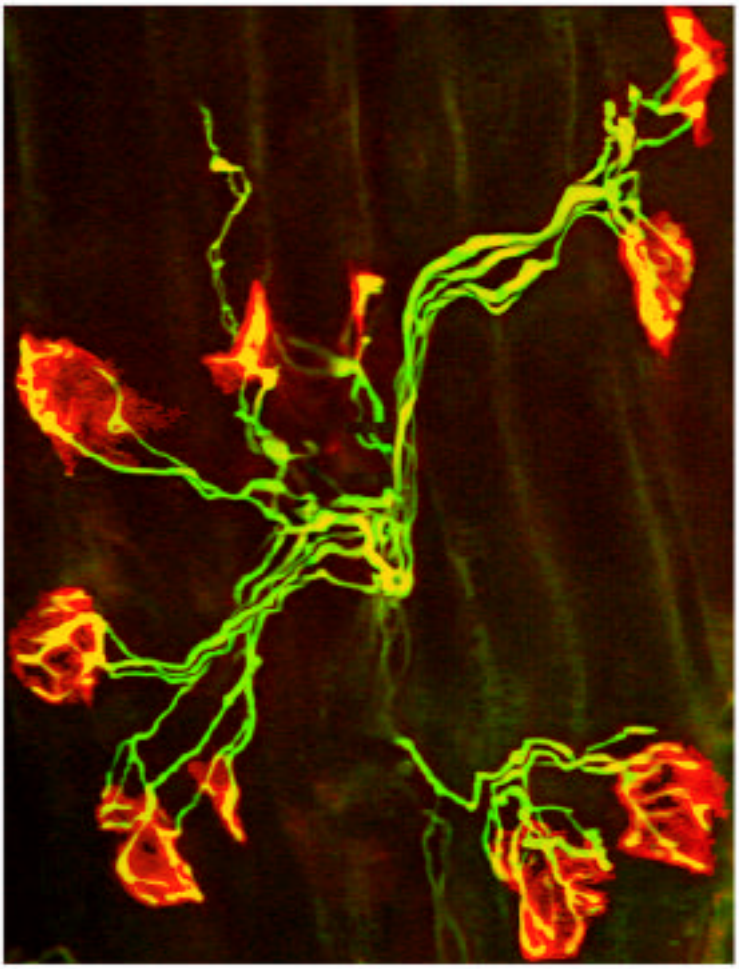
Washington University



Program in Neuroscience

Contents

COVER PHOTOS

***Front Cover**: Transgenic expression of a potent growth factor (GDNF) in muscle fibers causes neuromuscular junctions to be hyper-innervated. Shown are many motor axons (green) converging at each junction whose acetylcholine receptors are labeled (red). At the age shown ordinarily only one axon contacts each junction. From Nguyen et al (1998) Science 279:1725-9. Drs. Quyen Nguyen and Jeff Lichtman.*

Back Cover

Top Left: Neurons in the subventricular zone of the forebrain migrating towards the olfactory bulb. Dr. Yi Rao.

Middle Left: The microtubule cytoskeleton of cortical neurons in culture. Three dimensional image using confocal immuno-fluorescence. Dr. Mark Goldberg.

Bottom Left: A rendering of an electrophysiological assay of synaptic efficacy. Shown are the very weak synaptic potentials (blue) ranked by amplitude from an axon that is in the process of losing a competition with another axon that innervates the same postsynaptic muscle fiber during early postnatal life. Drs. Howard Colman and Jeff Lichtman.

Top Right: Tangles and plaques from a very mild case of Alzheimer's Disease, stained with two antibodies, one against paired helical filaments (to demonstrate the tangles) and one against β-amyloid (to stain the plaques). Dr. Joel Price.

Middle Right: Functional "reconstructed" motor synapse. Isolated nerve terminal boutons (green) have been positioned over postsynaptic receptor patches (red) of muscle fiber (shown blue). Dr. Robert Wilkinson.

Bottom Right: Three-dimensional computerized reconstruction of the human brain. Dr. David Van Essen and Ms. Heather Drury.

The **Neuroscience Program at Washington University** provides opportunities for graduate and postgraduate training in a variety of laboratories engaged in multidisciplinary research aimed at understanding how the brain works and how it malfunctions in disease. The program has great breadth, depth, intellectual vitality, and collegiality. This brochure provides information about graduate training, faculty research programs, and other activities in the neuroscience community, as well as information about Washington University and the St. Louis area. For information regarding the application process, see page 3 of this brochure.

To understand the brain in health and disease is one of the great challenges of our time. Progress has been dramatic over the past several years, but there is much we do not yet know. How does it mediate our perceptions, our thoughts, and our emotions? How is its intricate circuitry established during development and refined by experience? What goes wrong in the myriad of neurological diseases and mental disorders that impact nearly every person at some point in their life? The Program in Neuroscience at Washington University, one of the world's finest, has as its main goals the search for answers to these questions and the training of individuals to continue this search. At its heart are long-standing commitments to excellence in research and to interdisciplinary approaches to neuroscience. The program provides its students and postdoctoral trainees with superb resources and excellent training in courses and in the laboratory. For talented individuals interested in neuroscience, Washington University is an exceptional place to be.

Production of this brochure was supported by the McDonnell Center for Higher Brain Function and the McDonnell Center for Cellular and Molecular Neurobiology.

For more information visit our website: http://thalamus.wustl.edu/Neuroweb/ or contact Susan Danker (susan@v1.wustl.edu or 314-362-7043).

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http://thalamus.wustl.edu/Neuroweb/

Graduate Education

All neuroscience graduate students are enrolled in the Division of Biology and Biomedical Sciences, an interdepartmental umbrella organization that facilitates the educational and research goals of the University. The predoctoral programs within the Division include not only neuroscience, but also developmental biology, immunology, molecular biophysics, molecular cell biology, biochemistry, molecular genetics, molecular microbiology and microbial pathogenesis, evolutionary and population biology, plant biology, and bio-organic chemistry. These programs include faculty at the Hilltop and Medical campuses of Washington University. Graduate students are admitted to one program, but are encouraged when appropriate to participate in courses and/or laboratory opportunities that are offered by the others. Graduate students receive an assured annual stipend ($15,500 for 1990-00), full tuition remission, and paid health insurance. Admission to the graduate program in neuroscience is highly competitive. At present, 39 Ph.D. students and 27 M.D./Ph.D. candidates are enrolled in the program.

Neuroscience at Washington University has deep historical roots that include Nobel Prize-winning work on nerve conduction (Erlanger and Gasser), nerve growth factor (Levi-Montalcini and Cohen) and signal transduction (Sutherland). In recent years, the program has diversified and expanded greatly, allowing it to remain at the forefront of exciting developments in many different areas.

The interdepartmental nature of the neuroscience program encourages interaction between various laboratories, and collaborations between neuroscientists are quite common. This collaborative spirit is fostered by many research centers, program project grants and research training grants. The Center for Cellular and Molecular Neurobiology and the Center for Higher Brain Function, both endowed by the James S. McDonnell Foundation, support a wide variety of neuroscience projects. The Center for Study of Nervous System Injury supports basic and clinical research activities related to damage to the nervous system. The Alzheimer's Disease Research Center carries out a multi-faceted approach to under-standing and treatment of a major neurological disease.

Graduate Curriculum and Training

During the first academic year, graduate students are encouraged to enroll in two courses that make up the core curriculum. An intensive 8 week course in Cellular Neuroscience, designed expressly for neuroscience graduate students, is offered during the fall semester. This course integrates cellular physiology with molecular and developmental topics. In the spring semester, students enroll in Systems Neuroscience, which covers functional neuroanatomy as well as clinical neuroscience and the clinical implications of basic neuroscience research. During the second or third years, students may take elective courses on advanced topics, such as optical imaging or computational neuroscience and they participate in a forum that provides training and experience in oral scientific presentation. Several journal clubs and tutorials are available as well, according to individual interest. Laboratory experience during the first 18 months includes several laboratory rotations. Rotations may begin in the summer preceding the first academic year and may last from two to six months. They provide firsthand experience with diverse techniques and experimental approaches. All students obtain teaching experience by serving as a teaching assistant in either an undergraduate or graduate course for one semester. Preliminary examinations are taken during the summer following the first academic year. The student and an examining committee select a research topic about which the student writes a critical review of the current state of knowledge. The review is then defended orally. Students are evaluated on their ability to synthesize a coherent review of the present state of understanding, to identify important unanswered questions, and to propose a means of answering them.

Keeping Abreast in Neuroscience

Numerous seminar series related to neuroscience are conducted at both Medical School and Hilltop campuses. These events provide ample opportunity to keep up with the latest research progress by neuroscientists at Washington University, as well as by researchers outside the university who are invited to speak. In addition, a number of endowed lectureships honor some of Washington University's pioneers in neuroscience and related fields. These lectureships, dedicated to Viktor Hamburger, George H. Bishop, Mildred Trotter, Robert J. Terry, and Philip Dodge, bring renowned neuroscientists to the Washington University campus. The McDonnell Centers for Higher Brain Function and for Cellular and Molecular Neurobiology periodically sponsor major symposia that are held on campus on topics that are of broad interest to the neuroscience community. In addition, students have opportunities to give their own research presentations in one or another seminar series and in various journal clubs on specialized topics.

