular and genetic tools have been developed mainly in rodents, and additional work is required to extend their use to primates. **Translation to macaques of optogenetics and other molecular tools would be extremely useful to the field.** The ability to knock out particular genes in a primate would have obvious implications for gene therapy in humans, as well as expanding the potential of basic research in many areas of biology. Other molecular tools that would be helpful for research in primates include transynaptic transport approaches to tracing axonal connections, chemically activatible agents (such as a glycine channel that can be activated by the drug Ivermectin), a class of artificial drug-activated receptors called DREADDs (Designer Receptor Exclusively Activated by a Designer Drug, based on the M3 and M4 subtypes of muscarinic receptors), and siRNAs, which prevent translation of particular receptors within selected neurons. A number of laboratories are currently working toward these ends, but **a centrally coordinated effort would be a more efficient use of resources.** Extended, full-effort collaborations between molecular biologists and neuroscientists who work with macaques are necessary to achieve these goals.

Improvements in voltage-sensitive dyes would also be beneficial for the study of neural circuits. Current dyes based on fluorescence resonance energy transfer have time constants in the hundreds of microseconds, too slow to capture all neural signaling. Dyes based on the physical movement of a charged moiety have time constants in milliseconds but a lower signal-to-noise ratio. The new molecules need to be fast enough to capture action potentials, with a good signal-to-noise ratio and low light-induced toxicity. The ability to deliver the dyes through genetic targeting would also be helpful in allowing researchers to direct the sensors to particular cell types within brain tissue.

Overall, neuroscience research would be much more productive if the **genetic targeting of molecular tools** became more precise. Participants requested an improved ability to target cell types, connected networks, and active neurons. There are only a few classes of neurons that can be targeted by specific promoters, limiting the questions that researchers can ask. An important step in this direction

Participants identified ten infrastructure needs that would substantially improve researchers' ability to investigate key questions in the field. It should be practical to develop these techniques as extensions of existing approaches over the next decade or so.

Scientists discussing the most promising and challenging areas in the future of neuroscience. Clockwise from bottom left: Carlos Brody (Princeton), Annegret Falkner (New York University), Jay Myung (Air Force Office of Scientific Research), Graeme Davis (University of California, San Francisco), Mike Long (New York University), Dayu Lin (New York University), Randy Bruno (Columbia), Mark Mayford (Scripps Research Institute).

Photo credit: Keith Mulet, Office of the Executive Vice President for Research, Columbia University

would be the development of virus delivery systems that can carry larger amounts of genetic material, on the order of 40 kilobases of DNA, compared to the 4–8 kb that current viruses allow. The use of herpes viruses as a delivery system is one potential approach to this goal, which has given mixed results so far.

In addition, the **optical methods used to visualize activity indicators** would benefit from further refinement. Two-photon microscopy uses long-wavelength light, so that a reporter molecule must absorb two photons to emit a fluorescent signal. The technique has many advantages for imaging in the living animal, including low background emissions, a sixfold increase in imaging depth within the tissue, and low phototoxicity. However, the technology also has drawbacks: in particular, it is too slow to represent important neural dynamics. Solving this problem would increase the technique's usefulness.

Recent advances in electrode design now allow researchers to record from approximately one hundred neurons simultaneously. To investigate interactions between brain regions, researchers would like to have **systems to allow recording and perturbation of that many neurons in multiple brain areas.** This system would constitute a significant but manageable extension of current technology. Systems that allow long-term recording of multiple neurons in alert animals already exist, but they are expensive and unstable. Advances in miniaturization and wireless signal transmission have the potential to improve this approach into an off-the-shelf solution rather than a highly specialized resource of the technologically gifted.

Optical imaging, which records indirect measures of neural activity, has contributed a great deal to the understanding of cortical function. However, a **measure of true neural activity over millimeters of cortex, resolved in depth,** would be even more helpful. A possible basis for such a system would be bioluminescent detection of activity, using a calcium-sensitive photoprotein. This approach has been used successfully in freely moving zebra fish and insects, and recent proof-of-principle experiments have suggested that a stronger bioluminescent signal is detectable in mice. Further development of this technology in mammals could allow researchers to monitor activity in the same neurons over long periods of time, without restricting the animals' behavior.

