

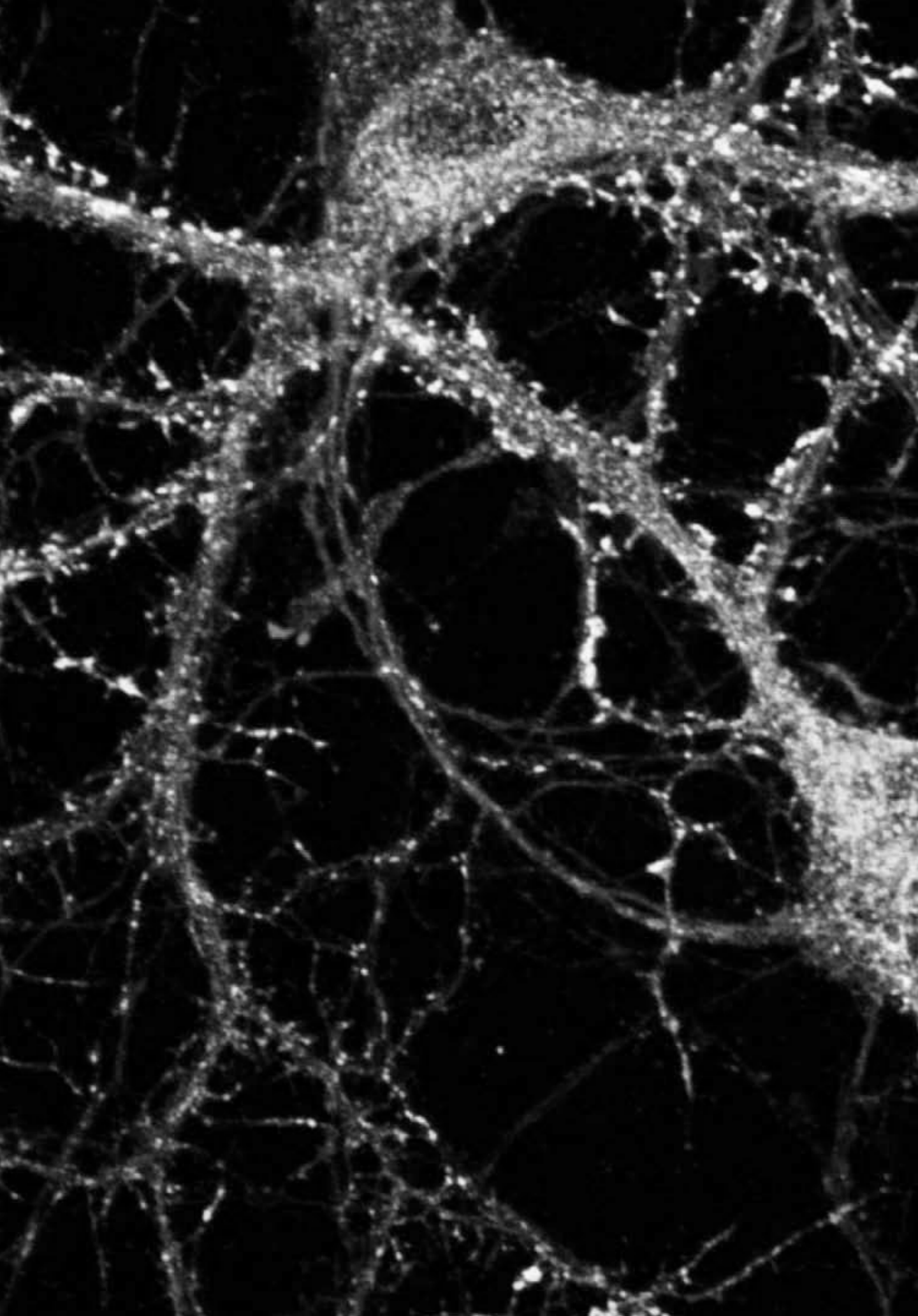
COLLABORATION


DISCOVERY

TRANSLATION

BSi







"AS LONG AS OUR BRAIN IS
A MYSTERY, THE UNIVERSE,
THE REFLECTION OF THE
STRUCTURE OF THE BRAIN
WILL ALSO BE A MYSTERY."

—SANTIAGO RAMON Y CAJAL

C O N T E N T S

- 3 From the Director
- 4 BSi Milestones
- 6 BSi Research Areas
- 8 Awards and Programs
- 10 Center for Brain Imaging Science
- 12 Neuro-Epigenetics
- 14 Schizophrenia Research
- 16 Neurogenetics of Wiring and Repair
- 18 Pattern Cognition and Aesthetics
- 20 Non-invasive Cerebellar Stimulation
- 22 Transcranial Magnetic Stimulation
- 24 Neuro-Education Initiative
- 27 BSi NeuroTranslational Program
- 28 Breaking New Ground: The Future of the BSi
- 30 BSi Staff and Advisors
- 32 Communications, Outreach and Education

The Johns Hopkins Medicine Brain Science Institute's (BSI) mission is to solve fundamental questions about brain development and function and to use these insights to understand the mechanisms of brain disease. This new knowledge will provide the catalyst for the facilitation and development of effective therapies.

The BSI achieves this work by bringing together brain scientists and others from across Johns Hopkins University's schools and campuses. The following outlines several BSI strategic initiatives in support of its mission:

- Formation of interdisciplinary research teams and working groups
- Cross-campus award funding
- University-wide new models of training
- Technology transfer and strategic partnerships
- Educational and outreach programs
- Creating effective translation of discovery into disease treatment

Dear Friends and Colleagues,

What a great privilege and pleasure it is to share the work the Brain Science Institute has accomplished since its inception almost two and a half years ago. The BSi has grown from an idea to a thriving Institute with a robust vision: To understand how the brain works, to apply this new knowledge across many disciplines, and to translate discoveries into treatments for diseases. These translational opportunities are limitless – from assisting in the development of new pharmaceuticals and cure of diseases to providing insights on learning and enhancing cognition through the arts.

It is a unique opportunity to have a donor family that is a true partner in both the vision and implementation of the BSi. Their excitement, engagement and inquiry inspire and motivate us to think in new ways and explore areas not yet understood, while at the same time supporting the important fundamental basic science required to unlock the mysteries of the brain. Words can't express our deep gratitude, but our hope is that our actions through research, new discoveries and applications will provide solutions to many of the most difficult brain-based health issues.

To be part of an institution that is steadfast in its commitment to foster the world's best brain research at such an unprecedented scale is a rare gift. The BSi brings together both basic and clinical neuroscientists from 17 different departments and six schools, numbering more than 540 faculty. Excluding BSi funding, the University receives over \$120 million in research support annually for brain research.

The quality of the investigators at Johns Hopkins is outstanding. Senior faculty includes some of the most productive and cited scientists in the world. Of the top 25 neuroscientists by citation over the past 10 years, four are at Johns Hopkins. Our scientists are well represented in the National Academy of Sciences, the National Academy of Sciences Institute of Medicine, and Howard Hughes Medical Institute. The quality of the junior faculty is also impressive, representing tomorrow's leaders in neuroscience. And JHU's training and clinical programs are consistently ranked among the top three in the nation.

Creativity and collaboration are the keys to realizing the potential of the brain sciences. With the support of Dean Miller, the BSi has created a comprehensive strategy to support talented faculty, researchers and scientists. Across disciplines and institution-wide, the vision of the BSi has taken shape through strong alliances.

Thank you to all that have participated in this amazing endeavor. We are excited to continue expanding the work of the BSi together.



Dr. Jack Griffin, *Director, Brain Science Institute*

2007

2008

FEBRUARY

- Launch of Brain Science Institute (BSi)

MARCH

- The JHU Gazette, Vol. 36 No. 26: JHM Launches Unique Brain Science Institute – Interdisciplinary endeavor will bring together experts from across the University

MAY

- First BSi funds awarded in Neurogenetics: \$3,956,254

SEPTEMBER

- First Research Collaboration Agreement between JHU and Biogen Idec
- Industry partner meetings
- Franklin Institute visit for consult on Neuroscience exhibition
- 2007 ASTAR National Judges' Science School at JHMI

NOVEMBER

- NeuroTranslational Program launched
- Special lectures by Biogen Idec
- First BSi newsletter published
- The Walters Art Museum seminar and convening of Center for Applied Research in the Arts (CARA) with keynote by Semir Zeki, University College, UK

DECEMBER

- Inaugural seminar of the Technology Development & Commercialization Seminar Series hosted by BSi & JH Technology Transfer
- Biogen Idec-JHU Joint Steering Committee proposal presentations
- BSi Mini Symposium - Regeneration & Repair in the Nervous System
- Visual and Auditory Perception working group forms
- Neuro-Education Initiative working group forms
- Biogen Idec awards announced

JANUARY

- Technology Development & Commercialization Seminar Series
- Neural Regeneration working group forms

FEBRUARY

- Technology Development & Commercialization Seminar Series
- BSi Planning Committee meets