An especially popular event is the annual Neuroscience Retreat, which is held each fall at a lodge in the countryside near St. Louis. This well-attended event includes a mixture of academic, social, and outdoor activities in a relaxed setting and attractive environment. The informal atmosphere encourages interactions among students, postdoctoral fellows, and faculty from different departments and different subdisciplines.

Graduate Application Procedure

The deadline for receipt of applications to the graduate program is January 1. Following admission to the Division of Biology and Biomedical Sciences, students can matriculate in June and begin rotations. It is advised that students matriculate by the third week in August to be present for orientation. Complete information regarding the application can be obtained from:

Division of Biology and Biomedical Sciences
Washington University School of Medicine Campus Box 8226
660 S. Euclid Avenue
St. Louis, MO 63110-1093
(800) 852-9074 or (314) 362-3365
FAX: (314) 362-3369
EMAIL: admissions@dbbs.wustl.edu

Other admissions information:
http://dbbs.wustl.edu/prostudinfo.html

Washington University in St. Louis

Washington University was founded in 1853 and has developed into an outstanding research university, known for its excellence in teaching and research and the quality of its faculty and student body. It ranks among the nations leading institutions in higher education, and it has one of the largest endowments of all United States universities.

Washington University is dedicated to challenging its faculty and students alike to seek new knowledge and greater understanding of an ever-changing, multicultural world. The University is counted among the world's leaders in teaching and research and draws students and faculty to St. Louis from all groups and from all 50 states and more than 100 other nations. The University is highly regarded for its commitment to excellence in learning. Its programs, administration, facilities, resources, and activities combine to further its mission of teaching, research, and service to society.

Washington University School of Medicine

The Washington University School of Medicine, established in 1891, is one of the top medical schools in the world. Faculty associated with the Neuroscience Program are distributed across 17 departments of the Medical School and 5 departments of the Hilltop campus.

The School of Medicine holds a rich history of success in research, education and patient care, earning it a reputation as one of the premier medical schools in the world. Since its founding in 1891, the School has trained nearly 6,000 physicians and has contributed ground-breaking discoveries in many areas of medical research. The School of Medicine is internationally known for research in neuroscience, genetics, diabetes, cardiovascular diseases, immunology, diagnostic imaging and many other areas. Fifteen Nobel Laureates have been associated with WUSM. The School currently has 1,200 full-time faculty members and is the fourth-largest recipient of NIH dollars among the 124 U.S. medical schools. The School of Medicine is affiliated with the region's foremost hospitals, including Barnes-Jewish Hospital and St. Louis Children's Hospital -- both members of the BJC Health System. BJC, with ties to 15 hospitals, is the largest academically linked health system in the country. Washington University Medical Center includes more than 60 buildings on nearly 230 acres. The combined, on-site hospital affiliates have more than 2,000 beds.

St. Louis

St. Louis is a prominent cultural and commercial city that offers numerous activities within easy reach of the University. It has all the amenities of big-city living, but at affordable prices. Numerous cultural and entertainment opportunities are available to the 2.5 million residents of the metropolitan area.

The Mississippi Riverfront, where the rich historical roots of St. Louis began, remains a major focus of the downtown area. Laclede's Landing, a newly renovated area along the Riverfront, is a lively center for business, dining and entertainment, with horse-drawn carriages, cobblestone streets and gas lamps. Just south of the Landing is the 630-foot high Gateway Arch, a remarkable sculptural edifice by the architect Eero Saarinen. St. Louis' Fourth of July celebration, held on the Arch grounds, features three days of dynamic air shows, free celebrity concerts and spectacular fireworks.

The St. Louis Symphony Orchestra is considered among the five best in the country, and its home, Powell Hall, is both attractive and acoustically superior. The Opera Theatre Company of St. Louis has a month-long season recognized for high quality and innovation. Ragtime and jazz music have a long tradition in this city and remain attractions in many local bistros and cafes along the Riverfront. A newly constructed outdoor venue, Riverport, brings in major popular musical events in the summer months, while such attractions are often presented at the historic Fox Theatre during winter months.

Interposed between the Hilltop and Medical School campuses is Forest Park, site of the 1904 World's Fair. The second largest city park in the United States, Forest Park contains public tennis courts, three golf courses, an ice skating rink, picnic areas and playgrounds, a small lake for canoeing and boating, and a seven-mile trail for cycling, jogging, and in-line skating. The park is home to the Missouri Historical Society and St. Louis Science Center, as well as the St. Louis Art Museum. Other attractions include the MUNY, a large outdoor amphitheater that hosts a long season of summer musical theater, and the 83-acre St. Louis Zoo with numerous outdoor and indoor exhibits.

St. Louis is a sports-minded city. Blues hockey games at the new Kiel Center, Rams football games at the new domed TWA Stadium, Cardinals baseball games (with home run champion, Mark McGwire) at the venerable Busch Stadium are just some of the professional and collegiate sports activities that are available.

St. Louis' highway system allows easy access to all parts of the city and St. Louis County. A new light rail line MetroLink runs from Lambert Airport through downtown and has a stop at the Medical Center.

A keynote to St. Louis is variety; any taste in cuisine, housing, lifestyle, and leisure can be found. Its strong European roots are evident in many neighborhoods, restaurants and other attractions around the city.

When it's time to get away for a long weekend, St. Louis' central location makes exploring cities as different as Memphis and Chicago, Kansas City and New Orleans relatively simple and inexpensive. Closer by are the Ozarks, which offer excellent venues for canoeing, hiking, and camping.

Research Themes in Neuroscience

Neuroscience research at Washington University can be grouped into five broad themes: cellular, molecular, systems, developmental, and clinical neuroscience.

Molecular Neurobiology

The cells of the nervous system express a large number of distinctive genes whose protein products underlie the development and function of neurons and supporting cells. Molecular neurobiologists at Washington University are currently identifying, cloning and sequencing many genes underlying basic neural functions. These include genes for ion channels, transmitter receptors, transmitter synthesizing enzymes, neuropeptides and their receptors. The analysis of neural development is being enriched by cloning genes responsible for cell-cell recognition and those involved in the response to trophic factors. Investigators also are directly purifying and analyzing proteins found in the nervous system; often the results of these studies complement and extend the results from cloned genes.

Cloning a gene involved in the nervous system is only the first step in obtaining an understanding of what role the gene plays in neural development, function or disease. Some of the most exciting research in the program involves testing hypotheses about the role of specific genes in the function of individual cells and networks. In some situations gene function can be reconstituted in simple systems of neurons or non-neural cells. In other studies, cloned genes are being introduced into transgenic mice to gain insight into their role in development and even behavior of the intact animal.

In keeping with the interdisciplinary nature of the Neuroscience Program at Washington University there is a continual effort to integrate the rapidly expanding cornucopia of molecular knowledge with concepts generated at the single cell and neural network level of organization.

Faculty conducting research in Molecular Neurobiology:

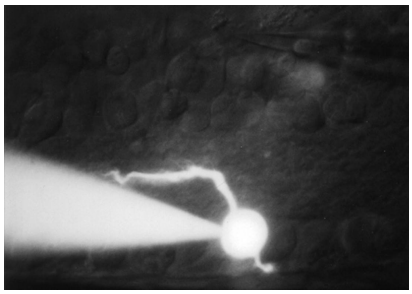
Stuart Adler
Nancy L. Baenziger
Richard Baird
Mark Bardgett
Todd Braver
Ross Cagan
Shimeng Chen
Dennis W. Choi
Michael Crowder
Ann Marie Craig
Aaron DiAntonio
Laura Dugan
Alex S. Evers
N. Gautam
Jonathan Gitlin
Alison Goate
David I. Gottlieb
David Gutmann
David A. Harris
M. Rosario Hernandez
David Holtzman
Chung Y. Hsu
Eugene M. Johnson, Jr.
Raphael Kopan
David A. Leib
Jeff Lichtman
Maurine Linder
Chris Lingle
John McDonald
Steven Mennerick
Jeffrey Milbrandt
Jeanne M. Nerbonne
Colin G. Nichols
Michael L. Nonet
John Olney
Karen L. O'Malley
Yi Rao
Keith Rich
Carmelo Romano
Kevin A. Roth
Lawrence B. Salkoff
Joshua R. Sanes
Robert E. Schmidt
Alan L. Schwartz
Joe Henry Steinbach
Paul H. Taghert
Richard D. Todd
Mark Willard
Jane Wu

Photo: Whole mount stain for b-galactosidase enzyme activity in adult mouse brain. The b-galactosidase gene was placed under the control of fibroblast growth factor 14 regulatory elements by homologous recombination and introduced into mouse germline. Mr. Qing Wang and Dr. David Ornitz.