To support these new imaging systems, researchers need **sophisticated computational tools for the analysis of large datasets.** New methods for dimensionality reduction to simplify recording and imaging data would make it easier for researchers to work with large datasets. Organizing collaborations between experimental neuroscientists and mathematicians is likely to be a productive approach to this aim.

Many participants agreed on the need for rigorous, reproducible, and sophisticated analysis of behavior in humans and animals. A common approach that could be compared easily across species would be particularly useful. Much behavioral analysis is currently done by researchers who are not trained in comparative behavior and may not be conversant with potential confounds and concerns. **The design and automation of a standard method by behavior experts that would provide a turnkey approach to behavioral analysis for researchers in many disciplines could move neuroscience forward significantly.**

Participants agreed that funding is needed for **support, such as specialized technicians, and service contracts for major equipment** like fMRI machines. In general, it is much easier to persuade funding agencies to make investments in shared equipment than to arrange to support that equipment after it is purchased. This situation is unfortunate because the ongoing value of research efforts relying on the equipment depends strongly on such support. Expansion of DURIP (Defense University Research Instrumentation Program) to cover support for fMRI machines would be one possible approach to this aim.

The Department of Defense could also move neuroscience forward by providing **support for neuroscientists to collaborate across disciplines** (especially between experimental and theoretical research), between researchers who study different animals, and with scientists in other fields, such as chemistry, mathematics, and genetics. The challenges of neuroscience have outgrown the boundaries of single disciplines within neuroscience. Advances will come from broad collaborations between physiologists, chemists, and computational, cellular, molecular, and developmental neuroscientists. Some of the most important recent advances in the field have resulted from such collaborations, and there is undoubtedly more to be gained from cross-fertilization with other areas of science.

Several participants pointed out that there are substantial barriers to forming good working relationships across disciplines. It often takes several years of conversation to reach across expertise boundaries and agree on what language should be used to describe phenomena, which variables are important to measure, and even what constitutes “understanding” a particular brain function. To work through such issues successfully, **collaborating researchers need funding stability and commitment to the process,** which could be encouraged by five-year Multidisciplinary University Research Initiative grants.

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INTERNATIONAL CENTERS OF EXCELLENCE

The United States has traditionally been a world leader in neuroscience research.

The United States has traditionally been a world leader in neuroscience research and remains strong in the field today. The failure of federal support for neuroscience even to keep up with inflation in recent years may jeopardize the U.S.'s leadership in this field. The best research from Europe in some areas is as good as the best research from the U.S., although the general level of research in the U.S. is still stronger. Germany and the United Kingdom stand out as strong centers of neuroscience. Israel is a leader in computational modeling of the brain. Japan also has world-class neuroscience research, especially in work with awake macaques.

Some developing countries have recently made substantial investments in neuroscience research. Two neuroscience institutes in China, at the Shanghai Institutes for Biological Sciences and at Beijing University, are producing important results. The Chinese government supplies its researchers with impressive resources, including top-quality equipment. Indian neuroscience is also coming up fast. The Center for Neuroscience at the Indian Institute of Sciences in Bangalore and the Center for Brain Research in Manissar are two developing resources in India, although their work may be hindered by increasing hostility to animal research there.

In the past few decades, most foreign scientists who were trained in the U.S. or Europe would spend the remainder of the careers abroad. **Now many foreign scientists are returning to their home countries to work, as conditions there become more attractive, permanent residency in the U.S. becomes more difficult to achieve, and the funding situation in the U.S. has become more difficult than in many other countries.** This trend is particularly noticeable for Chinese scientists. The movement of talented scientists from developing countries to the U.S. provided an advantage for this country, and its reversal is likely to reduce research progress here.