MARCH

- Technology Development & Commercialization Seminar Series
- Call for proposals in three core areas: New Approaches to Perception & Cognition, Regeneration & Repair in the Nervous System, and Schizophrenia
- BSi University Council meets

APRIL

- First monthly Brain Night
- Industry partner meetings
- Technology Development & Commercialization Seminar Series
- Biogen Idec-JHU BSi Joint Steering Committee meets

MAY

- Brain Night
- Technology Development & Commercialization Seminar Series
- BSi Planning Committee meets

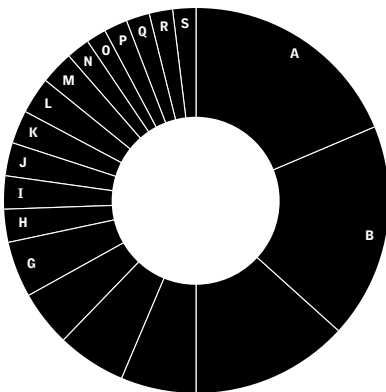
JUNE

- Technology Development & Commercialization Seminar Series
- Neuro-Education Initiative Learning Lunch
- BSi website launched
- BSi Mini Symposium – Neuroscience and Cognition
- Day of Science

AUGUST

- Biogen Idec Research Day at JH
- BSi Planning Committee meets

BRAIN SCIENCE INSTITUTE FACULTY REPRESENTATION IN FUNDED PROPOSALS



- A Neurology – 20%
- B Neuroscience – 19%
- C Psychiatry & Behavioral Sciences – 14%
- D Biomedical Engineering – 7%
- E Orthopaedic Surgery – 6%
- F Kennedy Krieger Institute – 4%
- G Molecular Biology & Genetics – 4%
- H Genetics Institute of Medicine – 3%
- I Otolaryngology – 3%
- J Pharmacology & Molecular Sciences – 3%
- K Psychological & Brain Sciences – 3%
- L Radiology & Radiological Science – 3%
- M School of Education – 3%
- N Anesthesiology & Critical Care Medicine – 1%
- O Applied Physics Laboratory – 1%
- P Mechanical Engineering – 1%
- Q Mind Brain Institute – 1%
- R Molecular & Comparative Pathobiology – 1%
- S Physical Medicine & Rehabilitation – 1%

SEPTEMBER

- Brain Night
- BSi University Council meets
- Johns Hopkins Biotechnology 2008 Conference "Neuroscience Investors Conference: Investing in Brain Research"
- BSi awards funding in core research areas: New Approaches to Perception & Cognition: \$3,783,175; Regeneration & Repair in the Nervous System: \$1,270,000; Schizophrenia: \$1,420,000
- Neuro-Education Initiative hosts Executive Function Seminar: Helping Teachers Understand How the Brain Learns

OCTOBER

- Brain Night
- Pain working group forms
- Biogen Idec second round of proposals submitted

NOVEMBER

- Brain Night
- JHU Deans meeting with BSi leadership
- BSi Planning Committee meets

DECEMBER

- Brain Night
- Biogen Idec-JHU Joint Steering Committee meets
- BSi University Council meets

JANUARY

- Brain Night
- Call for proposals for BSi Sustaining Innovation in the Neurosciences (SIN) awards
- Biogen Idec second round of awards announced

FEBRUARY

- Brain Night
- Technology & Life Science Entrepreneurs Boot Camp 2009 hosted by JH Technology Transfer, Dept of Biomedical Engineering and BSi
- Biogen Idec-JHU BSi Joint Steering Committee meets
- Launch of the Center for Brain Imaging Science (CBIS): \$1,052,262

MARCH

- Brain Night
- JHU Deans meeting with BSi leadership
- Industry partner meetings
- BSi Junior Faculty Advisory Committee forms
- Blood Brain Barrier/Cerebral Vasculature Initiative working group forms

APRIL

- Sustaining Innovation in Neurosciences funds awarded: \$260,000
- Joint faculty recruitment, School of Medicine and Arts & Sciences

MAY

- Brain Night
- Neuro-Education Initiative hosts Learning, Arts and the Brain Summit: Bringing Researchers and Practitioners Together to Shape the Future with the Dana Foundation

JUNE

- Synapses, Cognition and Cognitive Disorders working group forms
- JH Entrepreneurial "Speed-Dating" launched, hosted by JH Dept of Biomedical Engineering, BSi, JH Technology Transfer, Science & Technology Park
- Industry partner meetings

JULY

- JHU Deans meeting with BSi leadership
- NEI Certificate program in Mind, Brain and Teaching launches
- NIH grant applications submitted for BSi NeuroTranslational Program

AUGUST

- Industry partner meetings

SEPTEMBER

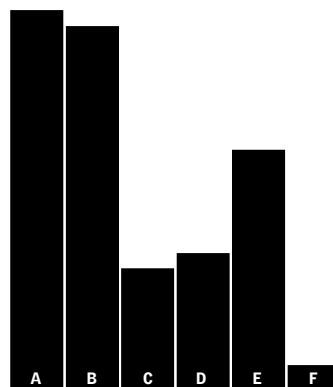
- Brain Night
- BSi Translational Alliance formed with Eisai Pharmaceuticals
- BSi Translational Alliance formed with Helsinn Healthcare

OCTOBER

- Brain Night
- Biogen Idec-JHU Joint Steering Committee meets
- Synapses, Cognition and Cognitive Disorders sub-working groups form: Development of Synaptic Connections and Circuits; Neuronal Circuits and Cognition; Mechanisms of Synaptic Plasticity; Animal Models of Synaptic Cognitive Disorders; and Clinical Approaches to Synaptic Cognitive Disorders

FUNDS AWARDED TO CORE CENTERS AND RESEARCH AREAS

A Neurogenetics	\$3,956,254
B New Approaches to Perception & Cognition	\$3,783,175
C Regeneration & Repair in the Nervous System	\$1,270,000
D Schizophrenia	\$1,420,000
E NeuroTranslational Program	\$2,500,000
F Sustaining Innovation in Neurosciences	\$260,000



Total Awarded \$13,189,429

"EACH OF US BELIEVES HIMSELF TO SENSE OBJECTS AND EVENTS PRECISELY, AND TO LIVE IN REAL AND CURRENT TIME. I ASSERT THAT THESE ARE PERCEPTUAL ILLUSIONS...EACH OF US LIVES WITHIN THE PRISON OF HIS OWN BRAIN."

—VERNON MOUNTCASTLE, EMERITUS PROFESSOR DEPARTMENT OF NEUROSCIENCE, JOHNS HOPKINS UNIVERSITY

The BSi Research areas have been identified to achieve the following goals:

- **Foster new programs in basic neuroscience discovery**
- **Initiate a translational research program that will develop new treatments for brain-based diseases**
- **Encourage collaboration, interdisciplinary teams, and new thinking that will have a global influence on research and treatment of the nervous system**

NEUROGENETICS

The goal is to understand how genes are involved in brain function in health and disease. Researchers are studying genes in mice and humans to discover how mutations in genes can affect normal brain function and contribute to disease.

NEW APPROACHES TO PERCEPTION AND COGNITION

This area includes novel approaches to understand how we perceive and think. New collaborative efforts to investigate brain structure and function as well as study how we recognize patterns and how neuroscience can inform education.

REGENERATION AND REPAIR IN THE NERVOUS SYSTEM

This research focuses on the functional and structural repair of the damaged nervous system. Interdisciplinary teams are studying how neurons recover and regenerate from injury and trauma. These studies may have significant impact on therapeutic treatment of brain traumas from stroke and spinal injury as well as veterans suffering from physical trauma returning from war.

RESEARCH IN SCHIZOPHRENIA

Research in this area addresses the processes underlying this devastating disease. Recent advances in molecular techniques have allowed genetic approaches towards this complex disorder. Collaborative studies in the forefront of this field are trying to identify the genes involved in schizophrenia and how disruption of these normal biological processes leads to illness.

NEUROTRANSLATIONAL PROGRAM

The program was created with the mission of identifying novel drug targets arising from JHU faculty's research and translating them into new drug therapies for neurological and psychiatric disorders.

To support and advance innovation in solving fundamental questions of brain development and function and translate these findings into therapies, the BSi has developed a series of award opportunities. Some of these awards have gone to unique core resources including Neuro-Epigenetics and the Center for Brain Imaging Science. Other funds have contributed to the purchase of essential equipment such as the 7Tesla MRI Magnet and the unique Transcranial Magnetic Stimulator built for use in the MRI.

Most awards have gone to interdisciplinary groups in several core research areas including Neurogenetics, Schizophrenia, New Approaches to Perception and Cognition, and Regeneration and Repair in the Nervous System (see award details on pages 8-9). The BSi believes that these areas are ripe for discovery or they represent opportunities for novel, creative approaches to key questions in the field. As part of the evaluation, all BSi proposals are reviewed using the following criteria:

- What is the fundamental importance of the scientific questions being addressed?
- Is there existing strength within Hopkins that can be leveraged by bringing research disciplines together?
- What is the potential for rapid progress in this field?
- Is there potential for discovery that may affect the whole range of research from fundamental science to clinical care?
- Is there balance among programs so that they range from molecular and cellular research to systems, circuits and complex behaviors?

