Spotlight on Neuroscience

A compilation of previously published articles from *Science* & *Science* Careers

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"As our knowledge of brain function explodes, there remains a major need to translate these findings into a meaningful understanding of human brain function in health and disease."

—Michael Ehlers

Neurodegenerative and Neuropsychiatric Disorders Research: A Cerebral Career Choice

By Emma Hitt October 5, 2012

As people live longer, the incidence of age-related diseases, such as Alzheimer's disease (AD), will also increase. By 2050, the number of people living with AD is expected to triple in the United States alone, from 5.2 million up to 16 million. This potential for increased incidence of AD, as well as other neurodegenerative diseases such as Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS), introduces a critical need for medical breakthroughs that prevent or slow the progression of these diseases. Likewise, neuropsychiatric disorders such as depression and schizophrenia contribute to a substantial proportion of disability among both younger and older individuals. As a result, the field of neuroscience holds a wealth of career opportunities for graduate students and postdoctoral scientists now and in the decades to come.

The math is inescapable," says Gregory Petsko, a researcher in neurodegenerative diseases and a professor of biochemistry and chemistry at Brandeis University, in Waltham, Massachusetts. "Unless we find a treatment for the prevention of the major neurodegenerative diseases— including Alzheimer's, Parkinson's, Lou Gehrig's, and so forth—within the next 30 or 40 years, we're cooked." According to Petsko, the increasing problem is fueled by not only the extended lifespan of the population but also by the fact that people are having fewer children. These two factors, says Petsko, will recharacterize the population pyramid, such that diminishing numbers of younger people will be supporting an ever-increasing aging population, changing the pyramid into a column or even an inverted pyramid.

According to Michael Ehlers, chief scientific officer for Pfizer Neuroscience, neuroscience-related diseases are "arguably the most significant unmet medical need in the industrialized world." As populations age, the burden of Alzheimer's disease and other dementias grows and is on a trajectory to consume a large percentage of all medical dollars, he says. "Neuropsychiatric diseases represent the largest cause of lost productivity and economic burden—more than all cancers and cardiovascular disease combined—with depression alone being the number one cause of disability. Yet, we have had very few novel therapeutics in this area for many years," he says. "As our knowledge of brain function explodes, there remains a major need to translate these findings into a meaningful understanding of human brain function in health and disease."

Michael Ehlers
CREDIT: Pfizer, Inc.

Not only is there a need for therapies, but there is also a need for research into the underlying causes of neurodegenerative and psychiatric disorders. "For many of these disorders, we still don't have effective treatments because the origin of these disorders and ways to target them is still under debate," says Heinz Reichmann, president elect of the European Neurological Society. "We are missing a significantly efficacious treatment, and it will be interesting, for example, to determine whether the alpha-synuclein and tau proteins, which contribute to the pathology of Parkinson's and Alzheimer's, respectively, can be targeted to provide more effective treatments," he said.

Heinz Reichmann

Addressing Important Needs

A key need in the field, Petsko says, will be to train physician scientists to translate basic research findings into clinical practice. According to Petsko, the number of Ph.D.s that have been trained in the last 30 years has increased dramatically, but the number of physician scientists has decreased somewhat. He believes that physicians who complete their M.D. training should be encouraged to go into research rather than having to enter clinical practice immediately for financial reasons (i.e., to pay off school loans). "There's nothing else we could do that would make more of an impact," he says. He adds that clinicians who also perform research may be more likely than basic researchers to understand how diseases manifest in people. "They are focused on the idea of cures or treatments in a way that many basic researchers are not," he says. "We need to bring smart people who are broadly trained into the field."

J. Timothy Greenamyre, professor and vice-chair of neurology at the University of Pittsburgh Medical Center and director of the American Parkinson Disease Association Advanced Center for Parkinson's Disease Research at the Pittsburgh Institute for Neurodegenerative Diseases, states that there is a need for students to receive formal training in topics s uch as "The Neurobiology of Human Disease," in which they not only learn disease mechanisms, but also interact with individuals affected by these diseases to learn how the disease impacts patients and their families.

J. Timothy Greenamyre

Along with adequate training of clinician scientists, research funding must also increase if sufficient headway is to be made in preventing and/or treating the looming increase of age-related disorders. According to Petsko, the total amount of money spent on Alzheimer's disease research is only about $500 million per year, and is much less for other neurodegenerative disorders. By contrast, about $2.4 billion per year is spent on AIDS, which affects a much smaller number of people. "AIDS provides a very valuable lesson, in that it is no longer considered a 'terrible' disease, in part, because of advances in biomedical science," he said. As the population ages, the same trend will hopefully take place in terms of increased funding in Alzheimer's disease and other neurodegenerative disorders.

According to David Nutt, president of the British Neurologic Association and professor at Imperial College London, in the United Kingdom, research opportunities exist in all areas of brain disorder research, but less than 10 percent of research funds are spent on this field even though these disorders cause about 30 percent of all disabilities. He suggests that people in the field should lobby for their discipline.

Specific Opportunities

A recent trend in academia has been for scientists to conduct increasingly collaborative research, and neuroscience-related research is no exception. Thus, graduate students and postdocs who focus on expanding their knowledge base and collaborating with others will create more opportunities for themselves. According to Greenamyre, the Pittsburgh Institute for Neurodegenerative Diseases was conceived and created to eliminate barriers that traditionally impede research on neurodegenerative (or any) disease. "As such, it is composed of about a dozen independent lab groups who share open lab space, and by virtue of both architecture and philosophy, there are no walls between lab groups," he says. Lab groups from neurology, neurosurgery, pharmacology, structural biology, and geriatrics all work together in the same space and on the same diseases.

Another recent effort for collaboration is the Massachusetts Neuroscience Consortium, which was initiated in June 2012. Their goal is to accelerate preclinical research, facilitate industry-academic partnerships, and create "a pioneering new model that is designed to leverage the rich research environment in Massachusetts," says Susan Windham-Bannister, president and CEO of the Massachusetts Life Sciences Center. The consortium brings together seven major industry partners who are willing to collaborate to develop significant advances in major neurological disorders such as Alzheimer's, Parkinson's, multiple sclerosis, and neuropathic pain. The companies contributing to the consortium are Abbott, Biogen Idec, EMD Serono, Janssen Research & Development, Merck, Pfizer, and Sunovion Pharmaceuticals. *(See sidebar for more information about this consortium.)*

The Massachusetts Neuroscience Consortium— a Collaborative Model

What do you hope to accomplish with the Massachusetts Neuroscience Consortium?