Research Themes in Neuroscience

Cellular Neurobiology

The nervous system contains a highly diverse collection of neurons and their supporting cells, the glia. Each cell type can be distinguished by its shape (much as different species of tree can be recognized), and by the electrical and chemical signals it uses to transmit information and communicate with other cells. Cellular neurobiologists aim to understand the common characteristics shared by many cell types as well as the distinctive characteristics that underlie specialized aspects of function. For example, all nerve cells generate electrical signals for local and/or long distance communication by using specialized ion channels that carry current across the cell membrane. To function properly, each cell must contain an appropriate subset out of the hundreds of different channel types that have been discovered, and these channels must be appropriately distributed within different regions of the cell used for receiving, integrating and transmitting information. Likewise, each cell uses only one or a few out of the dozens of chemical transmitters that can be used to transmit signals at synapses. Another form of specialization occurs in the various cell types responsible for transducing sensory information about the environment. In general, each modality (vision, hearing, etc.) is mediated by sensory receptors that are exquisitely specialized for transducing a particular type of external energy into appropriate electrical signals. Washington University has a long tradition of excellence in cellular neurobiology, beginning with the pioneering work of Erlanger, Gasser and Bishop, who were the first to use the oscilloscope to record and study nerve impulses. At present, our cellular neurobiologists have access to a number of sophisticated techniques including patch-clamping, imaging and genetic engineering. Often, all three techniques are used in the same lab, giving cellular neurobiologists an unprecedented ability to analyze the roles of individual molecules in the function of neurons.



Faculty conducting research in Cellular Neurobiology:

Joseph Ackerman
Nancy Baenziger
Richard Baird
Richard Bischoff
Walter Boyle
Paul Bridgman
Andreas Burkhalter
Ross Cagan
Dennis Choi
Anne Connolly
Douglas Covey
Ann Marie Craig
Anne Cross
Aaron DiAntonio
J. David Dickman
Laura Dugan
N. Gautam
Jeffrey Gidday
Alison Goate
Mark Goldberg
David Gutmann
David Harris
M. Rosario Hernandez
John Heuser
David Holtzman
Chung Hsu
James Huettner
Mark Jacquin
Eugene Johnson
Henry Kaplan
Chris Lingle
Peter Lukasiewicz
John McDonald
Steven Mennerick
Jeffrey Milbrandt
Stanley Misler
Louis Muglia
Jeanne Nerbonne
Colin Nichols
John Olney
Karen O'Malley
Alan Pearlman
Jay Pepose
Julio Pérez-Fontán
David Perlmutter
Yi Rao
Keith Rich
Carmelo Romano
Kevin Roth
Steven Rothman
Lawrence Salkoff
Joshua Sanes
Robert Schmidt
Alan Schwartz
Dwayne Simmons
Joe Henry Steinbach
Richard Todd
Mark Warchol
Ling Wei
Mark Willard
Rachel Wong
Tom Woolsey
Jane Wu
Ling-Gang Wu
Kelvin Yamada
Shan Ping Yu
Min Zhuo
Charles Zorumski

Photo: Photomicrograph of a living retinal slice preparation. A recording pipette is attached to a retinal ganglion cell to measure electrical signals initiated by light flashed onto the retina. Dr. Peter Lukasiewicz.

Research Themes in Neuroscience

Developmental Neurobiology

The field known as developmental neurobiology is principally concerned with the way in which the mature nervous system comes into being during embryonic and post-embryonic development. There is good reason to believe that the extraordinary complexity of the adult brain is the product of a set of somewhat simpler developmental programs, each of which is accessible to study. These developmental programs include: the creation of nerve cells and their supporting (glia) cells; migration of these cells to chemical and structural attributes of individual classes of neurons; elongation and navigation of the nerve cell output process (the axon) from the cell body to specific target areas; naturally occurring neuronal cell death; formation of synaptic connections by surviving neurons, and modifications in the organization of the synaptic circuitry as developing animals begin to use their nervous system. Washington University neuroscientists are investigating each of these issues.

The most remarkable examples of cell differentiation in biology occur in the nervous system, which has thousands of classes of nerve cells, each with a distinct morphology, function and biochemistry. It is no surprise that a sizable portion of the genome is concerned primarily or exclusively with the nervous system. Unlocking the way this remarkable cellular and molecular differentiation of the brain comes about is a central theme of modern biology.

Developmental neurobiology has a distinguished history here. Nerve growth factor, the first and best characterized neuronal trophic factor, was discovered in the laboratories of Victor Hamburger and Rita Levi-Montalcini. Since then many outstanding developmental neurobiologists have worked at Washington University, particularly on the cellular and molecular aspects of neural development.

Faculty conducting research in Developmental Neurobiology

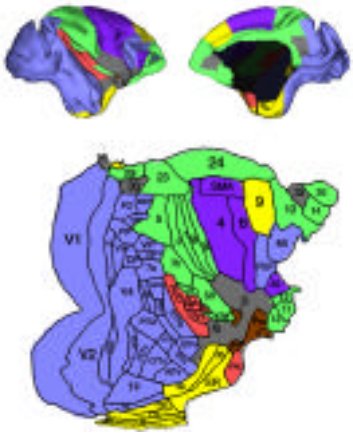
Stuart Adler
C. Robert Almli
Nancy Baenziger
Richard Baird
David Balota
Richard Bischoff
Paul Bridgman
Andreas Burkhalter
Ross Cagan
Ann Marie Craig
Aaron DiAntonio
J. David Dickman
Jeffrey Gidday
David Gottlieb
David Holtzman
Mark Jacquin
Eugene Johnson
Raphael Kopan
Jeff Lichtman
Peter Lukasiewicz
John McDonald
Jeffrey Milbrandt
Steven Mennerick
Louis Muglia
Michael Nonet
John Olney
Karen O'Malley
Alan Pearlman
Madeline Price
Yi Rao
Kevin Roth
Carl Rovainen
Lawrence Salkoff
Joshua Sanes
Dwayne Simmons
Lawrence Tychsen
Mark Warchol
Ling Wei
Rachel Wong
Tom Woolsey
Jane Wu
Charles Zorumski

Photo: Double-headed tadpole.
Dr. Yi Rao.

Research Themes in Neuroscience

Systems and Integrative Neuroscience

Our perceptions of the world, our coordinated motor actions, and our conscious and subconscious thoughts all arise from distinctive patterns of neural activity that course through the billions of nerve cells contained within the brain. To understand any of these events in detail, it is essential to consider how the constituent parts of the brain function as an integrated system that carries out its tasks efficiently and flexibly in a complex, real-world environment. This exciting challenge is being actively attacked in a number of neuroscience laboratories at Washington University. Questions about how the brain is organized and how it functions are pursued in a variety of systems using a wide range of experimental approaches.



Many systems neuroscience laboratories at Washington University concentrate their efforts on the cerebral cortex, which is the dominant structure of the mammalian brain and is responsible for many aspects of higher brain function. Studies of cortical areas involved in vision, somatic sensation, motor control and cognitive function provide valuable insights concerning the distinctive processing and also the common organizational plan under which all strategies that are specific to particular modalities and cortical areas operate. Most of this work is carried out on laboratory animals, where it is possible to analyze the physiological and anatomical characteristics of the cortex in increasing detail. These efforts are complemented by ongoing work in humans using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), which permit the visualization of neural activity patterns in the living brain.

Other laboratories at Washington University study structures such as the cerebellum, basal ganglia, vestibular system, spinal cord and the autonomic nervous system. These structures are simpler than the cerebral cortex in many ways and are more amenable to certain types of experimental analysis. Understanding how each of these systems functions is important in its own right, and the results also are significant in revealing how the nervous system mediates a wide repertoire of behaviors using a diversity of computational strategies and underlying neural architectures. This knowledge also provides the foundation for our ability to understand and treat clinical disorders ranging from hypertension and sudden infant death syndrome to Parkinson's disease and other motor diseases.

Faculty conducting research in Systems and Integrative Neuroscience:

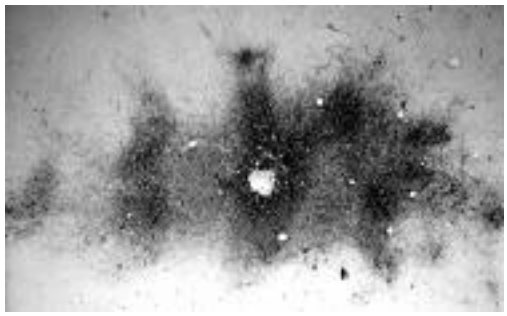
Adele Abrahamsen
Joseph Ackerman
C. Robert Almli
Charles Anderson
Dora Angelaki
David Balota
Deanna Barch
Mark Bardgett
Amy Bastian
Kevin Black
Barbara Bohne
Todd Braver
Randy Buckner
Andreas Burkhalter
Harold Burton
Andy Clark
John Clark
Maurizio Corbetta
John Csernansky
Ralph Dacey
Gregory DeAngelis
Colin Derdeyn
J. David Dickman
Alexander Dromerick
Stanley Finger
Jeffrey Gidday
Steve Highstein
Mark Jacquin
Jeff Lichtman
Arthur Loewy
Peter Lukasiewicz
Kathleen McDermott
Jonathan Mink
Steve Moerlein
Jeff Neil
Bruce Nock
John Olney
T.S. Park
Julio Pérez-Fontán
Joel Perlmutter
Steven Petersen
William Powers
Joseph Price
Marcus Raichle
Henry Roediger
Carl Rovainen
Robert Schmidt
Dwayne Simmons
Lawrence Snyder
Mitchell Sommers
Paul Stein
Nobuo Suga
W. Thomas Thach
Lawrence Tychsen
David Van Essen
Tom Videen
Ling Wei
Rachel Wong
Tom Woolsey
Min Zhuo

Photo: Flat map of monkey cerebral cortex showing different cortical areas.
Dr. David Van Essen and Ms. Heather Drury.