The “working group” concept is critical to the long-term success and vibrancy of the BSi. This interdisciplinary collaborative effort fundamentally encourages thinking outside of traditional channels, processes and systems. This process has consistently produced innovative and creative research proposals with the potential for high impact in the field. Some examples of past or emerging working groups include neural regeneration, pain, blood brain barrier and cerebral vasculature initiative, traumatic brain injury, visual and auditory perception, macro imaging, education, memory mechanisms and synapses, cognition and cognitive disorders.

Throughout this report are examples of some of the exceptional projects that have received BSi awards. Some projects, like the one underway at the Center for Brain Imaging Science illustrate novel neuro-imaging capabilities that will help researchers across the university use new techniques to answer basic questions about human cognition and disease. Other projects include a broad-based effort in systems physiology – led by the Mind Brain Institute’s Ed Connor – that identify common themes in handling visual, auditory and somatosensory information. David Valle is looking at the role of NRG3 in schizophrenia and Andy Feinberg is exploring the role of epigenetics in brain science by defining how DNA is modified to regulate gene function. You can find additional information on these specific projects or other BSi-funded initiatives at www.hopkinsmedicine.org/brainscience

Multidisciplinary working groups responded to a formal RFP process in three of the five BSi Research Areas. Selected faculty teams were contacted to submit proposals for Neurogenetics.

NEUROGENETICS

Eight applications were received from selected faculty. Four programs were funded.

The behavioral testing program; *Michela Gallagher and Mikhail V. Pletnikov; Departments of Psychological and Brain Sciences and Psychiatry and Behavioral Sciences*

The high throughput screening center for neurogenetics; *Min Li and Seth Blackshaw; Department of Neuroscience*

Neurogenetics of wiring and repair program; *David Ginty and Alex Kolodkin; Department of Neuroscience*

Neuro-Epigenetics program; *Andrew Feinberg, James Potash, Sarven Sabunciyany and Robert Yolken; Departments of Molecular Biology and Genetics, Psychiatry and Behavioral Sciences, and Pediatrics*

NEW APPROACHES TO PERCEPTION AND COGNITION

Thirty-three applications were received. Eight awards have been given to date.

Johns Hopkins University School of Education Neuro-Education Initiative; *Mariale Hardiman and Susan Magsamen; Johns Hopkins University School of Education*

Enabling technologies for two-photon imaging of brain activity; *Dwight Bergles, David Foster, Scot Kuo, Marshall Hussain Shuler, Eric Young, and David Yue; Departments of Neuroscience and Biomedical Engineering*

Pattern cognition and aesthetics; *Ed Connor, Xiaoqin Wang, Steven Hsiao, Steven Yantis, and Charles Limb; Departments of Neuroscience, Biomedical Engineering, Psychological and Brain Sciences, and Otolaryngology*

Transcranial magnetic stimulation; *John Desmond, James Pekar, Harry Charles, Reza Jalinous, and Marilyn Albert; Departments of Neurology, Radiology and Radiological Science, and Johns Hopkins Applied Physics Laboratory*

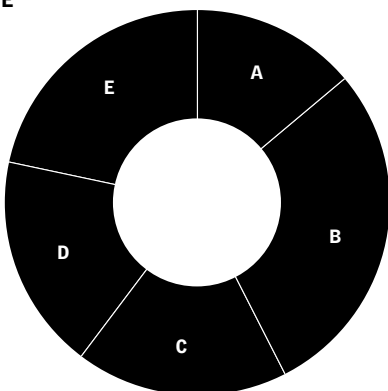
Mechanisms of proprioception and application to prosthetic hands; *Allison M. Okamura and Steven Hsiao; Departments of Mechanical Engineering and Neuroscience*

Genetically-based technologies for the visualization of cellular and subcellular structures: a resource for the neuroscience community; *Jeremy Nathans; Department of Molecular Biology and Genetics*

F.M. Kirby Research Center for Functional Brain Imaging/7T MR Research Center; *Peter vanZijl; Departments of Radiology and Radiological Science, and Kennedy Krieger Institute*

PROJECTS FUNDED TO DATE

A Neurogenetics	4
B New Approaches to Perception & Cognition	8
C Regeneration & Repair in the Nervous System	5
D Schizophrenia	5
E Sustaining Innovation in Neurosciences	6
Total Projects Funded	28



Center for Brain Imaging Science (CBIS);
Susumi Mori, Marilyn Albert and Michael Miller;
Departments of Radiology and Radiological Science,
Neurology and Biomedical Engineering

REGENERATION AND REPAIR IN THE NERVOUS SYSTEM

Thirty-two applications were received.
Five awards have been given to date.

Non-invasive cerebellar stimulation; *Pablo
Celnik and Amy Bastian; Departments of Physical
Medicine & Rehabilitation, Neuroscience, and
Kennedy Krieger Institute*

Imaging regenerating and sprouting
axons in the intact, living mammalian
brain: An experimental platform for
testing therapies to promote brain repair;
*David Linden, Joseph Steiner, Alex Kolodkin,
and Ron Schnaar; Departments of Neuroscience,
Neurology, Pharmacology & Molecular Sciences*

Epigenetic regulation in axon
regeneration; *Guo-li Ming, Hongjun Song,
Ahmet Hoke, and Fengquan Zhou; Departments of
Neurology and Orthopaedic Surgery*

The involvement of developmental
pathways in motor neuron regeneration;
*Shanthini Sockanathan, Ahmet Hoke, and Thomas
Brushart; Departments of Neuroscience, Neurology,
and Orthopaedic Surgery*

Human induced pluripotent stem cell
(hiPSC) platform; *Hongjun Song and Ted M.
Dawson, and Guo-li Ming; Department of Neurology*

RESEARCH IN SCHIZOPHRENIA

Twenty-six applications were received.
Five awards have been awarded to date.

Microarray detection of retrotrans-
posons and copy number variations in
schizophrenia; *Jef Boeke, David Valle, and Ann
Pulver; Departments of Molecular Biology and Ge-
netics, The McKusick-Nathans Institute for Genetic
Medicine, and Psychiatry and Behavioral Sciences*

Schizophrenia therapeutics: Adult stem
cell model development; *Christopher Ross
and Hongjun Song; Departments of Psychiatry and
Behavioral Sciences, and Neurology*

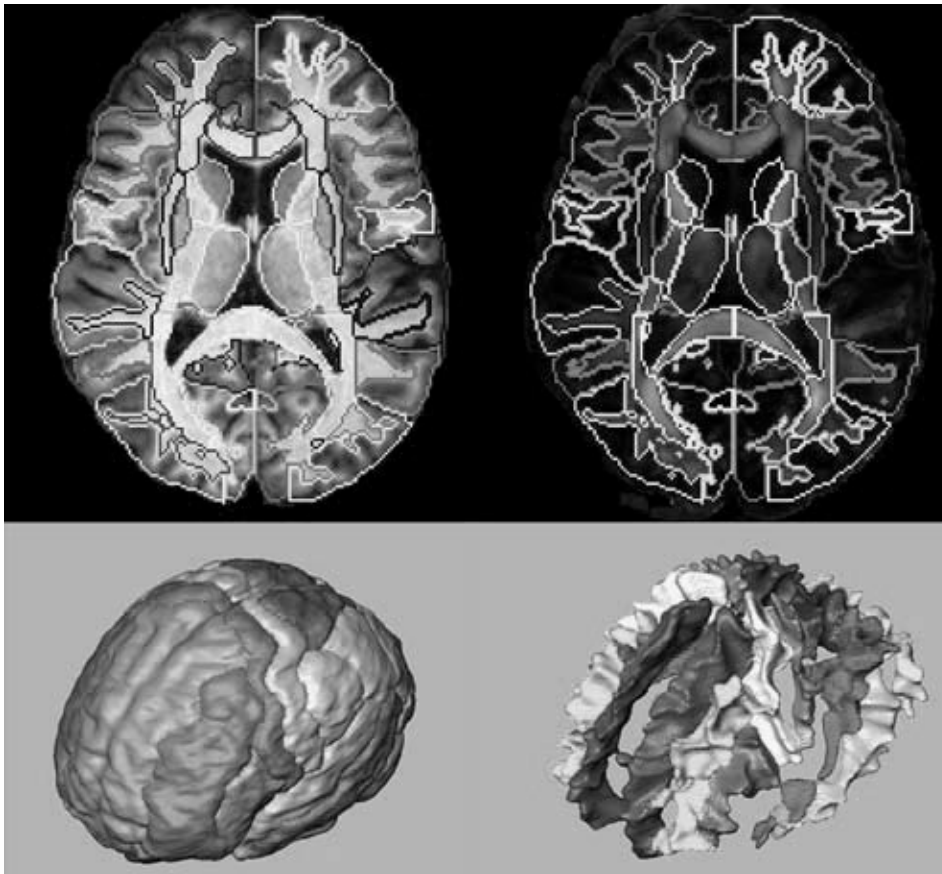
Glucose metabolism and oxidative
stress-associated cellular susceptibility in
schizophrenia: a systematic study using
patient tissues and cells; *Akira Sawa, Sandra
Lin, David Schretlen, Nicola Cascella, Peter Barker,
and Thomas Sedlak; Departments of Psychiatry and
Behavioral Sciences, Otolaryngology, and Radiology
and Radiological Sciences*