The Massachusetts Neuroscience Consortium is a pioneering new model for accelerating preclinical research, introducing academic researchers to the challenges of targeted research, and facilitating industry-academic partnerships. The pharmaceutical company sponsors will have facilitated access to all of Massachusetts academic and research institutions and will jointly fund projects that leverage the basic, translational, and clinical research expertise resident in the state—the world's highest density of neuroscience expertise.

According to Congressman Chaka Fattah (D-PA), an advocate for neuroscience research, "This new consortium...is an exciting development for future advances in brain science and medicine. The consortium can provide us with the model for a major national partnership of government, the pharmaceutical industry, leading academic researchers, and medical schools."

What are the major areas of need in this field in terms of research that you hope to address with the consortium's efforts?

Neuroscience is a complex discipline in need of both novel therapeutic *(cont.)*

PHOTO CREDIT: T. Hastings, University of Pittsburgh

For young scientists interested in translational neuro-science, pursuing research in the pharmaceutical industry is particularly rewarding and challenging, says Pfizer's Ehlers, and "offers the real potential to make discoveries that make medicines." His advice for young scientists is to think broadly and look outside of tradit-ional career paths. "Training programs for graduate students and postdocs can be quite one-dimensional, exposing trainees to the academic world but little else," he says. "There is a universe of scientific opportunities outside of the university."

At Pfizer Neuroscience, Ehlers says, they look specifically for young scientists with a combination of strong quanti-tative skills and deep knowledge in a specific area, but also with a broad curiosity about all areas of biology. "We also look for people with strong communication skills and an ability to work well collaboratively in teams," he says.

Graduate students and postdocs interested in a career in this field should also be on the alert for global opportuni-ties, as these diseases will afflict any modernized nation where lifespans are long. In Europe, says Heinz Reichmann, president elect of the European Neurological Society, each country has its own funding sources, both from industry and government, and there are manyfoundations that support research in this area.

New Technologies Provide Hope

Neurodegenerative diseases are among the most difficult to understand and treat, says Doug Williams, executive vice president of research and development (R&D) at Biogen Idec, a company that focuses on neurodegenera-tive diseases, including multiple sclerosis, Alzheimer's, and ALS. However, we are living in an era where new technologies such as genomic sequencing and advanced imaging will rapidly increase what we know about these diseases, he says. "By investing in translational medicine, including better neuroimaging and biomarker strategies, we will be able to make better decisions earlier in clinical development and improve the productivity of our R&D efforts." This type of investment, he says, "will also enable us to identify which patients may be more likely to benefit from a particular therapy, to determine if a compound is having the intended biological effect on its target, and to

(cont.) targets to treat neurological diseases as well as increased under-standing of basic mechanisms of function. Significant breakthroughs still elude us in this field, and millions of patients and their families are waiting to hear that we have developed better treatments for diseases such as Alzheimer's, multiple sclerosis, Parkinson's, ALS, chronic pain, and others. Interest has also been expressed by consortium members in projects to address the mechanisms of aging, cognition, and synaptic plasticity. Final priorities will be set by the charter members of the consortium.

What opportunities will the consortium and other similar models present for students or postdocs considering a career in neurodegenerative disease research?

We see the Neuroscience Consortium as an opportunity for academic research-ers—such as postdocs and graduate students—to build relationships with industry through funded projects and gain exposure to the industry style of research: short-term and results-oriented projects, industry standards for valida-tion, and resources. These opportun-ities will help young researchers as they determine their next steps in their careers and will facilitate even more effective and productive collaboration between academia and industry.

Given the cost and time involved with the development of new therapies, collaboration is more vital than ever in life sciences research. Traditional approaches to research and drug devel-opment have seen a dramatic decline in the number of new therapies moving through the R&D pipelines to patients. Collaboration is essential to accelerating R&D to make a positive impact on curing human disease and improving patient outcomes, especially in complex areas such as neuroscience. ∎

detect the progression of a disease even in the absence of new symptoms." Specific types of scientists who will be most sought after, says Williams, include computational biologists, cell biologists who understand modeling of human diseases, and stem cell biologists.
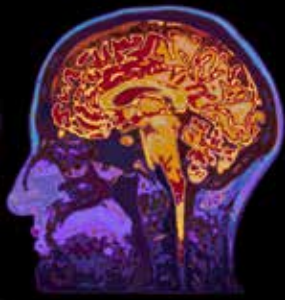
Jonathan Brotchie is founder and president of Atuka, Inc., a company with offices based in Canada, the United Kingdom, and China, that provides contract research and consultancy services for the biopharmaceutical industry, specifically to assist larger companies in developing novel therapeutics and diagnostics for Parkinson's disease.

According to Brotchie, advances may be slowed down not so much by a lack of ideas about drug targets and new therapies, but rather by a lack of understanding of the technologies and methodologies required to develop and validate these ideas. "There is a need to develop better animal models, to recapitulate and predict effects of agents on the molecular pathology of the disease process, and also to develop better imaging and biomarker technologies to assess, as early and precisely as possible, drug effects in clinical studies," he says.

According to Brotchie, job opportunities are likely to be plentiful at small companies that develop and use cutting-edge technology and capabilities. For example, a PET imaging company, Molecular Neuroimaging, in New Haven, Connecticut, which provides neuroimaging research services to the pharmaceutical and biotech industries, has sprung out of academia to support drug discovery in the field. "These approaches are not available within the pharmaceutical industry and are typically beyond the capabilities of academic groups," Brotchie says. The picture is very different now than before, he adds, when industry and academia rarely overlapped, but now "convergence, overlap, and cross-fertilization are all part of the environment today for anyone who wants to define a career with a mix of both approaches," he says.

The challenge now, says Biogen Idec's Williams, is to go beyond marginal improvements to making transformational changes in how we think about and treat neurodegenerative diseases. "We believe we are at the cusp of a new era when these advances will be possible, but they will require persistence, collaboration, and passion," he says.

Emma Hitt is a freelance medical and science writer residing in Marietta, Georgia.

> "Time and resources often prevent us from performing large well-powered studies but as long as the limitations of the study are borne in mind when interpreting the findings then the conclusions will not be misleading."
>
> —Katherine Button

Questioning the Validity of Neuroscience Results

By Elisabeth Pain April 30, 2013

Young (and perhaps many not so young) scientists often assume that most of what they read in the literature reflects real and well-established phenomena. But a recent analysis of scientific studies in neuroscience, which was published online in Nature Reviews Neuroscience earlier this month, urges caution both in reading the literature and in designing your own experiments. Neuroscience, the authors claim, suffers from a dearth of statistical power.