CONCLUSIONS

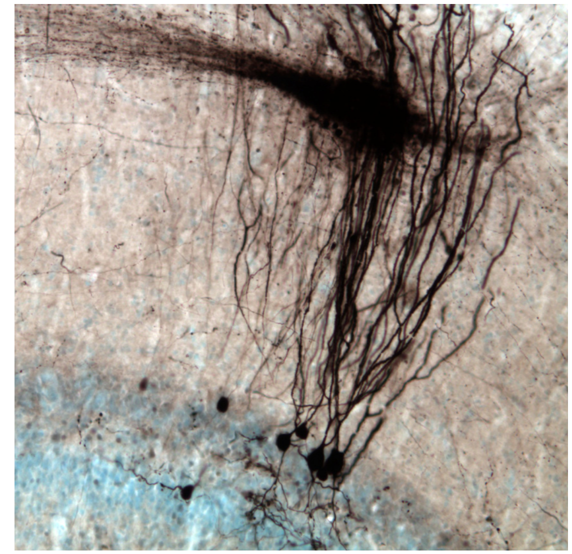
The next two decades should lead to substantial achievements in neuroscience. As described in this report, researchers are collecting large datasets and analyzing them with new mathematical approaches, which is providing insight into information coding by groups of neurons. New tools for recording and manipulating activity in selected sets of neurons have made it possible for scientists to ask questions that simply could not be addressed until a few years ago.

Participants were optimistic that many important problems are likely to be addressed in the foreseeable future, with direct potential impact on areas of interest to the Department of Defense, such as training, improved attention and observational thinking, enhanced decision-making, stronger social dynamics, and more productive human-autonomous system interfaces, as well as identification of susceptibility to and improved treatment of traumatic brain injury and PTSD.

Key opportunities for the Department of Defense to accelerate progress are:

- **To provide consistent support for the development of new technologies to allow researchers to peer more deeply into the brain**
- **To encourage long-term collaborations across various subdisciplines of neuroscience as well as between neuroscience and other fields, such as physics, chemistry, psychology, and economics**

The United States has led the creation of this relatively new field of neuroscience. Progress has been remarkable across many fronts, pointing the way to multiple promising fields of inquiry. Many of the participants felt that the next two decades should see transformative discoveries with critical translational impact, assuming creative and consistent support.



Use of biotinylated dextran amine (BDA) to image neuronal circuits in a fish brain. Once inside a neuron, BDA spreads across its entire span, revealing dendrites (the vertical lines) and their attendant round somata (at bottom). Axons can also be resolved (shown sweeping in from the top left), presumably forming synapses onto the dendrites.

Photo credit: Nathaniel Sawtell, Department of Neuroscience, Columbia University *hippocampus*

A brain region central to learning, memory, spatial navigation, and regulation of emotional response.

AXON

A LONG, THIN STRUCTURE THAT EMERGES FROM A NEURON, SPECIALIZED FOR THE LONG-DISTANCE TRANSMISSION OF INFORMATION BY TRANSMITTING ACTION POTENTIALS ALONG ITS LENGTH TOWARD ITS ENDS, WHERE SYNAPSES RESIDE.

cognition

Higher brain functions such as thinking, regulation of emotional responses, and declarative learning and memory.

GLOSSARY

ACTION POTENTIAL: A spikelike change in the voltage across the membrane of a neuron, lasting approximately one-thousandth of a second and able to travel down the axon to its ends, where it triggers the release of neurotransmitters.

AXON: A long, thin structure that emerges from a neuron, specialized for the long-distance transmission of information by transmitting action potentials along its length toward its ends, where synapses reside.

CEREBELLUM: A brain area occupying about one-seventh of the brain in most mammals, which integrates sensory information to drive perceptions, movement, and higher functions.

COGNITION: Higher brain functions such as thinking, regulation of emotional responses, and declarative learning and memory.

COMPUTATIONAL MODEL: A mathematical or computer simulation of a particular brain function, used by theoretical neuroscientists to test hypotheses about existing data and make predictions for new experiments.

CORTEX: The largest part of the human brain, occupying the great majority of the forebrain and three-fourths of total brain volume.

EXCITATION: Inputs that make a neuron more likely to fire.

FMRI (FUNCTIONAL MAGNETIC RESONANCE IMAGING): A noninvasive imaging method that uses the properties of oxygenated hemoglobin in blood to visualize where blood flow has increased in response to neural activity.