Research Themes in Neuroscience

Clinical Neuroscience

Clinical and basic neuroscience historically have been closely integrated at Washington University. As a manifestation of this integration, clinical neuroscience now encompasses a broad set of research activities. These range from the study of the cellular and molecular mechanisms that underlie the neuronal response to injury to the analysis of the complex systems in the brain that are responsible for movement, sensation and language. The discovery that excitatory amino acid neurotransmitters mediate neuronal death after many types of injury to the nervous system was made at Washington University. This area continues to be a major focus of interest because of the prospect that it will lead to therapies that could prevent neuronal death after stroke and other injuries. While some laboratories work directly on particular diseases, such as epilepsy or multiple sclerosis, others study more general topics with clinical relevance, such as cerebral blood flow and the mechanisms of stroke, or the receptors responsible for the action of anesthetics and opiates. Indeed, there is a sense in which all of the neuroscience research at Washington University has clinical relevance, since an understanding of the fundamental mechanisms of neural function is essential for understanding disorders of the nervous system. In the reverse direction, the analysis of diseases of the nervous system has contributed significantly to the understanding of neuronal function at both the cellular and the systems level. Thus, Washington University with its tradition of integration is well-positioned to bring to bear on delineating the continuing explosion of basic neuroscience information in the neurosciences to the fundamental mechanisms underlying neurological and psychiatric disorders.



Faculty conducting research in Clinical Neuroscience:

Joseph Ackerman
C. Robert Almli
Nancy Baenziger
Deanna Barch
Amy Bastian
Kevin Black
Virginia Buckles
Dennis Choi
David Clifford
Anne Connolly
Maurizio Corbetta
Ann Marie Craig
Anne Cross
Michael Crowder
John Csernansky
Ralph Dacey
Colin Derdeyn
Alexander Dromerick
Jeffrey Gidday
Jonathan Gitlin
Mark Goldberg
Robert Grubb
Chung Hsu
Mark Jacquin
Henry Kaplan
John McDonald
Jonathan Mink
Steve Moerlein
John Morris
Louis Muglia
Jeff Neil
John Newcomer
John Olney
T.S. Park
Julio Pérez-Fontán
Joel Perlmutter
Steven Petersen
William Powers
Madeline Price
Marcus Raichle
Carmelo Romano
Steven Rothman
Carl Rovainen
Eugene Rubin
Robert Schmidt
Yvette Sheline
Dwayne Simmons
Mitchell Sommers
Martha Storandt
Nobuo Suga
W. Thomas Thach
Richard Todd
Lawrence Tychsen
Tom Videen
Desiree White
Shan Ping Yu

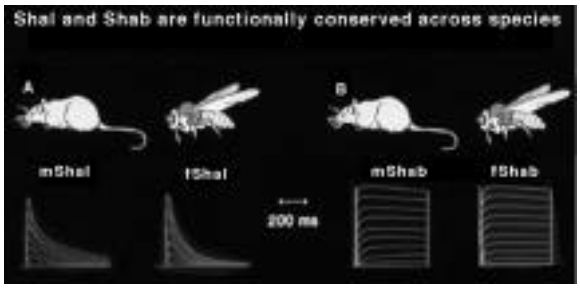
Photo: Intracortical connections of neurons in the interblob region of primary visual cortex of naturally strabismic monkey. Skipping pattern shows an abnormal preference for connections between ocular dominance stripes representing the same eye. Dr. Lawrence Tychsen.

Experimental Approaches in Neuroscience

Neuroscientists at Washington University apply a variety of experimental approaches to understand the nervous system in health and disease.

Genes: Cloning, Sequencing, and the Analysis of Expression and Function

Genes important for neural development and function are studied at Washington University with a wide range of experimental techniques. Cloning of specific genes can be achieved, for example, by starting with a protein of interest, getting a partial amino acid sequence and probing one or another gene library with an appropriate oligonucleotide sequence. Alternatively, genes often can be cloned on the basis of their homology with known members of large multigene families. Cloned genes then can be sequenced either manually or using large-scale automated sequencing methods.



Once this information is available, many experimental approaches are available for studying the pattern in which different genes are expressed, the way in which this expression is regulated and the function of different gene products. In situ hybridization and sensitive mRNA detection techniques can be used to tease apart the exquisite temporal and spatial control of gene expression during development and in the mature nervous system. Genes for ion channels and transmitter receptors can be injected into cell types lacking such proteins but capable of expressing the foreign genes. Mutated or rearranged versions of the gene can be injected to analyze the relationship between gene sequence and function. Increasingly, cloned genes are being used to modify and regulate the behavior of actual nerve cells. Cloned genes introduced into neurons by viral infection or other means can reveal their function in a "native" biological background. The ultimate extension of this approach is the introduction of cloned genes into the intact animal, an objective now attainable using transgenic mice.

Neuroscience Program Faculty using this approach:

Stuart Adler
Nancy Baenziger
Richard Baird
Mark Bardgett
Paul Bridgman
Ross Cagan
Shimeng Chen
Dennis Choi
David Clifford
Ann Marie Craig
Anne Cross
Michael Crowder
Aaron DiAntonio
N. Gautam
Jonathan Gitlin
Alison Goate
David Gutmann
David Harris
M. Rosario Hernandez
David Holtzman
Chung Hsu
James Huettner
Eugene Johnson
Henry Kaplan
Raphael Kopan
David Leib
Maurine Linder
Chris Lingle
John McDonald
Steven Mennerick
Jeffrey Milbrandt
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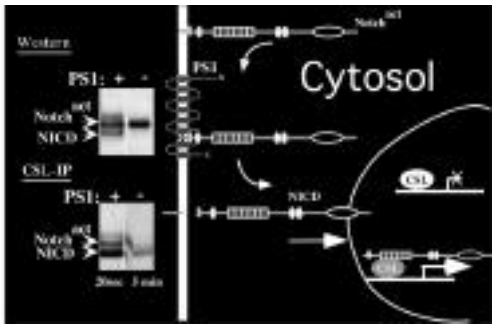
Jeanne Nerbonne
Colin Nichols
Michael Nonet
Karen O'Malley
Alan Pearlman
Jay Pepose
Yi Rao
Keith Rich
Carmelo Romano
Kevin Roth
Lawrence Salkoff
Joshua Sanes
Alan Schwartz
Joe Henry Steinbach
Paul Taghert
Richard Todd
Mark Willard
Jane Wu
Shan Ping Yu
Charles Zorumski

Photo: Potassium channels are encoded by a family of genes conserved in all animal species. The figure shows two examples of currents from genes cloned from fly and mouse (expressed in Xenopus oocytes). Dr. Lawrence Salkoff.

Experimental Approaches in Neuroscience

Protein Chemistry

Each cell type in the nervous system contains a unique constellation of specific transmitters, receptors, internal messengers, enzymes and cell-surface recognition molecules. Modern protein chemistry techniques allow ever-increasing numbers of these specific molecular constituents to be isolated and characterized. Characterization includes determination of amino acid sequence, sites of modification (such as phosphorylation) and folding and assembly into functional units. Such studies provide insights into how key nervous system proteins participate in the regulation of biological function.



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Karen O'Malley
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Alan Schwartz
Mark Willard
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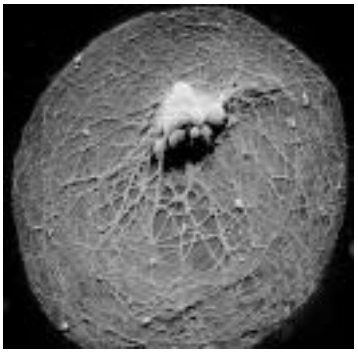
Photo: PS1, interacting genetically with the Notch pathway, is involved in Notch processing. Western blots of extracts (western) and CSL co-immunoprecipitations (CSL-IP) of mNotchDE transiently expressed in murine embryonic fibroblasts from PS1+/+ and PS1-/- embryos. NICD is present in the extract from PS1+/+ cells, and almost undetectable in PS1-/- cells. Enriching for NICD using coimmunoprecipitation with its nuclear binding partner CSL demonstrated that residual amounts of NICD are present in PS1-/- cells (5min exposure, compared to 20 sec in the other lanes). Dr. Raphael Kopan.

Experimental Approaches in Neuroscience

Cells and Systems in Culture

Experimentation is the essence of the analytical approach, but many questions about neural development and function have been unanswerable because of the complexity and relative inaccessibility of the intact nervous system. Advances in cell culture and organotypic slice methods now make it possible to study living neuronal and glial cells with experimental approaches such as patch-clamping and high- resolution microscopy, which are difficult or impossible to use in vivo. Neuroscientists at Washington University have helped to pioneer these approaches and are now using them to study immortal cell lines, cells dissociated from the nervous system and thin slices of various brain regions kept alive in defined conditions for hours to weeks. The questions being analyzed are equally diverse, ranging from the control of gene expression and the molecular basis of synaptic function to the signals that guide cell migration and axon elongation in development.