Katherine Button, a psychology researcher at the University of Bristol in the United Kingdom and first author of the paper, became aware of the problem when she was doing her Ph.D. at the university under the joint supervision of Glyn Lewis and Marcus Munafò. "I was frustrated by the research literature I was reading for my Ph.D. As a neuroscience undergraduate, I had thought that certain findings were established facts. Yet upon deeper reading, the evidence was conflicting and did not support the received wisdom," she writes in an e-mail to *Science* Careers. Munafò proposed an explanation: researchers' "reliance on small sample sizes." Together with researchers from the University of Oxford in the United Kingdom; Stanford University School of Medicine in Palo Alto, California; and the University of Virginia in Charlottesville, Button and Munafò set to quantify the problem of low statistical power in neuroscience.

Studying 49 neuroscience meta-analyses published in 2011, the researchers find that the median statistical power of the 730 included studies was 21%.

But the problem is not just that experiments are missing interesting effects. Over the last 50 years, neuroscience has seen an "increase in research flexibility and the complexity of study designs combined with the stability of sample size and search for increasingly subtle effects," the article's authors write. Such a combination "has a disquieting consequence: a dramatic increase in the likelihood that statistically significant findings are spurious." Low statistical power can also artificially amplify the magnitude of a true effect, and low-power studies are more likely to be affected by biases, such as the choice of statistical model, selective publication of outcomes, and inferior study design. There's an ethical dimension, too, beyond decisions about how many animals to use in an experiment. "[U]nreliable research is inefficient and wasteful."

Elisabeth Pain
CREDIT: Katherine Button

Early-career researchers in neuroscience and other biological fields are not adequately aware of the issue, Button writes in her e-mail: "Research methods and statistical inference are key to the current

model of bioscience research but their importance is not reflected in the time dedicated to their teaching in undergraduate courses." A lot is at stake. "Ignorance of basic methodological principles leads to poorly designed research and misleading conclusions. It undermines the whole point of scientific investigation."

More than an eye opener, the article offers practical advice on how to overcome some of these challenges, almost all involving increased openness and disclosure. More disclosure of how data were handled and reported, and making data available, can help other scientists spot false positives in your work. Making your materials available can facilitate efforts to reproduce your findings. And collaboration can allow data to be combined for larger sample sizes, a strategy that human genetic epidemiology has successfully used to boost the reliability of results in that field.

In her e-mail, Button advises young scientists to "[t]hink hard about the assumptions underlying [their] research design and be up front about any limitations. Time and resources often prevent us from performing large well-powered studies but as long as the limitations of the study are borne in mind when interpreting the findings then the conclusions will not be misleading." That may mean accepting that your findings are less exciting, she adds. "It is difficult as a young researcher balancing the pressures of a 'publish or die' culture with sound research practices, as these inevitably take longer and produce more measured conclusions. But I suppose it depends on whether your career aim is to … add genuine insight to human knowledge or confuse things by adding more false-positives."

Elisabeth Pain is contributing editor for Europe.

Over the past decade, the social neuroscience career trajectory has evolved quickly.

Peering Inside the Social Brain

By Siri Carpenter May 14, 2010

What makes it possible for people to love, hate, help, or betray one another? How do we decode facial expressions? How do we understand and regulate our own emotional experiences? How do we separate the self from the other, make moral judgments, or decide how much money to save for retirement? What causes some people to turn to religious extremism, heroin, or politics? How does the brain fail those with social deficits such as autism?

Questions like these sit at the junction of our social, emotional, and biological realities, and they drive the young but rapidly growing field of social neuroscience.

Until a few years ago, the idea that science could elucidate the neural foundations of social phenomena as complex as love, friendship, and trust "just basically seemed ludicrous," says Janine Simmons, chief of the National Institute of Mental Health's (NIMH's) program for affect, social behavior, and social cognition. Such "big questions" motivate many scientists to study neuroscience or psychology, she says—but soon they realize that the ability to address such questions is limited by technology. "It's just recently that people have not been laughed at for taking on these more complex questions," she says.

Janine Simmons
CREDIT: Barry Richmond

Scientists seeking to understand the neural mechanisms underlying social cognition and emotion have drawn on a variety of methods, including studies of patients with neurological damage and single-cell recording of brain activity in nonhuman animals. These research tools have proven valuable, but it was the ready availability, starting about a decade ago, of functional neuroimaging technology that fueled an explosion in social neuroscience.

An Exciting Field, with Limitations

When it became available for social science research, functional neuroimaging — which enables scientists to observe the brain in action — immediately appealed to social psychologists, and it immediately started to yield robust results. "Every year there is some finding that fundamentally shakes up how I think about the social brain," says University of California, Los Angeles, social psychologist Matthew Lieberman. "Within a very mature field like cognitive psychology, you're not going to see that. That's exciting — it makes you want to get out of bed in the morning and see what you're going to learn."

Neuroimaging, says Boston College social psychologist Lisa Feldman Barrett, allows scientists to tease apart the neural "ingredients" of complex psychological processes, which is hard to do

by studying behavior alone. "Imagine that you wanted to study how bread was made and all you could do was taste bread," Barrett says. "You couldn't really watch how the ingredients interacted with each other. You wouldn't really know much about how bread was made, and you'd have to guess a lot." The combination of behavioral and neuroimaging studies, she says, continues to provide a window into otherwise invisible mental processes.

Still, any careful researcher will tell you that functional neuroimaging has important limitations. One is that no single technology can reveal instantaneous changes in the activity of individual neurons, or even small populations of neurons, throughout the whole brain. Another is that the most widely available methods — functional magnetic resonance imaging (fMRI) and event-related potentials (a variation of electroencephalography) — reveal only how brain activity and behavior are correlated; their ability to demonstrate cause and effect is limited. Consequently, researchers need to be careful not to ascribe causality without justification, cautions University of Virginia social psychologist James Coan. "The critical issue is good logical theory and logical arguments about what the data are showing. Technology is not going to save us from that."

James Coan
CREDIT: Cat Thrasher

Another hazard for scientists armed with shiny new techniques is a tendency to miss or ignore what has come before. Dartmouth College social psychologist Todd Heatherton notes, "It's all too sad to see neuroscientists thinking they invented a concept, such as people working harder in the presence of others, when we have known about social facilitation for more than a century."