The role of NRG3 in schizophrenia;
*David Valle, Dimitri Avramopoulos, Ann Pulver,
Andy McCallion, Michael Zwick, Akira Sawa, and
Hongjun Song; The McKusick-Nathans Institute
of Genetic Medicine, Psychiatry and Behavioral
Sciences, Molecular and Comparative Pathobiology,
and Neurology*

BACE1-related NRG-ErbB4 signaling
and schizophrenia; *Philip Wong, Alena
Savonenko, Paul Worley, Don Price; Departments
of Pathology and Neuroscience*

"THE BRAIN REPRESENTS THE MOST FORMIDABLE CHALLENGES FOR BOTH MEDICINE AND BASIC SCIENCE. THE BSI HAS BROUGHT TOGETHER THE BRIGHTEST MINDS ACROSS SCHOOLS AND DEPARTMENTS AT JHU, TRANSFORMING THE WAY WE UNDERSTAND THE BRAIN AND TREAT DISEASE."

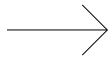
—EDWARD D. MILLER, MD, DEAN OF THE SCHOOL OF MEDICINE, CEO, JOHNS HOPKINS MEDICINE



> A deformable atlas of the human gray and white matter developed under BSi funding. In this atlas, 176 brain structures are defined based on anatomical definitions obtained from more than 80 normal subjects. This atlas is used to automatically segment and evaluate anatomical status of patient brains by non-linearly transforming the atlas. The upper and bottom rows show the 2D and 3D views of the atlas.

SUSUMI MORI
 MARILYN ALBERT
 MICHAEL MILLER

The Center for Brain Imaging (CBIS) is one of the important resources in the growth of the Brain Science Institute at Johns Hopkins University. It provides a tremendous resource for neuroscience investigators who would benefit from incorporating imaging into their studies along with support from imaging specialists.



The CBIS incorporates and consolidates expertise from Hopkins' various imaging-dedicated centers to create a university-wide resource in the understanding and use of imaging techniques for neuroscience research.

The translational goals of the CBIS are both immediate and long-term. Short-term the Center will make accessible very high-quality anatomical MRI, MR spectroscopy, functional MRI, and newer offshoots such as diffusion tensor imaging. The primary users are researchers with basic and clinical neuroscience studies in fields including neurology, psychiatry, developmental biology, psychology, genetics, pathology and biomedical engineering.

The Center's ultimate long-term purpose upholds the traditional meaning of translation by improved imaging in Hopkins' brain-oriented projects to hasten therapies for brain diseases.

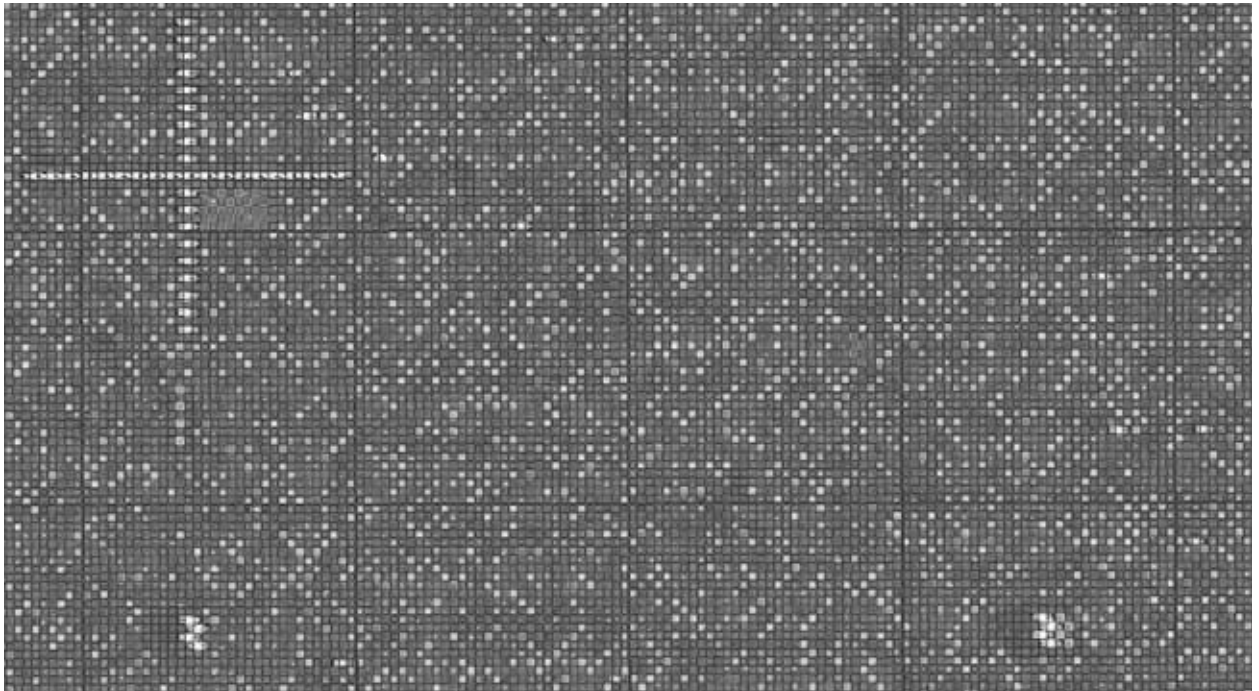
The timing is right for the creation of the CBIS. First, there's a bottleneck in the imaging field that interferes with the progress of biomedical research. This problem is not in the ability to acquire good data from imaging. Quality images are so easily generated that the volume overwhelms researchers and clinicians. The new bottleneck lies in not being able

to quantify information from a glut of images or interpret it rapidly enough. It's the access to good image analysis that must increase.

Once high-quality images are generated, the CBIS provides a bridge to analysis in several ways. Offering training – both individual and group – in the most widely used image analysis techniques. This educational arm of CBIS will make computers and training available on a daily basis. The demand for this training is high.

In addition, the CBIS centralizes services for image analysis, particularly for projects with high-quality anatomical images. While imaging analysis occurs now at Hopkins, CBIS's efforts will ultimately add workstations, improve the ease and quality of analysis and foster wider use of high-quality imaging.

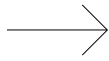
"INTERDISCIPLINARY, CROSS-CAMPUS COLLABORATIONS ARE A CRITICAL COMPONENT TO THE FUTURE OF RESEARCH, TEACHING AND CLINICAL CARE AT JOHNS HOPKINS. THE BSI HAS TAKEN A LEADERSHIP ROLE IN BUILDING STRONG MULTI-DEPARTMENTAL ALLIANCES AND DEEPENING OUR UNDERSTANDING OF HOW THE BRAIN WORKS." —RONALD J. DANIELS, PRESIDENT, JOHNS HOPKINS UNIVERSITY



> Image from Comprehensive High-throughput Array-based Relative Methylation (CHARM) analysis of human brain. Each square represents hybridization to one of 2.1 million oligonucleotide probes from across the genome, and the colors indicate relative methylation of the brain sample analyzed.

ANDREW FEINBERG
 JAMES POTASH
 SARVEN SABUNCIYAN
 ROBERT YOLKEN

Epigenetics, the study of heredity not coded in DNA sequences, is at the center of modern medicine because it can help to explain the relationship between an individual's genetic background, the environment, aging, and disease. It can do so because the epigenetic state varies among tissues and over the course of a lifetime, whereas the DNA sequence remains essentially the same.



As cells adapt to a changing internal and external environment, epigenetic mechanisms can “remember” these changes in the normal programming and reprogramming of gene activity. The role of epigenetic changes in cancer is well established, and enormous excitement has grown over its potential role in brain development and function and neuropsychiatric disease.

In the past year a major focus of the Neuro-Epigenetics core has been to develop a high throughput platform for analysis of DNA methylation across the human genome. Termed CHARM, for “Comprehensive High-Throughput Arrays for Relative Methylation,” this microarray-based method is agnostic to preconceptions about the location of DNA methylation. It allows interrogation of 4 million sites of DNA methylation per sample simultaneously. A key to the success of CHARM is a new mathematical approach which can extract quantitative methylation data regardless of the underlying DNA sequence.

The Neuro-Epigenetics core is already discovering remarkable information. Over the next several years this initiative will offer an array of services to assist

JHU brain researchers. It will also generate critical genome-wide methylation data in a variety of cortical and subcortical areas as well as the cerebellum, hypothalamus, midbrain, pons and the medulla oblongata. These targets will enable researchers to broadly sample across major brain regions while focusing on areas critical to neuropsychiatric diseases. This work will be completed in humans, mice, rats and rhesus macaques.