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Jeffrey Milbrandt
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Joshua Sanes
Robert Schmidt
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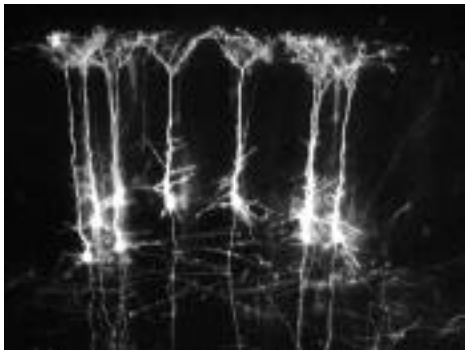
Kelvin Yamada
Charles Zorumski

Photo: Scanning electron micrograph of a cluster of postnatal hippocampal neurons grown in microculture. Axons and dendrites of the cells elaborate across, but not beyond, a round bed of confluent astrocytes. The micro-culture is approximately 200 µm in diameter. Ms. Ann Benz, Drs. Steve Mennerick, and Charles Zorumski.

Experimental Approaches in Neuroscience

Neuroanatomy



The field of neuroanatomy was once dominated by purely descriptive studies that often seemed dry and static. This situation has changed greatly in recent years, and neuroanatomists are now able to explore structural issues that can be closely linked to the analysis of neural function. Neuroanatomists at Washington University use an increasingly powerful and diverse collection of tools for studying the structure of the nervous system at many levels of resolution. At the microscopic level, techniques such as magnetic resonance imaging (MRI) permit non-invasive visualization of the structure of the intact human brain, thereby providing a framework for analyzing neural activity patterns with PET or other functional imaging techniques. At the ultrastructural level, electron microscopy can be used to study subcellular organization, including such intricacies as the immunocytochemical localization of specific molecular constituents. At intermediate levels of resolution, a wide range of techniques are available for studying the architecture of the brain and for tracing pathways between identified brain regions.

The very success of anatomists in acquiring data about brain structure poses a formidable problem in coping with the explosion of information. Efforts underway here and elsewhere address this problem by devising new strategies for the computerized visualization and communication of anatomical and functional data. The long-term aim is to provide more powerful and flexible ways for researchers, clinicians and students to access the vast amounts of experimental data available about the structure and organization of the brain.

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Lawrence Tychsen
David Van Essen
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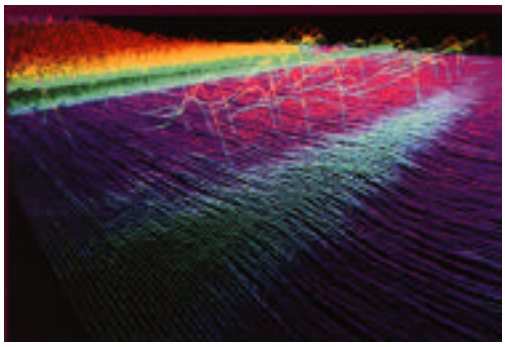
Rachel Wong
Tom Woolsey
Min Zhuo

Photo: Retrogradely labeled neurons in developing rat visual cortex showing dendritic trees and axon collaterals. Drs. Randall Johnson and Andreas Burkhalter.

Experimental Approaches in Neuroscience

Neurophysiology

Action potentials and synaptic potentials are the essential coinage for the computations carried out within individual neurons and for the communication of information within the brain. Neurophysiologists at Washington University use a broad array of techniques to tap into these signals at many different spatial and temporal scales. At the subcellular level, patch-clamping techniques allow the properties of individual membrane channels to be studied in detail. At the cellular level, conventional intracellular and extracellular recordings remain invaluable techniques for attacking questions of neural integration and information processing in preparations ranging from tissue slices to alert, behaving animals. At a still coarser level, positron emission tomography and other functional brain imaging techniques allow indirect assessment of neural activity in large neuronal ensembles, making it possible to study activity patterns in the intact human brain in health and disease.



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Lawrence Snyder
Paul Stein
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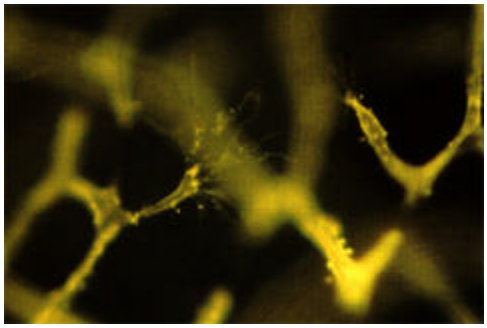
Shan Ping Yu
Min Zhuo
Charles Zorumski

Photo: A rendering of an electrophysiological assay of synaptic efficacy. Shown are the very weak synaptic potentials ranked by amplitude from an axon that is in the process of losing a competition with another axon that innervates the same postsynaptic muscle fiber during early postnatal life. Drs. Howard Colman and Jeff Lichtman.

Experimental Approaches in Neuroscience

Imaging

A revolution of sorts has taken place for biologists who are interested in seeing the nervous system at work. Modern computer-based imaging techniques and sophisticated imaging devices permit visualization of not only neural structure but also function. At one extreme, neuroscientists now can image aspects of cognitive function in awake humans with positron emission tomography (PET scanning -- a technique pioneered at Washington University) and functional magnetic resonance imaging. At the other extreme, the use of fluorescence microscopy and "ratio"-imaging (in which a computer calculates the ratio of two digital images taken at different wavelengths) allows neurobiologists to visualize local changes in the concentration of calcium ions within single neuronal processes. Other fluorescent probes are used to visualize aspects of neural structure vitally, so that in slices and even living animals the system can be viewed while it is functioning. New microscopical techniques like confocal microscopy give neuroscientists a highly resolved picture of the location of neuronal structures in three dimensions. Most of the new imaging techniques take advantage of digital image processing. As image processing computers become more powerful, the imaging technology in neuroscience rapidly follows. It is a very exciting time for imaging in neurobiology, and many scientists at Washington University are working in this rapidly advancing field.



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Robert Schmidt
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Dwayne Simmons
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Ling-Gang Wu
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Rachel Wong
Tom Woolsey
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Photo: Endothelial sprouts in developing cerebral cortex of an E17 mouse after a brightly fluorescent dye, DiA, was painted on the surface of the fixed brain. The endothelium behaved as a syncytium for this membrane-soluble dye. Drs. Stephen Senft, Thomas Woolsey, and Carl Rovainen.

Experimental Approaches in Neuroscience

Computational Neuroscience

The brain is far more complex than any electronic computer in existence or on the drawing boards. Even if we knew the complete wiring diagram of the brain and had a complete characterization of every brain-specific gene and protein, this information would not suffice to tell us how the brain works. This realization has helped neuroscientists to appreciate the importance of computational theory as an essential complement to experimental approaches to studying the brain.

Computational neuroscience provides a framework for hypothesizing what information processing strategies may be used to carry out specific tasks, for suggesting how these strategies could be implemented by a particular neural architecture and for proposing explicit experimental tests that can validate, refute or lead to the refinement of the original hypothesis. For these reasons, it is particularly important to have strong two-way interactions between computational and experimental neuroscientists. At Washington University, interest in computational neuroscience includes efforts to model specific aspects of sensory processing, sensory-motor coordination, learning and higher functions such as attention.

Neuroscience Program Faculty using this approach:

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Lawrence Snyder
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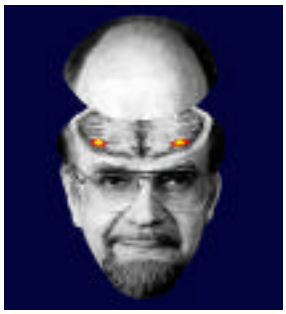
W. Thomas Thach
Richard Todd
Lawrence Tychsen
David Van Essen

Photo: State of a network designed to detect binocular disparity after it had learned to discriminate different disparities. Dr. Bruno Olshausen and Mr. Chris Lee.

Experimental Approaches in Neuroscience

Behavior and Perception



The brain evolved is responsible for mediating a wide range of behaviors in a complex natural environment. To understand how the brain mediates these behaviors, neuroscientists at Washington University use several approaches to analyze well-controlled laboratory situations that capture essential aspects of the natural behavioral repertoire. Psychological and psychophysical techniques offer an avenue for comparing brain function in normal humans with that in clinical subjects who have specific brain lesions caused by stroke or trauma. Functional brain imaging techniques provide a powerful way to monitor human brain activity during specific behavioral tasks. Analogous approaches in laboratory animals provide even greater resolution, as it is possible to painlessly monitor the activity of single neurons in identified brain regions in animals trained to carry out specific behavioral tasks related to processes such as sensory perception, attention and motor control.

Neuroscience Program Faculty using this approach:

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Lawrence Snyder
Mitchell Sommers
Paul Stein
Nobuo Suga
W. Thomas Thach
Richard Todd
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David Van Essen
Ling Wei
Desiree White
Min Zhuo

Photo: Hemispheric asymmetries in the dorsal frontal cortex during memory encoding tasks revealed by functional magnetic resonance imaging (fMRI). Activity was left lateralized for encoding words and right lateralized for encoding nonverbal materials. Mr. William Kelly and Dr. Steve Petersen.

Faculty Research

Adele Abrahamsen, Ph.D.
Associate Professor
Psychology; Linguistic Studies Commitee

As a psychologist studying language acquisition, I have pursued the question of how spoken language relates to other domains of development. For example, I have observed the emergence of language in toddlers who have observed manual signs used as an adjunct to speech. I have also written about the relations between disciplines in cognitive science and cognitive neuroscience and have examined implications of connectionist (neural network) models for developmental and cognitive psychology.