GLIA: Cells of the nervous system that are not neurons and that support brain function.

HIPPOCAMPUS: A brain region central to learning, memory, spatial navigation, and regulation of emotional response.

INHIBITION: Inputs that make a neuron less likely to fire.

NEURONS: Cells of the brain that process information and send it over long distances, including out to the body.

NEUROTRANSMITTER: A chemical messenger that is released from axon terminals at synapses and acts through receptors to excite or inhibit another neuron.

OPTOGENETICS: A technique for using light to activate or inhibit specific neurons with precise timing in living animals by inserting microbial opsin genes, which code for proteins that pump ions across cell membranes in response to light, into particular neurons under genetic control.

POPULATION CODING: Representation of information by a group of neurons in combination, which cannot be retrieved from any individual member of the group.

SYNAPSE: A junction between neurons where communication occurs, most often by the release of neurotransmitter from the axon of one neuron onto receptors in the dendrite of another neuron.

SYNAPTIC PLASTICITY: The capacity of neural tissue to change; a change in the properties of synapses, such as the strength of their connections.

APPENDICES

APPENDIX I: WORKSHOP ATTENDEES

NEUROSCIENCE RESEARCHERS

Michael Goldberg, Columbia University, meg2008@columbia.edu
Laurence Abbott, Columbia University, lfabbott@columbia.edu, *http://www.neurotheory.columbia.edu/~larry/*
Michele Basso, University of California, Los Angeles, mabasso@ucla.edu
Geoff Boynton, University of Washington, gboynton@u.washington.edu *http://faculty.washington.edu/gboynton/index.html*
Carlos Brody, Princeton University, brody@princeton.edu
Randy Bruno, Columbia University, randybruno@columbia.edu *http://neuroscience.columbia.edu/index.php?page=28&bio=562*
John Cunningham, Washington University, jpc74@cam.ac.uk *http://cunningham.wustl.edu*
Anniruddha Das, Columbia University, ad2069@columbia.edu *http://www.neuroscience.columbia.edu/index.php?page=28&bio=39*
Graeme Davis, University of California, San Francisco, Graeme.Davis@ucsf.edu *http://biochemistry.ucsf.edu/labs/davis/*
Robert Desimone, Massachusetts Institute of Technology, desimone@mit.edu *http://mcgovern.mit.edu/principal-investigators/robert-desimone*
Winrich Freiwald, Rockefeller University, wfreiwald@rockefeller.edu *http://www.rockefeller.edu/research/faculty/labheads/WinrichFreiwald/*
Stefano Fusi, Columbia University, sf2237@columbia.edu *http://www.neurotheory.columbia.edu/~fusi/*
John Krakauer, John Hopkins University, jkrakau1@jhmi.edu
Hakwan Lau, Columbia University, hakwan@psych.columbia.edu *https://sites.google.com/site/hakwan/lab*
Dayu Lin, New York University, dayu.lin@nyumc.org *https://linlab.med.nyu.edu*
Michael Long, New York University, mlong@nyumc.org, *http://longlab.med.nyu.edu/*
John Maunsell, Harvard University, maunsell@hms.harvard.edu *http://maunsell.med.harvard.edu/index.html*
Mark Mayford, The Scripps Research Institute, mmayford@scripps.edu *http://www.scripps.edu/research/faculty/mayford*
Ken Miller, Columbia University, ken@neurotheory.columbia.edu *http://www.neurotheory.columbia.edu/~ken*
Barry Richmond, National Institute of Mental Health, NIH, barry.richmond@nih.gov, *http://intramural.nimh.nih.gov/research/pi/pi_richmond_b.html*
Xiao-Jing Wang, Yale University, xjwang@yale.edu *http://wang.medicine.yale.edu/*
Robert Wurtz, National Eye Institute, NIH, non@lsr.nei.nih.gov