There have been impressive early returns on the investment in neuro-epigenetics. To help set priorities for the use of the neuro-epigenetics resources, the BSi Scientific Review Panel will review proposals and provide pilot grant support. Additionally, The School of Medicine is devoting new space for this work in the Institute for Basic Biological Sciences (IBBS). The Neuro-Epigenetics core is also home to the first course in Epigenetics at Hopkins.

"IDENTIFYING GENES THAT PREDISPOSE TOWARD SCHIZOPHRENIA AND CLARIFYING RELEVANT NEUROTRANSMITTER MECHANISMS OFFER THE GREATEST HOPE FOR UNDERSTANDING AND THERAPY. JHU IS FORTUNATE IN THE WEALTH OF OUTSTANDING RESEARCHERS IN BOTH ARENAS."

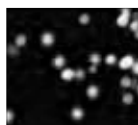
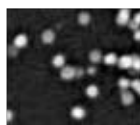
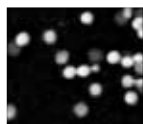
—SOLOMON H. SNYDER, UNIVERSITY DISTINGUISHED PROFESSOR, JOHNS HOPKINS UNIVERSITY, SCHOOL OF MEDICINE

CHROMOSOME 10



```

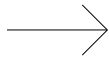
..TCAGAGATTTCATCCATAAGCGGTTAGC..
      ATCCATAAGCGGTT
      TTCATCCATAAGCGG
      GATTCATACATAAGC
      GAGATTTCATCCATAA
  
```



> Next generation sequencing of a segment of the *NRG3* gene on chromosome 10. The location of the *NRG3* gene on chromosome 10 is indicated by the vertical yellow line and the short sequencing reads are shown aligned below the reference sequence shown in yellow. A mutation (C > A) is indicated by the base highlighted in red. The colored dots on black squares (left) show sequencing of individual DNA molecules (dots) with each color indicating addition of one of the 4 bases as identified by a color code (red, green, blue, yellow).

DAVID VALLE	JENNIFER MULLE
DIMITRI AVRAMOPOULOS	MICHAEL ZWICK
ANN PULVER	AKIRA SAWA
ANDY MCCALLION	HONGJUN SONG

Schizophrenia is a devastating illness that usually begins during adolescence with symptoms that include paranoia, delusions and hallucinations. It is a common chronic, debilitating neuro-psychiatric disorder caused by a mix of environmental and genetic factors. Despite compelling evidence for a substantial genetic contribution, few genes have been consistently implicated as contributing to the development of Schizophrenia.



The long-term goals of this study are to identify the genes and genetic variants that increase the risk of schizophrenia. This research is anticipated to lead to an understanding of the biological systems involved and the nature of the functional alterations that cause schizophrenia. In turn, this will help in the rational development of individually tailored therapeutic strategies for the treatment of this illness.

This work depends on a more than 15-year effort by Dr. Ann Pulver, Department of Psychiatry, to collect and rigorously characterize individuals with schizophrenia and their family members. Although her collection includes patients from several ethnic backgrounds, Dr. Pulver chose to focus on individuals of Ashkenazi Jewish (AJ) origin in order to reduce the genetic heterogeneity in her patient sample. She has now collected and characterized more than 750 unrelated AJ patients and families as well as more than 1,500 AJ controls. This collection provides an unparalleled resource for these studies.

In earlier work this team used linkage and candidate gene methods to search the entire genome for genes contributing risk for schizophrenia. They identified several genomic regions likely harboring such genes. The focus of the

current work has been on a region on the long arm of chromosome 10 that gave the strongest evidence for containing one or more genes conferring risk for schizophrenia. Among the 70 genes in this region, the best candidate is a large gene, designated *NRG3*, that is expressed primarily in brain and encodes a protein known as Neuregulin 3. The team assayed or "genotyped" a common form of genetic variation known as single nucleotide polymorphisms or SNPs in patient samples and found highly significant evidence for multiple variants of the *NRG3* gene in schizophrenics.

Currently this research team is using advanced genotyping methods and new "next-generation" DNA sequencing methods to search through a large segment of *NRG3* gene to find the causative variants for schizophrenia in a subset of patient samples. These methods will detect both small single nucleotide variants as well as much larger deletions and duplications known as copy number variants.

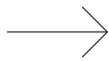
The studies are already identifying the specific signaling pathways that are disrupted in schizophrenia and may lead to novel therapeutic treatments for this devastating psychiatric disease.

"BSI IS CREATING STRONG INTERDISCIPLINARY CONNECTIONS BETWEEN THE HOPKINS CAMPUSES. THE STRENGTH OF THIS COMMUNITY EFFORT ENABLES US TO UNIQUELY ADDRESS COMPLEX ISSUES ABOUT HOW THE BRAIN FUNCTIONS LIKE NO OTHER INSTITUTION CAN." —GUY MCKHANN, PROFESSOR, JOHNS HOPKINS UNIVERSITY



> Mouse Limb. Whole mount staining reveals the pattern of sensory neuron (red) and motor neuron (green) innervation of the developing mouse forelimb.
Image by Rasi Wickramasinghe.

Our ability to understand how complex connections among neurons are achieved and how injury or disease impacts upon these wiring patterns is limited by experimental realities. While clinical studies are greatly informative, neuroscientists need additional ways to probe the nervous system experimentally. Enter the mouse.



Although mice and humans are quite different, there are many remarkable similarities between these two mammalian species. Our genomes share great similarity, the overall components and connectivity of our nervous systems are closely related, and mice perform a range of behaviors that are increasingly being recognized to model more complex activities in humans. So, if we could randomly disrupt gene function in the mouse, and link those disruptions (or mutations) to defects in nervous system development, wiring, structure and ultimately function, we would be able to model in the mouse similar disruptions that affect the human nervous system. The Neurogenetics of Wiring and Repair project seeks to do just that.

For the past several years researchers on this project have explored ways of making mutations in the mouse that affect nervous system connectivity. Novel approaches for generating and identifying mutations that affect mouse neural development, both in the embryo and at postnatal times, have been explored and developed. Several genes that control spinal cord and brain development, organization and wiring have already been discovered.

One exciting “hit” led to the identification of a new gene and a novel developmental process that controls neural tube closure. We will know soon whether disruptions in this gene in humans cause spina bifida or other disorders of the neural tube. Other exciting hits reveal how the sensory and motor systems develop, and how major brain tracts are assembled.

Finally, the Neurogenetics of Wiring and Repair project is developing technologies that will jumpstart the entire gene discovery pipeline for projects at Johns Hopkins. A goal is for the Hopkins research community to join in the use of mouse tools and approaches developed under the auspices of the Neurogenetics of Wiring and Repair project to help establish the genetic basis of development, function and disease, not only of the nervous system, but for all organ systems of the body.

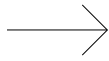
"PEOPLE HAVE BEEN PUZZLING OVER THE MEANING OF 'BEAUTY' FOR MILLENNIA. NOW, NEUROSCIENCE HAS OPENED A WHOLE AVENUE OF RESEARCH WHICH MAY EVENTUALLY HELP US UNDERSTAND HOW WE RECOGNIZE AND REACT TO BEAUTY." —GARY VIKAN, DIRECTOR, THE WALTERS ART GALLERY



> Evolutionary sampling of 3D object shape. These stimuli evolved under feedback guidance from a neuron in high level object vision cortex. Neural response to each stimulus is represented by background color. High response stimuli varied in global shape but share common local structure. Neural signals for 3D structure must help determine the nature of visual aesthetic experience. Neural signals for 3D structure must help determine the nature of visual aesthetic experience.

ED CONNOR
 XIAOQIN WANG
 STEVEN HSIAO
 STEVEN YANTIS
 CHARLES LIMB

Perception and evaluation of complex sensory patterns is central to human cognition and awareness, yet the underlying neural coding mechanisms are almost completely unknown. The human brain is a spectacular pattern analyzer, able to make sense of the most complex images and sounds. Human pattern cognition is so rich, varied, and intense that it is a source of aesthetic pleasure and a ground for creativity.



The aim of this project is to learn how brain mechanisms for pattern cognition determine the nature of aesthetic experience in art and music. The Pattern Cognition and Aesthetics program is a collaboration across five laboratories in the Schools of Medicine, Engineering and Arts and Sciences.