Abrahamsen, A. A., Lamb, M., Brown-Williams, J., and McCarthy, S. (1991) Boundary conditions on language emergence: Contributions from atypical learners and input. In: Theoretical Issues in Sign Language Research, P. Siple and S. Fischer, eds., University of Chicago Press, pp. 231-254.

Bechtel, W., Abrahamsen, A., and Graham, G. (1998). The life of cognitive science. In: A Companion to Cognitive Science. W. Bechtel and G. Graham, eds., Oxford: Blackwell, pp. 1-104.

Bechtel, W. and Abrahamsen, A. (1999). Connectionism and the mind: Parallel processing, dynamics, and evolution in networks (2nd ed.). Oxford: Blackwell.

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Richard A. Abrams, Ph.D.
Associate Professor
Psychology

My research examines questions about the mental mechanisms that underlie overt movements of the eyes and limbs, and covert movements of visual attention. I seek answers to fundamental questions about such behaviors including: To what extent do eye, limb and attention movement systems obey similar operating principles or perhaps employ shared mental mechanisms? To what extent do these systems share spatial information? In what reference frames are the various movements planned and implemented?

Abrams, R. A., and Dobkin, R. S. (1994). Inhibition of return: Effects of attentional cuing on eye movement latencies. Journal of Experimental Psychology: Human Percept, & Perform., 20, 467-477.

Pratt, J., and Abrams, R. A. (1996). Practice and component submovements: The roles of programming and feedback in rapid aimed limb movements. Journal of Motor Behavior, 28, 149-156.

Abrams, R. A., Oonk, H. M., and Pratt, J. (1998). Fixation point offsets facilitate endogenous saccades. Perception & Psychophysics, 60, 201-208.

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Joseph J.H. Ackerman, Ph.D.
Professor
Chemistry; Radiology; Internal Medicine

Our work is concerned primarily with the development and application of magnetic resonance spectroscopic and imaging techniques for the study of functional biophysical and physiologic events in intact biological systems. Such systems include isolated cell preparations, perfused organs, laboratory animals, and humans.

Duong, T.Q., Ackerman, J.J.H., Ying, H.S., and Neil, J.J.Evaluation of extra- and intracellular apparent diffusion in normal and globally-ischemic rat brain via 19F NMR. Magn. Reson. Med. 40:1-13 (1998).

Neil, J.J., Duong, R.Q., and Ackerman, J.J.H.Evaluation of intracellular diffusion in normal and globally-ischemic rat brain via 133Cs NMR. Magn. Reson. Med. 35:329-335 (1996).

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Stuart Adler, M.D., Ph.D.
Research Assistant Professor
Obstetrics & Gynecology; Cell Biology & Physiology

Ongoing research is directed toward understanding the regulated expression of neuroendocrine genes, including regulation by steroid hormones. A variety of molecular approaches including transgenic mice are being used to study transcriptional regulation of Corticotropin Releasing Factor, produced both in neurons in the paraventricular nucleus of the hypothalamus and in human placenta.

Scatena, C.D. and Adler, S. (1998) Characterization of a Human Specific Regulator of Placental Corticotropin Releasing Factor. Molecular Endocrinology 12, 1228-1240.

Meyers, C.Y., Lutfi, H. and Adler, S. (1997)Transcriptional Regulation of Estrogen-responsive Genes by Non-steroidal Estrogens: Doisynolic and Allenolic Acids. J Steroid Biochem & Mol Biol 62, 477-489.

Scatena, C.D. and Adler, S. (1996) Trans-Acting Factors Dictate the Species-Specific Placental Expression of Corticotropin-Releasing Factor Genes in Choriocarcinoma Cell Lines. Endocrinology 137, 3000-3008.

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C. Robert Almli, Ph.D.
Associate Professor - Occupational Therapy; Neurology; Psychology

Neural-behavioral interactions are studied during normal development of motor and cognitive systems, and following perinatal nervous system injury/abnormality. Normal and brain injured (hypoxia-ischemia) neonatal rodents and humans are studied behaviorally and with MRI technology to investigate neural-behavioral interactions during normal and abnormal brain development, and development of neural-behavioral protective treatments.

Dugan, L.L., Turetsky, D.M., Du, C., Lobner, D., Wheeler, M., Almli, C.R., Shen, C.K., Luh, T., Choi, D.W., Lin,T. (1997). Carboxyfullerenes as neuroprotective agents. Proceedings of the National Academy of Sciences, USA, 94, 9434-9439.

Altemus, K.L., Almli, C.R. (1997). Neonatal hippocampal damage in rats: Long-term spatial memory deficits and associations with magnitude of hippocampal damage. Hippocampus 7, 403-415.

Neil, J.J., Shiran, S.I., McKinstry, R.C., Schefft, G., Snyder, A.Z., Almli, C.R., Akbudak, E., Aronovitz, J.A., Miller, J.P., Lee, B.C.P., Conturo, T.E. (1998). Diffusion tensor imaging of normal infant brain: Apparent diffusion coefficient and anisotropy. Radiology, 209, 57-66.

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Charles H. Anderson, Ph.D.
Research Professor - Anatomy & Neurobiology; Biomedical Computing; Physics

My primary research interests are in modeling neuronal systems from the perspective of information processing, statistical inference, resource management and process control. A unified framework is emerging that is applicable to sensory and motor systems in vertebrates as well as invertebrates. The basic computational element is taken to be ensembles of neurons, which encode hypotheses about the state of the external world and possible actions to be taken.

Olshausen, B., Anderson, C.H., and Van Essen, D.C. (1993) A neural model of visual attention and invarient pattern recognition. J. Neurosci., 13:4700-4719.

Anderson, C.H., and Van Essen, D.C. (1994) Neurobiological Computational Systems, In: Computational Intelligence: Imitating Life, Ed. J. M. Zurada, R. J. Marks II, C. J. Robinson, pgs 213-222, IEEE Press.

Van Essen, D.C. and Anderson, C.H. (1995) Information processing strategies and pathways in the primate retina and visual cortex. In: Introduction to Neural and Electronic Networks. S.F. Zornetzer, J.L. Davis, and C. Lau, eds., Academic Press, Orlando, 2nd ed., pp. 45-76.

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* ***Faculty with an appointment in the Division of Biology & Biomedical Sciences**

Dora Angelaki, Ph.D.*
Associate Professor
Anatomy & Neurobiology

Our laboratory is interested in two fundamental questions concerning the neural basis of behavior: (1) How do neuronal circuits transform sensory information into neural commands for movement? (2) How is behavior modified by the environment and what are the underlying neural processing mechanisms that govern adaptive behavior? We combine computational with electrophysiological techniques to study the sensory-to-motor transformations required to direct gaze in three-dimensional space.

Angelaki D.E., Bush G.A. and Perachio A.A. (1993) Two-dimensional coding of linear acceleration in vestibular nuclei neurons, J. Neuroscience 13:1403-1417.

Hess B.J.M. and Angelaki D.E. (1997) Kinematic principles of primate rotational vestibulo-ocular reflex. I. Spatial organization of fast phase velocity axes, J. Neurophysiol. 78:2193-2202.

Angelaki, D.E., McHenry, M.Q., Dickman, J.D., Newlands, S.D. and Hess B.J.M. (1999) Computation of inertial motion: Neural strategies to resolve ambiguous otolith information J. Neuroscience 19(1):316-327.

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==========

Nancy L. Baenziger, Ph.D.*
Associate Professor (Research)
Anatomy & Neurobiology

My lab explores molecular structures and regulation of receptor systems for bradykinin (BK) and histamine (HIS) which modulate neuronal excitability in such functions as pain perception and arousal. When prompted by feed-back signalling pathways in Alzheimer's and other disease states, cells generate these receptors in forms which in turn perpetuate an exaggerated signalling response in a vicious circle. We are defining mechanisms of this aberrant signalling behavior in neuronal and other cell culture model systems.

Jong, Y.-J.I., Dalemar, L.R., Wilhelm, B., and Baenziger, N.L. Human lung fibroblasts express multiple means for enhanced activity of bradykinin receptor pathways. Immunopharmacology 33:9-15, (1996).

Dalemar, L., Jong, Y.-J.I., Wilhelm, B., and Baenziger, N.L. Protein kinases A and C rapidly modulate expression of human fibroblast B2 bradykinin receptor affinity forms. Eur. J. Cell Biol. 69:236-244, (1996).

Jong, Y-J.I., Dalemar, L.R., Wilhelm, B., and Baenziger, N.L. Human bradykinin-B2 receptors isolated by receptor-specific monoclonal antibodies are tyrosine phosphorylated. Proc. Nat. Acad. Sci. USA 90:10994-10998, (1993).

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==========

Richard Baird, Ph.D.*
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Central Institute for the Deaf
Anatomy & Neurobiology
Otolaryngology

Transduction and information processing in developing, repairing, and regenerating vestibular hair cells.
KEYWORDS: Inner ear, vestibular, hair cells, supporting cells, proliferation, regeneration, transduction

Baird, R.A., Steyger, P.S., and Schuff, N.R. Intracellular distributions and putative functions of calcium-binding proteins in the bullfrog vestibular otolith organs. Hear. Res. 1997 103: 85-100.