Rapid Growth

Over the past decade, the social neuroscience career trajectory has evolved quickly. When Harvard University social neuroscientist Jason Mitchell was starting out, he says that "there was all sorts of anxiety about whether what we were doing was even going to gain any kind of toehold in the field, or whether it was some weird, freakish sideshow." Scientists often had to book magnet time in the middle of the night when busy hospitals could spare the equipment. "I joke with my students about how I had to walk uphill both ways to get to the scanner," he says.

Those days are long gone. As the cost of high-resolution brain scanners dropped over the course of the 8 to 10 years, universities snapped them up for research. "Every year there would be twice as many scanners as the year before," Mitchell says.

The field's scholarly footprint has grown with the number of scanners. Today, the field boasts two scientific societies (the Society for Social Neuroscience and the Social and Affective Neuroscience Society), and two specialist journals (Social Neuroscience and Social Cognitive and Affective Neuroscience). Stand-alone meetings draw hundreds of scientists. Social neuroscience research regularly appears in high-impact journals such as *Nature*, *Science*, and *Neuron* and has been a subject of intense — if sometimes insufficiently critical — interest from the popular media. Four of the five recipients of this year's Janet Taylor Spence Award for Transformative Early Career Contributions are social neuroscientists.

Job opportunities in social neuroscience have expanded, too. Most top psychology departments in the country have hired at least one social neuroscientist, and many departments have hired several. In addition, a number of universities have hired a cluster of scholars working in the closely allied field of neuroeconomics, which deploys neuroimaging methods to study economic behavior.

Heatherton predicts that as more universities build imaging centers, the demand for scientists who use neuroscience methods to study social psychological questions will increase further. And even now, "There are more good jobs than there are qualified people available for those jobs, in part because the best candidates are still receiving training," he says.

Matthew Lieberman
CREDIT: Stuart Wolpert, UCLA

At the same time, the field is becoming more intellectually sophisticated and more challenging. "Our students have to be smarter and work harder than we did," Lieberman says. "There's going to be less and less low-hanging fruit, and when you go and interview for a job, there might be someone sitting in the audience who actually knows something about this work and can evaluate it."

Still, no formal social neuroscience graduate programs exist in the United States, although many universities have developed informal training tracks. The best, Heatherton says, provide interdisciplinary training by blending deep, expert, classical social science training with training from neuroscientists in imaging techniques. Less ideal are training programs in

Learn More About Social Neuroscience

Listed here are a few important papers in social neuroscience, which have increased our understanding of a range of social phenomena, including knowledge about the self, fear, social exclusion, and inferences about others. Access from the publisher's site may require a subscription or site license. Some papers are also available on the authors' Web sites.

Kelley, W. M., Macrae, C. N., Wyland, C. L., Caglar, S., Inati, S., & Heatherton, T. F. Finding the Self?: An Event-Related fMRI Study. *Journal of Cognitive Neuroscience* , 14, 785 (2002).

Adolphs, R., Gosselin, F., Buchanan, T. W., Tranel, D., Schyns, P., & Damasio, A. R. A mechanism for impaired fear recognition after amygdala damage. *Nature,* **433,** 68 (2005).

Eisenberger, N. I., Lieberman, M. D., & Williams, K. D. Does rejection hurt? An fMRI Study of Social Exclusion. *Science,* **302,** 290 (2003).

Mitchell, J. P., Macrae, C. N., & Banaji, M. R. Dissociable Medial Prefrontal Contributions to Judgments of Similar and Dissimilar Others. *Neuron,* **50,** 655 (2006).

which social psychologists or economists provide the imaging training, or in which neuroscientists who aren't trained in social psychology or economics are responsible for training others in those fields. Even after the most rigorous interdisciplinary graduate training, it's often necessary to seek a postdoc to fill in gaps.

Building Collaborations

Cutting-edge social neuroscience demands expertise in a wide range of fields, from social psychological theory and measurement to neurobiology and physics. The only way to achieve the necessary breadth without sacrificing depth is to build stable, interdisciplinary collaborations. "If you tried to do everything yourself, you'd just go crazy," Coan says. "The old model of the young faculty member who goes out and establishes his or her name with a theory and publishes a bunch of papers, ... a person just can't do that without jettisoning their quality of life."

The best way to become interdisciplinary is to become expert in one area first, then learn from colleagues in other disciplines, says social psychologist John Cacioppo of the University of Chicago in Illinois. "If you're not an expert in something, you have very little to offer an interdisciplinary group. Over time, you can become an expert in multiple areas."

As in any multidisciplinary field, communication skills are essential. "You have to learn to speak many scientific languages, because neuroscience is itself a multidisciplinary kind of field," Barrett says. For example, some neuroscientists work on rats, she notes, others with clinical patients, and still others on normally functioning brains. Even though her own work doesn't include nonhuman animals, she has to be able to read that literature and understand it. That isn't easy because, for one thing, parts of the brain are not labeled consistently across species. "It's not like somebody published a list of translations. You have to learn this along the way."

Cacioppo points to one more skill that's essential for doing team science: a tolerance for feeling ignorant. "There's a real level of tension that you have to be able to put up with as you learn," he says. "You feel like you're an expert, and then you dive into something you know nothing about. That's hard."

Lisa Feldman Barrett
CREDIT: Mark Karlsberg

People and Other Vital Resources

"It's not just about access to a magnet. That's the easy part," Coan says. More important is access to people: collaborators, students, and technical staff.

It's also important to work in a department that rewards scholarship in a way that's appropriate to the interdisciplinary nature of the field. "If I'm requiring someone to publish by themselves, I'm interfering with great interdisciplinary research," Cacioppo says.

The time to find out what resources a department can provide is when you're interviewing. "Places that can support this kind of work know what it needs," Coan says. Be firm about your

basic needs. If your department doesn't already employ technical personnel for neuroimaging, for example, "You need to negotiate a startup package that includes technical staff for at least 3 years. Then you need to get right on that grant-writing horse and ride away."
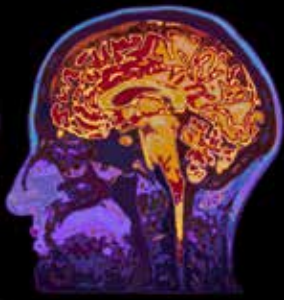
Money

Compared with other areas of behavioral science, social neuroscience is well funded. The National Institutes of Health have provided more funding for social neuroscience than any other public or private funder, and in the last several years, at least half a dozen NIH institutes have issued requests for applications specifically in social neuroscience.

The National Science Foundation also has a significant investment in social neuroscience, which it funds through its social psychology and cognitive psychology programs. Private funders such as the Templeton, Rockefeller, McDonnell, and Dana foundations have embraced areas of social neuroscience from the study of positive emotions to examinations of pandemic disease transmission.