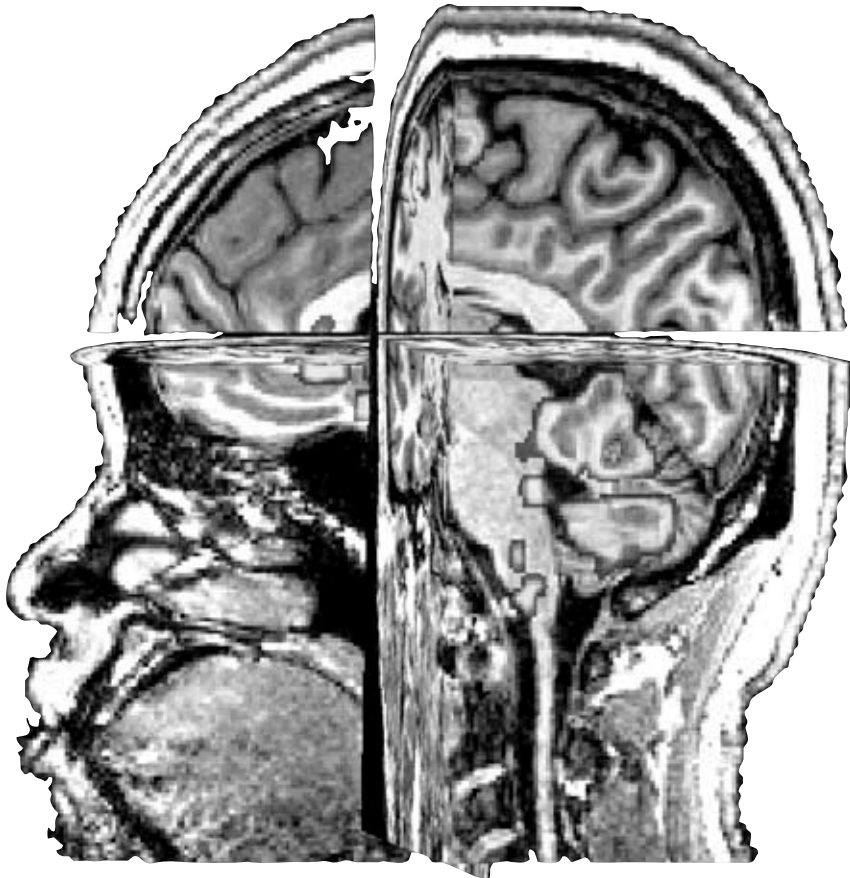
In the visual arts the goal of this project is to understand the neural basis of 3D shape aesthetics. This work is motivated by the hypothesis that 3D aesthetic preferences are driven at least in part by neural mechanisms for 3D visual perception in the brain. Artists and architects must exploit these neural mechanisms to produce profound visual experiences. The specific hypothesis is that highly abstract, minimalist sculptures capture essential forms that resonate with neural mechanisms for 3D shape vision.

The Pattern Cognition and Aesthetics program uses computer morphing technology to study 3D shape aesthetics. Experiments are based on 3D laser scans of sculptures by the 20th century modernist Jean Arp from MoMA and other sources. The laser scans serve as the basis for arrays of morphed shapes in which geometric characteristics like surface curvature, axis curvature, and volume distribution are gradually varied. Subjects are asked to choose their favorite and least favorite

sculptures in each array. The results are analyzed to determine how these geometric characteristics influence aesthetic preference. Findings in this experiment will be used to design targeted tests of aesthetic responses in the human brain using functional magnetic resonance imaging.

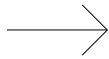
In music, the objective is to understand the neural basis of tonal aesthetics. Functional magnetic resonance imaging is used again to examine responses to pleasant and unpleasant tonal arrangements. As in the visual project, stimuli are based on examples with known aesthetic value. In this case, major and minor scales and triads are presented in ascending, descending, and random order. Pilot data have revealed two surprising phenomena. First, ordered major scales receive the highest aesthetic rating, yet produce the lowest activation in auditory cortex. This implies that aesthetic preference does not relate to strength of activation in sensory cortex. Second, randomly ordered major scales produce strong activations in visual cortex. This suggests that complex, unexpected tonal patterns may induce visual imagery of spatial structure, which would have implications for multisensory appreciation of music.

"THE BSI FUNDING ALLOWED US TO START A NEW COLLABORATION AND EXPLORE HOW NON-INVASIVE BRAIN STIMULATION CAN AFFECT THE PROCESS OF LEARNING A NEW WALKING PATTERN." —AMY BASTIAN, ASSOCIATE PROFESSOR, JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE



> Brain and cerebellar activation during performance of motor tasks. Using this image we can guide non-invasive brain stimulation to specific target areas. This knowledge will ultimately be useful to develop novel rehabilitation interventions for patients with brain disorders.

The cerebellum is a part of the brain important for learning movement and coordinating the walking pattern. The purpose of this exciting project is to determine if non-invasive brain stimulation can enhance how people learn a new movement pattern.



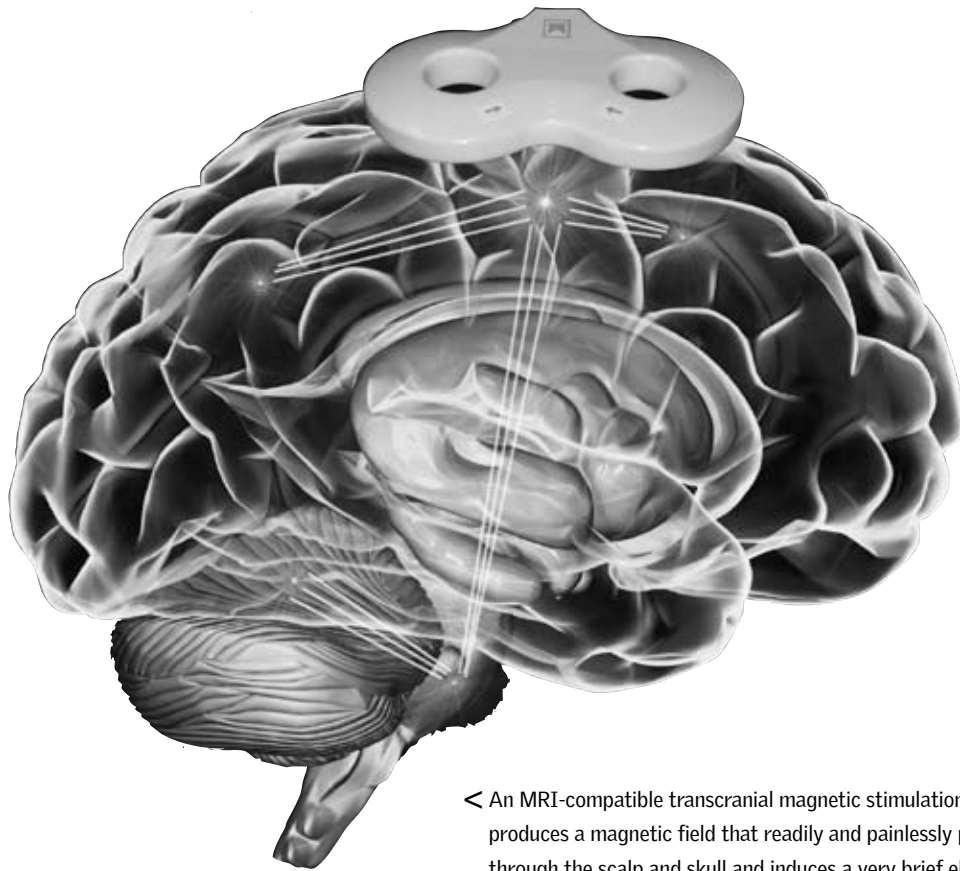
The ultimate goal of the work is to develop new treatments for patients with neurological damage from stroke or disease. This program investigates how a type of brain stimulation called transcranial direct current stimulation, or tDCS, affects the ability of healthy subjects and stroke survivors to learn a new walking pattern.

Stimulation of the cerebellum using this method is painless, and is believed to enhance the speed at which a new movement pattern can be learned. In these studies, subjects practice walking on a novel “split-belt” treadmill, which has two separate belts, one under each foot, while the cerebellum is stimulated. Subjects learn to walk with one leg moving 3 times faster than the other leg, with or without stimulation of the cerebellum.

This year the non-invasive cerebellar program has met two important milestones. First, they have found that tDCS of the cerebellum causes the expected changes in brain activity. Before stimulating the cerebellum during learning, they had to ensure that the basic stimulation worked in the expected manner. Second, they determined the normal cerebellar activity changes that are associated with learning of this split-belt walking pattern. Importantly, these changes occur only when a new walking is being learned, and not simply when walking in a challenging environment.

Since we now know the changes occurring in the cerebellum when people learn the walking pattern, and how tDCS affects the cerebellum, we can apply tDCS during learning. The initial results in healthy subjects suggest that it can enhance the motor learning. In the second year the non-invasive cerebellar program will address whether tDCS can improve learning of a new walking patterns in stroke survivors. If so, it might evolve into a useful rehabilitation strategy.

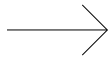
"IN ITS SHORT HISTORY, THE BSI HAS CREATED A MODEL THAT ENCOURAGES THE SPIRIT OF CROSS-INSTITUTIONAL ENTERPRISE THROUGH ITS WORKING GROUPS AND FUNDING AWARD CRITERIA." —LLOYD MINOR, PROVOST, JOHNS HOPKINS UNIVERSITY



< An MRI-compatible transcranial magnetic stimulation coil produces a magnetic field that readily and painlessly passes through the scalp and skull and induces a very brief electric current in the underlying neural tissue. This current causes neurons at the stimulation site, as well as neurons connected to that region, to increase their rate of firing and redirect more oxygenated blood to the region. Using concurrent functional magnetic resonance imaging, regional increases in blood oxygen can be detected, thereby resulting in a map of connectivity to the stimulated region.