DEPARTMENT OF DEFENSE

Neil Gupta, AAAS S&T, Policy Fellow, neil.gupta.ctr@osd.mil
Kaleb McDowell, Translational Neuroscience Branch Chief, Army Research Laboratory, kaleb.g.mcdowell.civ@mail.mil, *http://www.arl.army.mil/www/default.cfm*
Tom McKenna, Program Manager, Office of Naval Research, tom.mckenna@navy.mil
Jay Myung, Program Manager, Air Force Office of Scientific Research, jay.myung@afosr.af.mil
Elmar T. Schmeisser, Program Manager in Neuroscience, Army Research Office, elmar.t.schmeisser.civ@mail.mil
Robin Staffin, Director for Basic Research, Office of the Assistant Secretary of Defense for Research and Engineering
Valerie Trabosh, Senior Scientist, Army Medical Research & Material Command-Military Operational Medicine Research Program, Valerie.A.Trabosh@us.army.mil *https://momrp.amedd.army.mil/*
Stuart Wolf, IPA, Office of the Assistant Secretary of Defense for Research and Engineering (Basic Science), Director, Institute for Nanoscale and Quantum Scientific and Technological Advanced Research (nanoSTAR), University of Virginia, stuart.wolf@osd.mil, *http://www.virginia.edu/nanostar*

WRITER AND RAPPORTEURS

Sandra Aamodt, Science Writer, sandra.aamodt@gmail.com, *www.sandraaamodt.com*
Annegret Falkner, New York University, Annegret.Falkner@nyumc.org
Linus Sun, Columbia University, ducaliner@gmail.com, *http://www.cumc.columbia.edu/dept/neurology/education/res/2011/sun.html*
Mulugeta Semework, Columbia University, mulugetas@gmail.com, *http://goldberglab.neuroscience.columbia.edu/*
Sara Steenrod, Rockefeller University, sarasteenrod@gmail.com
Pragna Gaddam, Columbia University, pg2412@columbia.edu

COORDINATORS

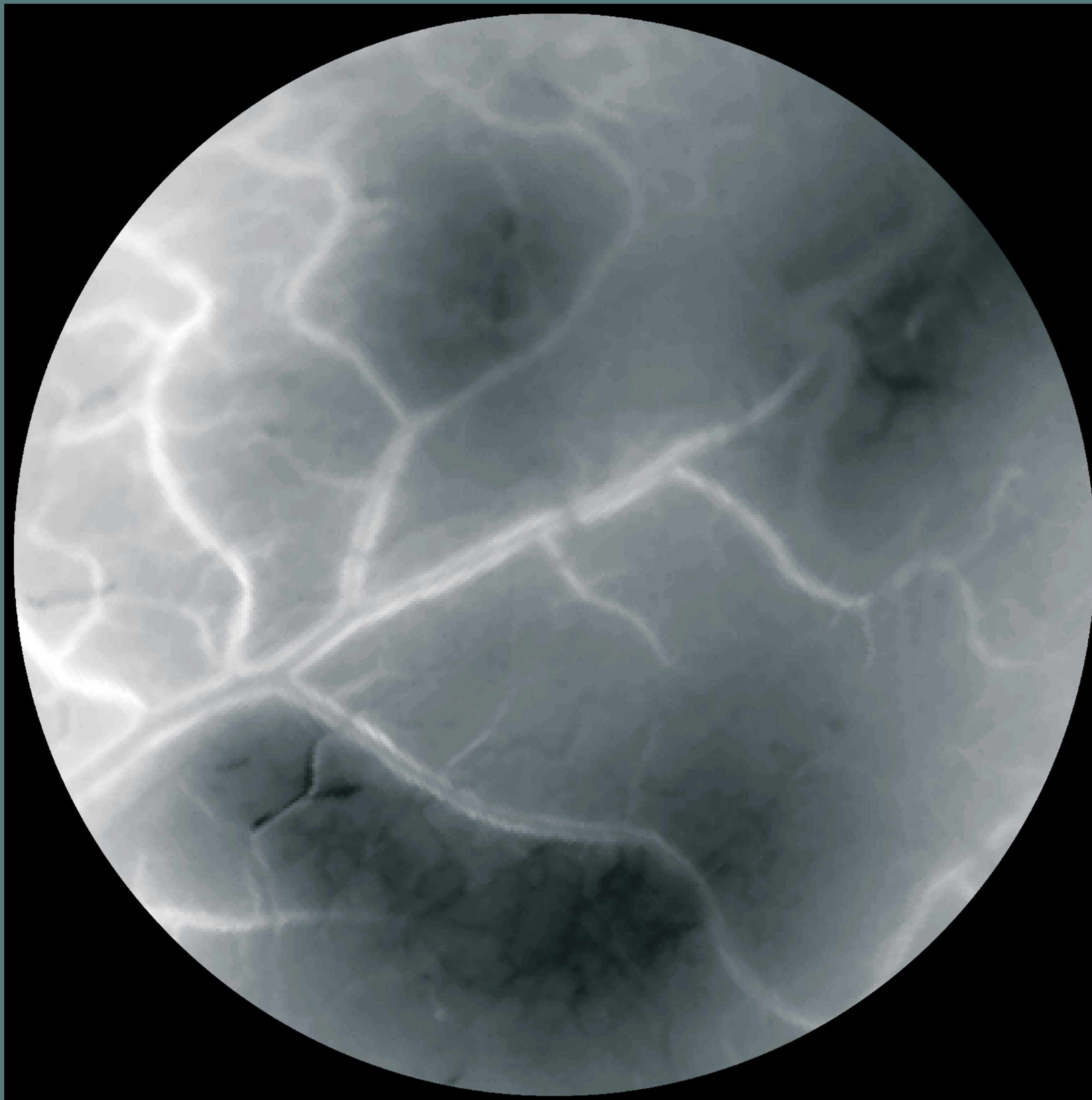
Victoria Hamilton, Director, Research Initiatives, Columbia University, vh2160@columbia.edu
Cynthia Barley, Executive Assistant to the Vice President for Research Operations, cb145@columbia.edu
Keith Mulet, Research Initiatives Administrative Coordinator, Km2774@columbia.edu