Social neuroscience researchers successful in winning NIH grants tend to demonstrate interdisciplinary strength, NIMH's Simmons says. "In my ideal world as a program officer, what you would get is either individuals or groups of people who bring incredible strength in the historical depth and theoretical framework of social psychology together with what we know about how neurobiological systems and circuits work," she says.

Simmons also notes that scientists applying for social neuroscience funding at NIH institutes should demonstrate that they've been careful in designing experiments, that the studies they propose are feasible, and that they are aware of the limitations of neuroimaging methods. Because NIH does not yet have a study section dedicated specifically to social neuroscience, she recommends spelling out what gaps in the literature your proposal helps fill and why it's important to do so. "Because this field is new, people may not know what's new and what's not new," she says.

Siri Carpenter is a freelance writer based in Madison, Wisconsin.

Neuroscience has come a long way since the staining and identification of the neuron by Camillo Golgi and Ramón y Cajal over a century ago. Now the field has joined forces with other disciplines such as chemistry, computer science, engineering, and psychology, creating areas of focus that range from individual cells to social communities. Combining specialties has helped progress the understanding of social behavior as well as various psychological disorders, which some say are the final frontiers in biological science.

The Many Fields of Neuroscience: Shifting from Synapses to Society

By Jacqueline Ruttimann Oberst November 04, 2011

Ask neuroscientists to define the area that they are studying and one is bound to get a different answer every time. No longer fitting into one niche, the field can delve into the microcosm of molecules and cells but also expand out into the macrocosm of mankind itself.

"The complexity of issues we're addressing now is at a completely different level than what we did 15 years ago," says Nora Volkow, director of the U.S. National Institute on Drug Abuse at the National Institutes of Health (NIH). "In the past, it used to be one receptor in one area of the brain. Now we have the tools to monitor the complete system at any given point in time — that is, the entire brain and how it changes at short- and long-term intervals. We now can start to study all the proteins in the cell and their interactions, how cells communicate with one another to create networks, and how these relate to behaviors."

Nora D. Volkow, M.D.
CREDIT: National Institute on Drug Abuse

Within the past 10–20 years, three areas have come on the scene: transdifferentiation, optogenetics, and social neuroscience. From the Lilliputian to the large-scale, these subfields all aid in puzzling together the various pieces that comprise the brain.

Cell Fate Realized: Transdifferentiation

Stem cells and regenerative medicine have worked their way into the field of neuroscience in the form of transdifferentiation. In this process, either a tissue-specific stem or precursor cell begets cells that it normally was not destined to produce. Transdifferentiation occurs in nature, albeit rarely. For example, when the lens of the eye is removed in salamanders, iris cells fashion themselves into lens cells.

Fifty years ago, cell fate conversion consisted of a cloning technique called somatic cell nuclear transfer, which allows somatic cell DNA to be inserted into an enucleated egg cell. The technology has spawned such animals as Dolly the sheep but has fallen short of cloning non-human

primates. In 2005, the field became checkered when a South Korean research team, led by Woo Suk Hwang, claimed to have derived human embryonic stem cells using this technology, only to subsequently admit that they fabricated the data.

However, the field was redeemed one year later when Shinya Yamanaka's group at Kyoto University in Japan utilized four embryonic stem cell genes—*Oct3/4, Sox2, c-Myc,* and *Klf4*—to convert mouse and human skin fibroblasts into embryonic stem cell–like cells called induced pluripotent stem (iPS) cells. Since then other researchers have used different gene or chemical concoctions to turn fibroblasts into iPS cells.

Story Landis
CREDIT: NINDS, NIH

"One uses recipes kind of like in 'The Joy of Cooking,'" explains Story Landis, director of the U.S. National Institute of Neurological Disorders and Stroke at the NIH. "Now you don't have to start at an embryonic stem cell or induce a pluripotent stem cell. Instead, you can take a fibroblast and treat it in a special way to directly turn it into various cell types."

The technique has various applications in neuroscience.

"Transdifferentiation gives you an unprecedented opportunity to study neurological diseases such as autism, schizophrenia, Alzheimer's disease, and Parkinson's disease," explains Sheng Ding, senior investigator of the Gladstone Institute of Cardiovascular Disease at the University of California, San Francisco. "We hope to readily reprogram easily accessible somatic cells from a patient with one of these neurological diseases into iPS cells or directly into neurons to model the disease and develop personalized treatments."

Postdoctoral researchers and graduate students interested in the field should enter now, according to Ding. He proposes that new therapeutics developed through iPS cell technology will be available in 10 years.

Sheng Ding
CREDIT: Chris Goodfellow

Shedding Light: Optogenetics

The brain consists of approximately 100 billion neurons—about the same number as stars in a galaxy. Each neuron can also have anywhere from 1,000 to 10,000 synapses. Depending on the type of information that a neuron is sending, the signaling speeds can vary from 0.6 m/s (in the case of transmitting pain) to upwards of 120 m/s (in the case of muscle stimulation). Hence neuronal mass and speed make studying brain functions daunting.

Scientists have used a variety of techniques to elucidate neuronal function, but each has its own shortcomings. Electrophysiological techniques that physically delve electrodes into brain tissue are restricted by the depth to which probes can be placed and have limited ability to distinguish a single cell type amongst the myriad of cells interspersed throughout the brain. Pharmacological or genetic manipulations can help isolate signals from specific cell types; however, the results are often slow to take effect, from hours or days to months.

Karl Deisseroth
CREDIT: Christopher Kroeger

Enter optogenetics or "the merging of optics and genetics to allow control of very well-defined events within a particular cell," explains Karl Deisseroth, associate professor of psychiatry and bioengineering at Stanford University, who coined the term.

Gero Miesenböck, a physiology professor at the University of Oxford describes the technique as using "two flavors of light-responsive proteins: sensors that light up when a neuron becomes active and actuators that absorb light and turn activity on or off."

Deemed "Method of the Year" by *Nature Methods* in 2010 and highlighted in the "Insights of the Decade" special section by *Science* that same year, optogenetics is a newcomer in the neuroscience realm, emerging less than 10 years ago.

This field however, borrows from observations and discoveries made 30–40 years ago. In 1979, Francis Crick pointed out the difficulty of using electrodes to pinpoint specific neurons in the brain and later speculated that light might be able to hone in on one type of cell and leave others unaltered. At the time though, no neuroscientist knew how to make neurons responsive to light. Over the years, biologists discovered many different kinds of light-responsive proteins, or opsins. Among these, ion channels that open when a chemical co-factor, all-trans-retinal, absorbs photons were found in algae.