JOHN DESMOND
 JAMES PEKAR
 HARRY CHARLES
 REZA JALINOUS
 MARILYN ALBERT
 JEFF YAU

The overall goal of this research is to investigate the combined use of transcranial magnetic stimulation (TMS) and functional MRI (fMRI) for characterizing connectivity in the human brain. Our current knowledge of brain regional connectivity is largely based on highly invasive methods that are only possible in animal studies.



The challenge addressed by the present proposal is to make full use of the latest technologies that are available in order to develop the best possible tools for non-invasively investigating human neuroanatomy and function.

With TMS, an electric current is passed through a coil placed on the scalp of a human subject. This current produces a magnetic field that briefly, painlessly, and non-invasively stimulates the nerve cells beneath the coil. When this technique is performed during an fMRI brain scan, we can image not only the activation produced directly beneath the coil, but also the activity in other regions of the brain that are connected to the targeted region.

The impact of stimulating specific brain regions on the activity and function of other brain regions can be examined using the combination of these two techniques. The broad impact of this research will be the development of new tools for exploring neuroanatomy and function of the human brain and filling gaps in our knowledge of human neuroanatomy, and for exploring altered connectivity in patient populations.

Although considerable advances have been made independently in TMS, as well as in functional and structural MRI

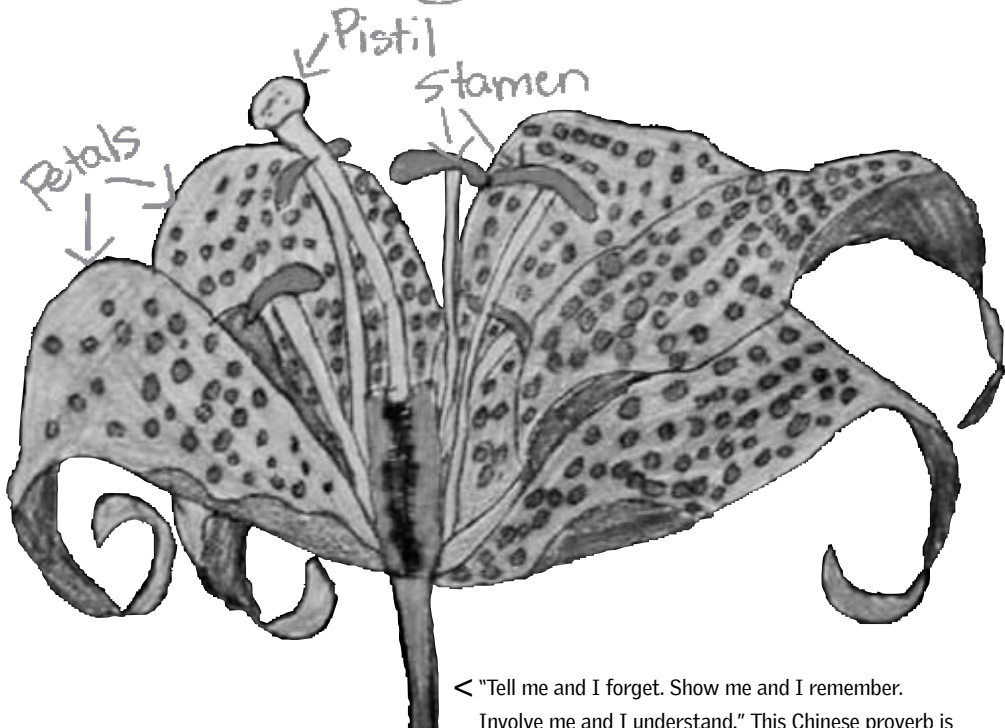
imaging, few laboratories or imaging facilities have explored the potential of combining these methods for investigating connectivity in the human brain. This is due to the engineering challenges of combining these techniques.

The Transcranial Magnetic Stimulation Program has been working with Magstim, Inc, a leader in transcranial magnetic stimulation technology, along with engineers and scientists at the Kirby Center to create a combined TMS/fMRI system customized for the Johns Hopkins and Kennedy Krieger neuroimaging community.

Plans are underway to conduct tests to insure the safety and stability of the equipment in the MRI environment, develop customized scanner software to "interleave" TMS stimulation with fMRI data acquisition and seek approval from the FDA to begin testing with human subject volunteers. Once this approval has been obtained, exploration will begin to create the optimum combination of stimulation parameters and data analysis approaches to maximize the information obtained on brain connectivity.

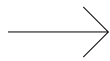
"THE COLLABORATION BETWEEN THE DANA FOUNDATION AND JOHNS HOPKINS HAS HELPED TO GIVE IMPETUS TO THE GROWING FIELD OF NEURO-EDUCATION. THE WORK BEING DONE IN A GROWING NUMBER OF INSTITUTIONS WILL DIRECTLY INFLUENCE HOW WE TEACH, HOW WE LEARN, AND HOW WE THINK." —WILLIAM SAFIRE, DANA FOUNDATION

Flower



< "Tell me and I forget. Show me and I remember. Involve me and I understand." This Chinese proverb is the essence of the arts and learning. "...Arts training works through the training of attention to improve cognition for children with interests and abilities in the arts." says Michael Posner, University of Oregon and speaker at the Learning, Arts and the Brain Summit.

Imagine being able to use evidence-based knowledge about how the brain works to inform other fields of study outside of medicine. What if you could use this knowledge to inform teaching and parenting practices. What if, by explaining how we learn to children and adults, we could all become more active learners? The implications for higher achievements individually and as a society are staggering. This is precisely the goal of the Neuro-Education Initiative.



Located in the School of Education, the Neuro-Education Initiative (NEI) bridges the gap between the brain sciences and education by bringing together an interdisciplinary group of researchers, educators, and other key stakeholders to explore the intersection, knowledge, and current application of brain research in education, and to identify and support potential areas of translational research. The NEI has established a strong collaborative network across the University, planned and conducted regional and national conferences and summits, explored research opportunities, developed and implemented academic programs and developed a communications outreach framework to effectively reach educators, parents and researchers.

In partnership with the Dana Foundation, NEI hosted its inaugural national summit in May 2009 to explore the intersection of neurological and cognitive sciences, the arts and learning. The Learning, Arts and the Brain Summit included over 300 educators, scientists, school administrators, parent representatives and policy-makers who shared an interest in advancing the science of learning through the lens of the arts.

Future annual summits will address topics that have significant interest for educators, parents and policy makers and are currently under study by researchers across

multiple domains in the brain sciences. In May 2010, the NEI will host its second summit called Attention and Engagement in Learning.

In July 2009, the NEI launched its first academic program: The Mind, Brain and Teaching Certificate. As one of the first academic programs for educators in the country focused on the intersection of the brain sciences and education, the certificate has attracted a strong regional and national audience.

Communications and outreach is an integral aspect of the success of the NEI. Because it is critical to share useful information to a wide range of individuals, carefully framing the content and method of communication is vital. NEI is developing a comprehensive communications and outreach strategy to guide its contact and messaging with a diverse audience. Recently NEI affiliated with New Horizons for Learning website.

Because of the great interest in the emerging field of neuroeducation, over the last year, the NEI has had significant academic and popular media coverage including Education Week, WYPR, WEAA, *The Washington Post*, Dana Foundation website and newsletters, and *The Baltimore Sun*.

The BSi NeuroTranslational Program was created with the mission of identifying novel drug targets arising from JHU faculty's research and translating them into new drug therapies for neurological disorders. To accomplish this, BSi has taken the practical approach of complementing Hopkins' strengths in basic research with seasoned pharmaceutical professionals who have decades' worth of experience in drug discovery and early stage development.

The BSi NeuroTranslational staff has expertise in medicinal chemistry, assay development, animal pharmacology, the conduct of preclinical studies, and the expertise necessary to bring novel drugs to the clinic. The BSi NeuroTranslational Program's scientists will work hand-in-hand with faculty interested in translational medicine to create dedicated, multidisciplinary project teams. These teams will work collaboratively to obtain funding and progress targets through the drug discovery and pre-clinical development process. The data packages arising from this work will enhance out licensing and new venture opportunities.

Raising the bar of medical excellence through an interdisciplinary education is a hallmark of the Johns Hopkins community. The BSi NeuroTranslational core staff, with breadth of industrial pharmaceutical expertise, will also participate in this tradition by providing drug discovery educational opportunities for faculty, staff, and students at Hopkins.