Numerous illustrations and information for legends were located with the help of Carl Schoonover, Ph.D. candidate in Neuroscience, Columbia University. This image as well as the illustrations on the inside front cover, pages 12, and 21, can be found and elucidated in *Portraits of the Mind: Visualizing the Brain from Antiquity to the 21st Century,* by Carl Schoonover, published by Abrams, www.abramsbooks.com.

APPENDIX II: QUESTIONS FOR ATTENDEES

OBJECTIVE: Where and how could creative intellectual and funding leadership enable transformative progress in 10 to 20 years?

- What research is moving the fastest?
- Where is there room to grow?
- What new areas do you see emerging in the next 10 to 20 years?
- What are the particular challenges to success?
- Are there particular infrastructure needs that the Department of Defense should be investing in? Why?
- Should the cottage industry of individual investigators and small group be replaced by big science (neuroCERN)?
- What questions do you want to ask today, but can't?
- Neuroscience originally drew people from all kinds of disciplines. Are there disciplines that could bring valuable tools or insights to neuroscience today?
- If you were the Department of Defense and there was an incremental 5% of funding made available to expend on bleeding-edge, but potentially high payoff research areas, where would you place the mad money?
- What have been the major breakthroughs in neuroscience over the last decade?
- Do you see new areas emerging in the next 5 to 10 years?
- What accomplishments or capabilities will be attainable in 5 to 10 years?
- Where are existing and emerging global centers of excellence in systems neuroscience?



As a monkey stared at the illustration of a smiley face, this ghostly image of a face appeared in the monkey's visual cortex, captured by a method called intrinsic signal optical imaging, in which a high-speed video camera captures minute variations of local blood volume.

Yevgeniy B. Sirotin, Shelby White and Leon Levy Center for Mind, Brain and Behavior, Rockefeller University, and Aniruddha Das, Department of Neuroscience, Columbia University.

Although the brain is stunningly complex, there is enormous leverage in understanding how people think and act as a result of their innate biology, particular experiences, and environmental pressures.

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Front Cover: Cortex in Metallic Pastels; Greg Dunn, 2012; Ph.D. student in neuroscience at the University of Pennsylvania; http://www.gregadunn.com