However, the genes encoding these opsins were not identified until 2003, and neurobiologists focused rather on cell-directed tools that used combinations of custom-made chemicals and genes to alter neuronal function. Until 2005, when Deisseroth's group discovered that these microbial opsins could precisely control neurons in response to light and, in 2006, showed that even adult vertebral tissues, including the brain, express natural all-trans-retinal.

Prior to these studies, Miesenböck's lab had developed other strategies for optogenetic control of nerve cells by reassembling fruit fly (*Drosophila*) opsin signaling pathways in neurons or combining light-activated chemicals with introduced genes. In 2005, they "remote-controlled" fly behavior with light. His group also developed a genetic means to visualize nerve cell activity by creating synapto-pHluorin, a pH-sensitive form of green fluorescent protein.

Deisseroth's group subsequently demonstrated the use of microbial opsins for neuronal control in freely moving mammals. They described fiberoptic interfaces that can be implanted in the brain to provide the light needed to activate these channels and target specific neurons in the recesses of the brain. Now, optogenetics is ubiquitous in neuroscience, and a variety of tools can be used to either activate or inhibit a neuron.

"It offers the best of all worlds: You can manipulate a specific cell type within a specific brain region, and you can do so with millisecond precision. This means that we can start to tease apart the functions of different cell types, activating or inactivating them to causally test their roles in brain function and behavior," comments Joanna Mattis, a graduate student in Deisseroth's lab.

Feng Zhang, a former graduate student of Deisseroth who is now an assistant professor of neuroscience at the Massachusetts Institute of Technology, adds: "By turning on or off specific neurons, one can identify their place in particular neurocircuits and how these circuits function in normal behavior or go haywire in disease. We can use this technology to identify molecular targets and develop better drugs."

Optogenetics studies from Miesenböck and Deisseroth's groups, as well as others, have literally and metaphorically shed light on neural codes relevant to Parkinson's disease, autism, schizophrenia, drug abuse, anxiety, and depression.

Feng Zhang

For future and current graduate students in neuroscience, Deisseroth advises that they follow their passion. "Students should pursue the things that interest them," comments Deisseroth. "The history of optogenetics is a parable for maintenance of basic science research. These days everybody is trying to justify their biology work in terms of disease relevance. Whereas deep insights into neurology and psychological diseases have been provided using optogenetics, the essential tools for this work were taken from algae and archaebacteria, remote and odd forms of life that were studied for many decades by people who had no consciousness of disease relevance and studied them just for their beauty."

Because of the breadth and depth of data that is now coming into the field, Zhang advises students to get multidisciplinary training. "Things are becoming high throughput and experiments are done on a shorter timescale. Before, it took a year to test a hypothesis, now one can do it in a couple of months," he says. "Don't just get training in biology, but also in computational biology and physics. The more versatile a person is, the more contributions this person will be able to make."

Strength in Numbers: Social Neuroscience

The brain does not work in isolation and neither do humans. We are, after all, social creatures.

A new field has arisen from this idea—social neuroscience—the study of the neural, hormonal, cellular, and genetic mechanisms that define social species.

For 40 years, traditional neuroscience considered the nervous system as an isolated entity devoid of any significant influences from the social environment.

"Biology and social sciences, at best, were at odds," explains John Cacioppo, who is one of the founders of the field and is now director of the Center for Cognitive and Social Neuroscience at the University of Chicago. "Biologists thought social processes had little relevance to the basic structure and function of human biology. Social scientists thought we were centuries away from biology being able to contribute to solutions to world wars, great depressions, and social injustices. There have been a lot of changes since then."

John Cacioppo

These changes came from the convergence of data from psychology and biology studies using traditional animal models. For example, knowledge about social bonding (attachment, altruism, trust) advanced from the discovery that oxytocin and vasopressin receptors are localized in different brains regions of the more social prairie vole compared to the more solitary montane and meadow voles. Because of this research, clinical studies are emerging investigating intranasal oxytocin as a treatment for autism. "Social neuroscience has an application for various mental disorders, for example, depression and autism, since these all have a social component," states Cacioppo.

The field draws upon numerous neurobiological techniques such as functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation, electrocardiograms, and studies of patients with focal brain lesions.

"Social neuroscience is becoming more of a heavyweight in science now that we have tools, theories, and a common language to communicate with one another," says Greg Norman, a post-doc in Cacioppo's lab. "This is the science of the mind—not just psychology, not just biology—but the integration of the human condition. It encompasses many fields. You can be a geneticist or a sociologist and still be a social neuroscientist."

This multidisciplinary approach can be both a strength and a weakness. Although more data is generated from collaboration, each discipline has its own jargon, often obfuscating each level of analysis.

"There is a challenge in trying to get people to use a common language instead of just talking past each other. And trying to understand how all the pieces fit into a whole is really difficult," adds Norman. "Our field encompasses genetics all the way to the study of societies. You can be in this field for 100 years and still not comprehend its breadth."

To avoid competition among the disciplines and bring them together, the Society for Social Neuroscience, for which Cacioppo is president, has separate awards—one for animal science and one for human science. But he hopes that in time, "we won't have this distinction."
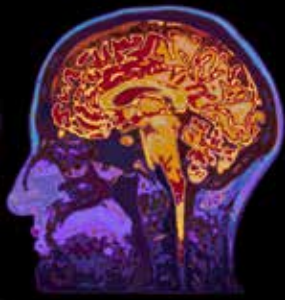
State of (Neuro)Science

These additional facets of neuroscience—transdifferentiation, optogenetics, social neuro-science—reflect the overall state of science.

"Fifty years ago a solitary genius was doing the work, now the geniuses are working in teams," says Cacioppo. It's not only how science is performed that has changed, but also budgets.

"It's the best of times and it's the worst of times," says Landis. "There are wonderful opportunities to use all of this technology but not enough funding for all of the possible projects. Choosing the most promising areas to pursue will require difficult choices."