The following highlights the capabilities of the BSi NeuroTranslational Program staff:

- Medicinal Chemistry expertise including hit identification, hit-to-lead selection and lead optimization
- Design, synthesis, purification, and characterization of small molecule drug candidates
- High throughput screening assay development
- Receptor pharmacology
- Enzyme kinetics and mechanisms
- Primary cell culture and establishment of cell lines
- Preclinical toxicology
- Drug metabolism and pharmacokinetics
- Investigational New Drug (IND) enabling preclinical studies
- FDA regulatory filing
- Intellectual property creation

Housed in the John J. Rangos Building in the new Science and Technology Park adjacent to the JHU East Baltimore campus, this program occupies approximately 4,000 square feet of state of the art laboratory space. The new facility includes two 800-square foot chemistry laboratories. The facility also includes a dedicated biology laboratory and a separate equipment room.

"A NEW LEVEL OF INTERACTION BETWEEN INDUSTRY AND ACADEMIA WILL BE NEEDED TO SPEED THE DEVELOPMENT OF NEW THERAPIES, AND ACHIEVING THESE INTERACTIONS WILL REQUIRE NEW MODELS OF PARTNERING."

—JEFFREY NYE, MD, PHD, EXTERNAL INNOVATION LEADER FOR NEUROSCIENCE, EAST COAST RESEARCH AND EARLY DEVELOPMENT, JOHNSON AND JOHNSON PHARMACEUTICAL R&D, LLC

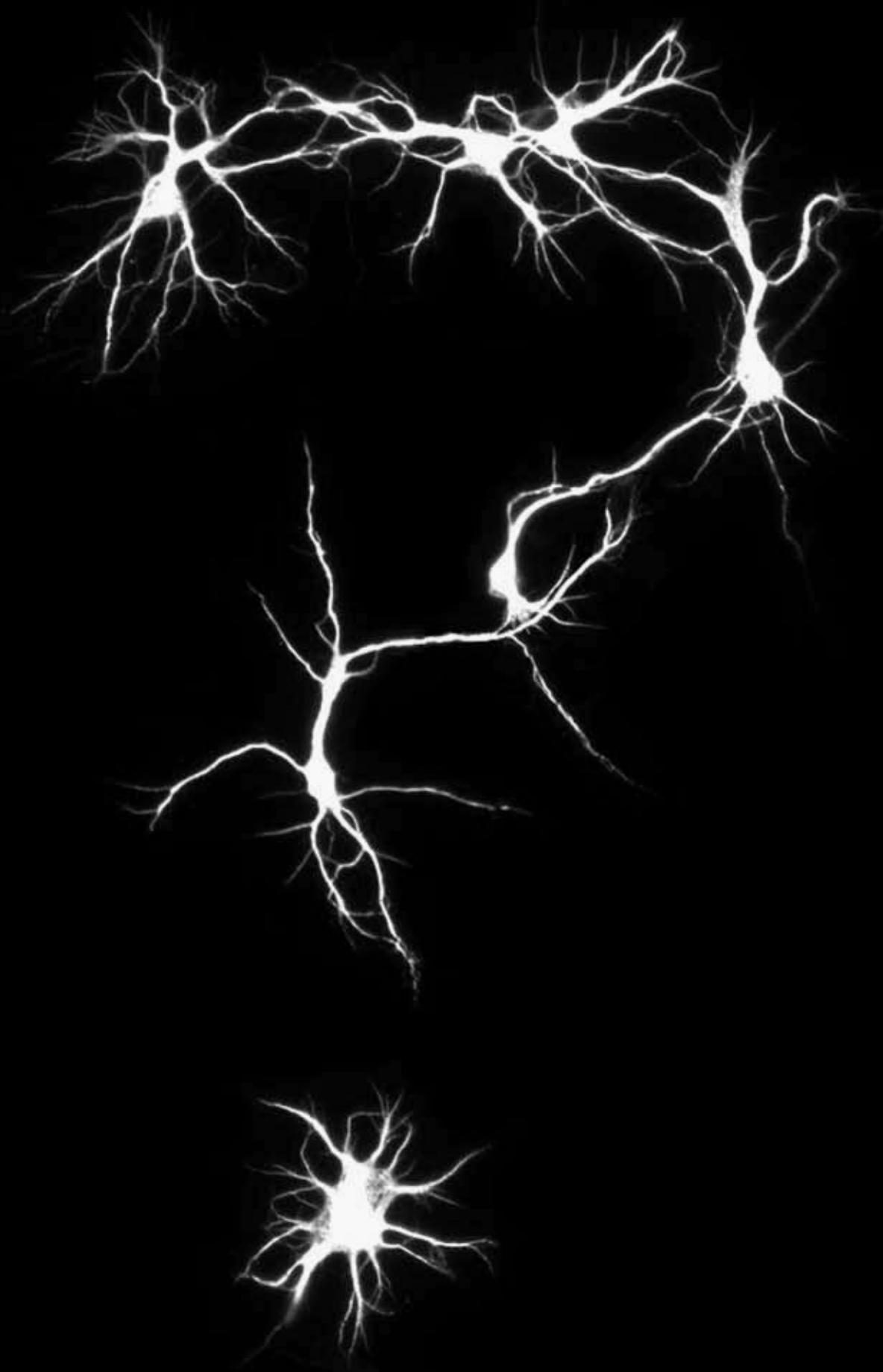
The BSi is committed to developing new partnerships with industry and biotechnology with the goal of fostering translation of discoveries to treatments of disease. Working together with the NeuroTranslational Program, the BSi has hosted industry representatives from around the world to share the scope of basic and clinical neuroscience in anticipation of developing long-term research relationships geared to specific disease targets. Through these industry showcases BSi has met with Wyeth, Eli Lilly, Johnson & Johnson, GSK, and Lundbeck among others.

Biogen-Idec has signed a "model" agreement that includes research support for proposals chosen on a competitive basis by a joint Biogen Idec-BSi steering committee. The agreement is unique because it streamlines intellectual property and reduces regulatory barriers. The first two awards were announced in 2007. A third project award was announced in 2009. Target research areas include Multiple Sclerosis, Alzheimer's disease and pain.

To facilitate further development and partnership the BSi has developed several other initiatives. The first in co-sponsorship with the Johns Hopkins Office of Technology is called the Technology Commercialization Seminar

Series. These ongoing talks address critical issues on technology transfer and commercialization. Another hugely successful program is Entrepreneurial Speed-Dating where scientific investigators with start-up company ideas meet business entrepreneurs. The purpose of this event is to connect Hopkins inventor scientists with business entrepreneurs experienced in starting companies. The goal is to accelerate the formation of new life science companies. Researchers get a chance to meet with multiple entrepreneurs in one setting to see if there is a "chemistry", a first step in creation of new venture. There is also an opportunity to network with entrepreneurs and venture capitalists.

Other efforts to bring industry partners together for collaboration and discussion include a large, successful JH Biotechnology Conference "Neuroscience Investors Conference: Investing in Brain Research." The BSi team has also developed the BSi Venture Capital initiative with Atlas Ventures, Quaker Bioventures, Polaris Venture Partners, and Red Abbey Venture Partners. And finally, together with JHU, a very productive Entrepreneurs Boot Camp with Wilson Sonsini Goodrich Rosati was held.



From synapses to systems research, genetics to translation, the BSi has identified and aggressively pursued a broad and strategic course since its inception. We believe it is only by fusing together these wide-ranging but related targets that we will be able to unravel the mysteries of brain function and development, and create new therapies to treat and ultimately cure nervous system and brain-based diseases.

The early efforts of the BSi has shown the enormous energy unleashed by the Hopkins neuroscience community when difficult challenges are met with innovative and collaborative solutions through non-traditional and generous funding.

The results of our first efforts are truly impressive. New initiatives, green housed by the BSi, are already receiving acknowledgement through Federal funding. Upcoming science publications validate the caliber, output and productivity of our enormously talented researchers. Some of these early findings have the potential to produce major changes in their fields, from forward genetics to new approaches to the arts in education. The BSi has also made investments in core equipment to support university-wide advancements.

Yet with its successes, the BSi is just getting started. The field of brain science, by its nature, is a work in progress. New findings lead to additional experiments, which lead to new insights and discoveries. We anticipate facilitating the development of new programs in cognitive neuroscience and in neuroaesthetics.

The BSi is committed to addressing two critical challenges that are shared by all university neuroscience programs. The first is how to integrate efforts across the enormous field that we call brain science. Neuroscientists and investigators

in related disciplines such as engineering, physics and mathematics are scattered across manifold disciplines, departments, and schools. The BSi believes the future breakthroughs depend on our ability to harness the best expertise in the institution and remove these arbitrary barriers. We will work with our internal and external advisors to provide creative and innovative solutions to this challenge that align with the Hopkins culture and might serve as a model for other institutions.

The second challenge is how to develop interactions with industry that break through the impasses to development of new therapies. These translational obstacles are being met at Hopkins by a new willingness to surmount the problems by creating novel approaches and partnerships. The NeuroTranslational Program and master agreements with industrial partners are steps that will allow real exchange of expertise and joint efforts on therapeutic goals. The measure of this effort will be whether or not the translational process is more effectively and rapidly pursued and ultimately whether new treatments result.

The cornerstone of the BSi, on which all else is built, is the excitement of the science. It is a privilege to be part of this great undertaking and to look forward to what is to come.