Steyger, P.S., Burton, M.D., Hawkins, J.R., Schuff, N.R., and Baird, R.A. Calcium-binding proteins are early markers of non-mitotically regenerating vestibular otolith hair cells. Int J. Develop. Neurosci. 1997 15, No. 4/5: 417-432.

Steyger, P.S., Gillespie, P.G., and Baird, R.A. Myosin Iβ is located at tip-link anchors in adapting and non-adapting vestibular hair bundles. J. Neuroscience 1998 18: 4603-4615.

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David A. Balota, Ph.D.
Professor
Psychology

My work focuses on cognitive psychological approaches to attention, memory, and language in young adults, healthy older adults, and in individuals diagnosed with Dementia of the Alzheimer's Type. Although I collaborate with researchers who use imaging techniques, my primary focus is on theory development based on behavioral experimentation.

Balota, D.A., & Paul, S.T. (1996). Summation of activation: Evidence from multiple primes that converge and diverge within semantic memory. Journal of Experimental Psychology: Learning, Memory, and Cognition, 22, 827-845.

Fiez, J.A., Raife, E.A., Balota, D.A., Schwarz, J.P., Raichle, M.E., & Petersen, S.E. (1996). A positron emission tomography study of the short-term maintenance of verbal information. Neuroscience, 11, 20-35.

Spieler, D.H., & Balota, D.A. (1997). Bringing computational models of word naming down to the item level. Psychological Science, 6, 411-416.

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Deanna Barch, Ph.D.
Assistant Professor
Psychology

I study cognitive and language deficits in disorders such as schizophrenia, and the neurobiological mechanisms that contribute to such deficits. My research includes behavioral,pharmacological, and neuroimaging studies with normal and clinical populations. One line of research examines discourse-level components of language production in terms of working memory function (in normal populations) and dysfunction (in schizophrenia), and the mediating role of prefrontal cortex and modulatory neurotransmitters (e.g., dopamine).

Barch DM, Cohen JD, Servan-Schreiber D, Steingard S, Steinhauer S, and van Kammen D (1996). Semantic priming in schizophrenia: An examination of spreading activation using word pronunciation and multiple SOAs. Journal of Abnormal Psychology 105: 592-601.

Barch DM, Braver TS, Nystrom LE, Forman SD, Noll DC and Cohen JD (1997). Dissociating working memory from task difficulty in human prefrontal cortex. Neuropsychologia.35: 1373-1380.

Barch DM and Carter CS. (1998). Selective attention in schizophrenia: Relationship to verbal working memory. Schizophrenia Research 33:53-61.

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Mark Bardgett, Ph.D.
Assistant Professor - Psychiatry

Many hypotheses regarding the neurobiological bases of psychotic disorders and antipsychotic drug action focus on the interaction between neurons in the limbic system and mesolimbic dopamine system. Our research uses laboratory animals to understand how these systems are integrated, how experimental-induced limbic system deficits alter this integration, and what components of each system are required for antipsychotic drug action. Our approaches include behavioral analyses, neurochemical assessments, neuroanatomical techniques, and the use of transgenic or knockout mice.

Bardgett, M. E., Jackson, J. L., Taylor, B. M., & Csernansky, J. G. (1998) The effects of kainic acid lesions on locomotor responses to haloperidol and clozapine. Psychopharmacology, 135, 270-278.

Brenner, D. M. & Bardgett, M. E. (1998). Haloperidol blocks hyperlocomotion elicited by carbachol infusion into the ventral CA1/subiculum. Pharmacology, Biochemistry, & Behavior, 60, 759-764.

Csernansky, J. G., & Bardgett, M. E. (1998). Limbic-cortical neuronal damage and the pathophysiology of schizophrenia. Schizophrenia Bulletin, 24, 231-248.

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Amy Bastian, Ph.D., PT
Assistant Professor
Physical Therapy
Anatomy & Neurobiology

The research in my laboratory is on human movement disorders caused by CNS damage. We are interested in the mechanisms of faulty movement following CNS damage and patterns of recovery. We employ several techniques to quantify movement including: 3-D tracking and reconstruction of movement kinematics, EMG recordings from muscles, and modeling of forces involved in making movement.

Bastian AJ and Thach WT. Cerebellar outflow lesions: a comparison of movement deficits resulting from lesions in the cerebellum vs. the ventrolateral thalamus. Annals of Neurology 38: 881-92, 1995.

Bastian AJ, Martin TA, Keating JG, and Thach WT. Cerebellar ataxia: Abnormal control of interaction torques across multiple joints. Journal of Neurophysiology 76: 492-509, 1996 .

Bastian AJ, Mink JW, Kaufman BA and Thach WT. Posterior vermal split syndrome. Ann Neurol. 44(4):601-10, 1998.

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Richard Bischoff, Ph.D.*
Associate Professor
Anatomy & Neurobiology

My research involves the growth and regeneration of skeletal muscle tissue. We are studying factors that regulate the proliferation, migration, and differentiation of myogenic stem cells in response to muscle injury. Experiments utilize both in vitro and in vivo approaches.

Bischoff, R. (1990) Cell cycle commitment of rat muscle satellite cells. J. Cell Biol. 111:201-208.

Bischoff, R. and Heinz, C. (1994) Enhancement of skeletal muscle regeneration. Dev. Biol. Dev. Dynamics 201:41-54.

Bischoff, R. (1994) The satellite cell and muscle regeneration. In: Myology vol. I, 2nd edition. A.G. Engel and C. Franzini-Armstrong, eds. McGraw-Hill.

Bischoff, R. (1997) Chemotaxis of skeletal muscle satellite cells. Dev. Dynamics 208:505-515.

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Kevin Black, M.D.
Assistant Professor
Radiology
Neurology

My research interests include: 1) PET and fMRI studies of dopamine receptor function; 2) movement disorders, including Tourette Syndrome; 3) diagnostic issues in clinical neuropsychiatry.

Black KJ, Gado MH, Perlmutter JS: PET measurement of dopamine D2 receptor-mediated changes in striatopallidal function. J Neurosci 1997; 17(9):3168-3177.

Black KJ, Gado MH, Videen TO, Perlmutter JS: Baboon basal ganglia stereotaxy using internal MRI landmarks: validation and application to PET imaging. J Comput Assist Tomogr 1997; 21(6):881-886.

Hershey T, Black KJ, Stambuk MK, Carl JL, McGee-Minnich L, Perlmutter JS: Altered thalamic response to levodopa in Parkinson's patients with dopa-induced dyskinesias. Proc Natl Acad Sci U S A 1998; 95(20):12016-12021.

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Barbara A. Bohne, Ph.D.
Professor
Otolaryngology

I investigate degeneration, repair and regeneration in the mammalian auditory system. Degeneration is important for determining mechanisms of damage and, ultimately, preventing certain types of inner-ear damage. Knowledge of repair processes may allow us to develop a biological means to limit the extent of damage after a traumatic insult. Regeneration of nerve fibers in the damaged inner ear may be useful in restoring function in hearing impaired ears. Chinchillas and mice serve as animal models.

Lawner, B.E., Harding, G.W. and Bohne, B.A. (1997) Time course of nerve-fiber regeneration in the noise-damaged mammalian cochlea. Int. J. Devl. Neuroscience 15:601-617.

Bohne, B.A. and Harding, G.W. (1997) Processing and analyzing the mouse temporal bone to identify gross, cellular and subcellular pathology. Hearing Res. 109:34-45.

Bohne, B.A., Maghami, E.G., Bahadori, R.S., Harding, G.W. (1998) The role of micro-noise trauma in the etiology of aging-related changes in the inner ear. Hearing Res. 124:132-145.

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Walter A. Boyle, III, M.D.*
Associate Professor
Anesthesiology; Molecular Biology & Pharmacology

Studies in this laboratory are directed at understanding the molecular mechanism responsible for modulation of smooth muscle contraction. Intact resistance blood vessels are studied under physiologic conditions in vitro utilizing a computer-based image analysis system developed in this laboratory.

Akata T, Boyle WA. Is guanosine-5'-triphosphate involved in calcium-activation of contractile proteins in vascular smooth muscle? Jpn J Pharmacol 1997 75:1-12.

Boyle WA, Muralidharan S, Maher GM, Nerbonne, JM. Vascular actions of "cage" phenylephrine analogs depend on the structure and site of attachment of the 2-nitrobenzyl group. J Photochem Photobiol 1997 41:233-244.

Akata T, Boyle WA. Dual action of halothane on intracellular calcium stores of vascular smooth muscle. Anesthesiology 1996 84:580-595.

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Todd Braver, Ph.D.
Assistant Professor
Psychology

I study the cognitive and neural mechanisms underlying memory, attention, and controlled processing. My research approach combines computational modeling, functional neuroimaging, and behavioral studies (in normal and clinical populations, and under pharmacological challenge). Ongoing research projects exaamine how the prefrontal cortex represents and maintains information in working memory, and how the dopamine neurotransmitter system regulates control over these processes.

Braver, T.S., and Cohen, J.D. (1999). On the control of control: The role of dopamine in regulating prefrontal function and working memory. In Monsell, S. and Driver, J. (Eds.) Attention and Performance XVIII. MIT Press: Cambridge, MA:

Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E. & Noll, D.C. (1997). A parametric study of prefrontal cortex involvement in human working memory. NeuroImage, 5, 49-62.