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18

> "Your connectome is 100 billion times larger [than *C. elegans*], with a million times more connections than your genome has letters. Genomes are child's play compared with connectomes."
>
> —Sebastian Seung

It's been 20 years since Francis Crick and Edward Jones, in the midst of the so-called Decade of the Brain, lamented science's lack of even a basic understanding of human neuroanatomy. "Clearly what is needed for a modern human brain anatomy is the introduction of some radically new techniques," the pair wrote in 1993. Clearly, researchers were listening. Today, they are using novel technologies and automation to map neural circuitry with unparalleled resolution and completeness. The NIH has dedicated nearly $40 million to chart the wiring of the human brain, and the Allen Brain Institute has poured in millions more to map the mouse brain. The data will take years to compile, and even longer to understand. But the results may reveal nothing less than the nature of human individuality. As MIT neuroscientist Sebastian Seung writes, "You are more than your genes. You are your connectome."

This Is Your Brain: Mapping the Connectome

By Jeffrey M. Perkel January 18, 2013

When Seung says in *Connectome: How the Brain's Wiring Makes Us Who We Are,* "You are your connectome," what he means is that neural connectivity is like a fingerprint. Each person has their own unique blend of genetics, environmental influences, and life experience. Those factors influence the detailed circuitry of the brain, such that even identical twins likely differ at the level of neural connectivity.

By mapping those connections, researchers hope to understand the normal variability of human connectomes and how they change and rewrite themselves as humans learn, mature, and age. They can begin to probe how connectomes become dysfunctional in traumatic brain injury or neurodegenerative disorders, or in patients with, say, schizophrenia or autism—conditions that Seung terms "connectopathies."
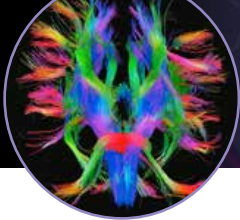
Yet the very scale of the problem is daunting. Only one connectome has been mapped to completion, and that was the roundworm, *Caenorhabditis elegans*. *C. elegans* contains just 300 neurons joined by 7,000 connections, yet charting its neural connectivity took more than a decade to complete. "Your connectome is 100 billion times larger [than *C. elegans*], with a million times more connections than your genome has letters," Seung writes. "Genomes are child's play compared with connectomes."

Nevertheless, researchers are making a stab at the problem. From the so-called macroscale of magnetic resonance imaging, to the microscale of electron microscopy, the connectome is slowly coming into focus, one synapse at a time.

The Human Connectome Project

When thinking about the connectome, says Hongkui Zeng, senior director of research science at the Allen Institute for Brain Science, think Google Maps. Neuroscientists would like to navigate the brain in virtual space as modern

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travelers do on the Internet: by zooming in and out and panning at will, from entire brain regions down to individual cells and synapses. In this metaphor, says Zeng, macroscopic MRI efforts reveal only neural superhighways. Still, she says, that can be useful, providing "an overview of the global sense of how regions are connected to each other, and how the world is organized."

That goal lies at the heart of the Human Connectome Project (HCP), a $40 million NIH effort launched in September 2010 to map the wiring of the live human brain. Two research consortia were funded under the HCP, with $30 million going to Washington University in St. Louis and the University of Minnesota, and $8.5 million to Massachusetts General Hospital (MGH) and the University of California, Los Angeles (UCLA).

While both teams are pursuing technology development, the WashU/Minnesota team also focuses on production, pushing 1,200 normal adults—400 sets of twins and their non-twin siblings—through a series of behavioral, genetic, and imaging scans to produce a reference against which other connectomes may be compared.
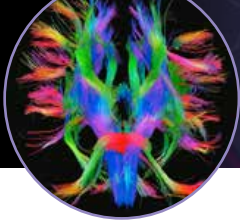
Both consortia employ magnetic resonance imaging of one form or another. At WashU, subjects are scanned for anatomic features and functional connectivity (i.e., regions linked by common purpose). To map physical connections, the consortia use diffusion MRI, a form of imaging that tracks the motion of water molecules as a marker of axonal fiber orientation. "Water molecules move more rapidly parallel to fibers than perpendicular to fibers," explains Van Wedeen, who heads the MGH team.

Wedeen invented and uses one form of diffusion MRI, called diffusion spectrum imaging (DSI); the WashU and Minnesota teams use HARDI, or high-angular resolution diffusion imaging. In both cases, the idea is to divide the brain into thousands of volumetric pixels, or "voxels," each about one cubic millimeter in size, and calculate for each one the different directions in which water diffuses. Then, in a process called "tractography," or track tracing, those vectors are connected to produce brilliant multicolor images of cables, or "fiber tracks," snaking their way through the brain's white matter.

The result is a map not of individual axons but rather thousands of axons in aggregate. "These are just numerical integrals of differential equations," says Wedeen. "These are not microscopic images of fibers." Nevertheless, collecting even those relatively low-resolution data requires some souped-up hardware. A standard clinical MRI, Wedeen says, has a magnetic field strength of 3 Tesla (T) and a gradient strength of 40 mT/m. The WashU/Minnesota group is using a specially made Siemens 3T scanner with a gradient strength of 100 mT/m, while the MGH/UCLA team's "Connectome Scanner" sports a 300 mT/m gradient.

That increased gradient strength offers two benefits for connectivity mapping, Wedeen says. "You get both more signal and better signal," he says, just as a telescope with a larger mirror can peer deeper into space.

Kamil Ugurbil, director of the Center for Magnetic Resonance Research at the University of Minnesota and co-PI of the WashU/Minnesota consortium, says his team has seen "significant tech-

nological gains" with their new scanner—resolution has been increased two- to three-fold and some 30 subjects have already been scanned, each over a two-day period.

But Ugurbil is no longer working with the 100 mT/m 3T scanner, which was shipped to WashU for the project's "production" mode. He has taken possession of a new 7T scanner, also from Siemens, which should provide even sharper images, and is awaiting shipment of an even larger $10 million, 10.5T instrument. At the moment, though, that latter magnet is sitting untested on the floor of a factory, he says, thanks to a "worldwide shortage of liquid helium."

"To cool this huge magnet we need something like 40,000 L of liquid helium, and we can't get it."

Mapping Mesoscale Connections

The Allen Institute is mapping the mouse connectome at what Zeng calls the "mesoscopic" scale—a mapping strategy first articulated by Cold Spring Harbor Laboratory neuroscientist Partha Mitra and colleagues in 2009. To build that map, Zeng's team uses "serial two-photon tomography."

Mice are injected in discrete brain regions with a recombinant adeno-associated virus (AAV, supplied by University of Pennsylvania Vector Core) that expresses a fluorescent protein. The mice are subsequently sacrificed and their brains fixed and embedded in agarose. That block is then mounted inside a two-photon fluorescent microscope tricked out with an ultrafine cutting apparatus, or vibratome—a system that has been commercialized by TissueVision.
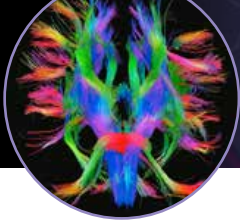
In this configuration, the top face of the block is fluorescently imaged at 0.35 μm lateral resolution, revealing the neuronal "arbors" traced out by the cells in whatever region was injected. Then the vibratome slices off the top 100 μm to reveal the next surface, and the process repeats.

"You image, cut, image, cut, image, cut," Zeng says. The entire process is automated, she explains, producing about 750 gigabytes of raw image data in about 18 hours—per brain. A complete dataset comprises approximately 500 injection points, and thus at least 500 brains, all of which must then be integrated and registered onto a three-dimensional template for comparison and navigation and to generate a detailed, brain-wide connectivity matrix.

Technically, says Zeng, the Allen Institute is not collecting a "connectome." Their virus is non-replicative, meaning it can only infect cells once. It also cannot cross neural synapses. Therefore, she says, what her project is really imaging is a "projectome."

According to Zeng, data for most brain regions has already been collected, and some has been publicly released. (These data are freely navigable using the Institute's Brain Explorer software and freely downloadable via the Allen Connectivity Atlas data portal, www.brain-map.org.) Now she is going back and repeating the process with viruses that are specific to individual neural subtypes, to understand, for instance, how projectomes of excitatory and inhibitory neurons differ.

At the Cold Spring Harbor Laboratory, Mitra is pursuing a similar strategy. He injects each of 262

grid points on each mouse brain, but does so using four tracers—two "anterograde" and two "retrograde." That's about 1,000 mouse brains per dataset.

Anterograde tracers, like AAV and biotinylated dextran (obtained from Life Technologies), penetrate the cell body and then "piggyback on anterograde transport mechanisms that carry molecules away from the [cell body] along the axon to the [synaptic] terminals," Mitra explains. Retrograde tracers like cholera toxin (obtained from List Biological Laboratories) and rabies viruses (Duke University Viral Vector Core), enter cells via synapses, travel up axonal arbors to the cell body, and do actually provide some long-range connectivity information, Mitra says.

Mitra images each mouse brain (manually cryosectioned into 20 μm sections spaced 40 μm apart) on a Hamamatsu Nanozoomer 2.0 automated slide scanning fluorescence microscope. When reconstructed, the resulting dataset contains a trillion voxels measuring half a micron on a side. Those are just one-billionth the size of a diffusion MRI voxel. At one terabyte per injection site, he says, his lab has collected nearly a petabyte of information, some of which was released in June (www.brainarchitecture.org).

To The Microscale

Dense as mesoscale information is, it doesn't actually reveal synaptic connections. "If one is going to be a purist about this, we are not mapping connections per se," says Mitra. "To really show that there's a connection, I'd have to show you there is a synapse and there are neurotransmitters crossing that synapse."
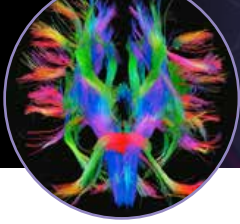
Such information certainly isn't available on the mesoscale. But it is at least partially observable on the microscale. In Zeng's Google Maps analogy, this is like viewing the driveways and walkways leading into individual houses. The tool for seeing those details is electron microscopy.

At Harvard University, for instance, neuroscientist Jeff Lichtman embeds pieces of thalamus measuring just 400 x 400 x 250 μm in plastic ("That's not even one fMRI voxel," he notes), and sections them into 9,000 ultrathin slices on a home-built instrument, basically a deli-slicer, called an automatic tape-collecting ultramicrotome. Each slice is attached to a moving strip of tape as it emerges from the blockface, producing something like an old movie film reel of brain slices. That tape is then fed into a scanning electron microscope (Lichtman has instruments from Zeiss, FEI, and JEOL), which images each section one by one like a movie projector.

According to Lichtman, sections are imaged at 4 nm resolution in 16 tiles of 25,000 x 25,000 pixels each, collected at 20 megapixels per second. The process generates a terabyte of image data per day, 24/7, for 100 days, Lichtman says.

The goal, he says, is to map the organization of retinal ganglion cells in the thalamus. "We will get a good sense of the way that first stage of central processing of retinal information is organized from this dataset."

Lichtman recently acquired a new EM that collects data at twice the current speed, 40 megapixels per second. Yet even at that rate it is wholly impractical to map an entire human brain at

this nanoscale resolution, both for reasons of data management—a single cubic millimeter is about 1,000 terabytes—and of time; even at 40 megapixels per second, it would still take years to image just a cubic millimeter.

A next generation instrument, though, could help. Zeiss is developing a new automated EM, Lichtman says, that will image sections with 61 electron beams at once (current machines use only one), speeding data acquisition up some 60-fold; he hopes to receive a prototype of this new device within a few years.

But collecting the data is only half the battle, says Moritz Helmstaedter of the Max-Planck Institute of Neurobiology in Martinsried, Germany; data analysis is the other.

As a postdoc, Helmstaedter worked with Winfried Denk at the Max-Planck Institute in Heidelberg. There Helmstaedter, with postdoc Kevin Briggman, used serial blockface electron microscopy (SBEM)—in which a piece of plastic-embedded brain is imaged and cut, imaged and cut, much as the Allen Institute does but on a nanometer scale—to image a piece of retinal tissue comprising about 1,000 neurons.

According to Helmstaedter, the SBEM-enabled scanning EM ran continuously for some eight weeks straight, collecting 13,000 images, each 2.5 gigapixels in size. (Both Zeiss and FEI EMs were used with a custom microtome; a complete system called 3View is now available from Gatan.) But it took more than two years to reconstruct the resulting neuronal circuits.

Helmstaedter's solution to that problem borrows from the crowdsourced protein-folding game, FoldIt. His team trains computers to assemble the images to trace neurites. But to ensure accuracy, they have hired some 200 undergraduates, at $10/hour, to sit in front of a computer and navigate through the computed neurite forest by essentially "flying through the data" as if with a flight simulator. These students helped validate much of a 900-neuron retinal connectome, Helmstaedter says.

Now Helmstaedter is upping the ante with a piece of neocortex 500 µm on a side, containing some 10,000 neurons. For that, they'll need an even wider hive-mind, which they hope to tap using an in-development game version of their application for use on mobile devices.

In connectomics, says Helmstaedter, the bottleneck is network reconstruction. "We have to take these extreme measures to get it done."

Radical new techniques, indeed.

Jeffrey M. Perkel is a freelance science writer based in Pocatello, Idaho.

Spotlight on Neuroscience

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