Cohen, J.D., Braver, T.S., & O'Reilly, R.C. (1996). A computational approach to prefrontal cortex, cognitive control and schizophrenia: Recent developments and current challenges. Philosophical Transactions of the Royal Society, Series B, 346, 1515-1527.

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Paul C. Bridgman, Ph.D.*
Associate Professor
Anatomy & Neurobiology

I study the basic cellular properties of developing nerve and muscle with emphasis on relating structure to function. One study involves the mechanism of nerve growth cone locomotion and the relationship between growth cone motility and nerve outgrowth, focusing on the mechanoenzymes that are likely to participate in growth cone motility. Cellular and molecular methods are being used to locate and disrupt the activity of mechanoenzymes thought to be important for locomotion. Another study concentrates on a unique mechanoenzyme, myosin V, that appears to be important for normal central nervous system function.

Evans, L.L. and Bridgman, P.C. (1995) Particles move along actin filament bundles in nerve growth cones. Proc. Natl. Acad. Sci. USA, 92:10954-10958.

Evans, L.L., Hammer, J., and Bridgman, P.C. (1997) Subcellular localization of myosin V in nerve growth cones and outgrowth from dilute-lethal neurons. J. Cell Science 110:439-449.

Evans, L.L., Lee, A.J., Bridgman, P.C. and Mooseker, M.S. (1998) Vesicle-associated brain myosin-V can be activated to catalyze actin-based transport. J. Cell Science 111:2055-2066.

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Virginia D. Buckles, Ph.D.
Research Assistant Professor
Neurology & Neurological Surgery (Neurology)

As Assistant Director of the Memory and Aging Project, I am involved in the longitudinal study of healthy aging and dementing diseases employing clinical, psychometric, and other biomedical techniques. In addition, my research interests include attention, driving abilities and fine motor control in Alzheimer's disease, Parkinson's disease and healthy aging.

Goldman WP, Baty JD, Buckles VD, Sahrman S, Morris JC. Cognitive and motor functioning in Parkinson's disease with and without questionable dementia. Archives of Neurology 1998;55:674-680.

Duchek JM, Hunt L, Ball K, Buckles V, Morris JC. Attention and driving performance in Alzheimer's disease. Journal of Gerontology-Psychological Sciences 1998;53B:2:130-141.

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Randy Buckner, Ph.D.*
Assistant Professor
Psychology
Anatomy & Neurobiology
Radiology

As the Principal Investigator of the Cognitive Neuroscience Laboratory, my research interests include the use of functional MRI (fMRI) to investigate human brain areas involved in memory processes, both including memory encoding and retrieval, and also to determine how these processes break down (or change) in patients with memory difficulties (e.g., stroke patients and patients with probable Alzheimer's Disease). I have also been involved with methods development with the goal of expanding the range of questions we can ask using brain imaging techniques.

Buckner, R.L., Goodman, J., Burock, M., Rotte, M., Koutstaal, W., Schacter, D.L., Rosen, B., and Dale, A.M. (1998) Functional-anatomic correlates of object priming in humans revealed by rapid presentation event-related fMRI. Neuron. 20, 285-296.

Schacter, D.L., and Buckner, R.L. (1998) Priming and the brain. Neuron. 20, 185-195.

Wagner, A.D., Schacter, D.L., Rotte, M., Koutstaal, W., Maril, A., Dale, A.M., Rosen, B., and Buckner, R.L. (1998) Building memories: Remembering and forgetting of verbal experiences as predicted by brain activity.Science.281: 1188-1191.

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Andreas Burkhalter, Ph.D.*
Associate Professor
Anatomy & Neurobiology Neurology & Neurological Surgery

We are interested in the development and mature organization of circuits by which higher visual cortical areas influence lower areas and the synaptic mechanisms that underlie this process. In these studies we use light and electron microscopy to view synapses and transmitter receptors and recording of synaptic responses in brain slices of wild type and genetically manipulated mice.

Gonchar Y, Burkhalter A. Differential subcellular localization of forward and feedback interareal inputs to parvalbumin expressing GABAergic neurons in rat visual cortex. J Comp Neurol 1998 Forthcoming.

Shao Z, Burkhalter A. Role of GABA-B receptor-mediated inhibition in reciprocal interareal pathways of rat visual cortex. J Neurophysiol 1998 Forthcoming.

Johnson RR, Burkhalter A . A polysynaptic feedback circuit in rat visual cortex. J Neurosci 1997 17:7129-7140.

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Harold Burton, Ph.D.*
Professor
Anatomy and Neurobiology
Cell Biology & Physiology
Radiology

Studies are on the somatosensory cortical areas responsible for object recognition using touch. A principal aim is finding out the neurophysiological properties of each area and learning its unique contribution to tactile discrimination behavior. Specific experiments examine the influence of higher cognitive processes, like selective attention and tactile memory, on the responses of cortical neurons in monkeys, on the distribution of activated loci using neuroimaging techniques in man, and on psychophysical measurements of touch perceptions.

Burton H, MacLeod A-MK, Videen TO, Raichle ME. Multiple foci in parietal and frontal cortex activated by rubbing embossed grating patterns across fingerpads: a positron emission tomography study in humans. Cereb Cortex 1997 7:3-17.

Burton H, Sinclair RJ, Hong SY, et al. Tactile-spatial and cross-modal attention effects in the second somatosensory and 7b cortical areas of rhesus monkeys. Somatosen Mot Res 1997 4:237-267.

Lin W, Kuppusamy K, Haacke EM, Burton H. Functional magnetic resonance imaging in human somatosensory cortex activated by touching textured surface. J Mag Res Imag 1996 6:565-572.

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Ross L. Cagan, Ph.D.*
Assistant Professor
Molecular Biology & Pharmacology

Our laboratory uses the developing Drosophila retina to explore patterning and cell fate mechanisms. Our genetic and tissue culture evidence has implicated the EGFR/Ras signal transduction pathway in initiating and patterning the first cell type. Once established, this pattern is refined through selective use of programmed cell death. Using laser ablation, organ culturing, and a large-scale genetic screen, we have identified the cells that regulate death and a variety of potential death regulators.

Cagan, R.L., Kramer, Helmut, Hart Anne C., and Zipursky, S.L. (1992). The bride of seven-less and sevenless interaction: internalization of a transmembrane ligand. Cell 69: 393-399.

Dokucu, M.E., Zipursky, S. L., and Cagan, R. L. (1996). Atonal, Rough, and the resolution of proneural clusters in the developing Drosophila retina. Development 133: 4139-4147.

Miller, D. T. and Cagan, R. L. (1998). Local induction of patterning and programmed cell death in the developing Drosophila retina. Development 125(12):2327-2335.

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Shiming Chen, Ph.D.
Assistant Professor
Ophthalmology & Visual Sciences
Molecular Biology & Pharmacology

Our laboratory is interested in studying the molecular mechanisms controlling cell-type specific gene expression in the retina, and the implications of these mechanisms for understanding both the normal and diseased retina. We are focusing on identification and characterization of key transcription factors that determine expression of the photoreceptor-specific genes.

Chen S, Zack DJ. Ret 4, a positive acting rhodopsin regulatory element identified using a bovine retina in vitro transcription system. J Biol Chem 271:28549-28557, 1996.

Chen S, Wang Q-L, Nie Z, Sun H, Lennon G, Copeland NG, Gilbert DJ, Jenkins NA, Zack DJ. Crx, a novel Otx-like paired-homeodomain protein, binds to and transactivates photoreceptor cell-specific genes. Neuron 19:1017-1030, 1997.

Swain PK, Chen S, Wang Q-L, Affatigato LM, Coats CL, Brady KD, Fishman GA, Jacobson SG, Swaroop A, Stone E, Sieving PA, Zack DJ. Mutations in the cone-rod homeobox gene are associated with the cone-rod dystrophy photoreceptor degeneration. Neuron 19:1329-1336, 1997.

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Dennis W. Choi, M.D., Ph.D.*
Professor and Head (Neurology)
Neurology & Neurological Surgery (Neurology)

Basic cellular mechanisms underlying CNS injury in acute and chronic neurological disease states, emphasizing the role of cell-cell signaling in modulating vulnerability to injury, and the development of practical therapeutic countermeasures. Topics addressed include excitotoxicity, pathological programmed cell death, free radical damage, and zinc toxicity. Investigations are carried out in primary cell cultures, transfected cell lines, and rodent models of brain ischemia, spinal cord trauma, or Huntington's disease.

Koh JY, Suh SW, Gwag BJ, He YY, Hsu CY, Choi DW: (1996) The role of zinc in selective neuronal death following transient cerebral ischemia. Science 272: 1013-1016.

Yu SP, Yeh C-H, Sensi SL, Gwag BJ, Canzoniero LMT, Farhangrazi ZS, Ying HS, Tian M, Dugan LL, Choi DW: (1997) Mediation of neuronal apoptosis by enhancement of outward potassium current. Science 278:114-117.

Ying HS, Weishaupt JH, Grabb M, Canzoniero LMT, Sensi SL, Sheline CT, Monyer H, Choi DW: (1997) Sublethal oxygen-glucose deprivation alters hippocampal neuronal AMPA receptor expression and vulnerability to kainate-induced death. J Neurosci 17:9536-9544.

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Andy Clark, Ph.D.
Professor
Philosophy

The philosophy/neuroscience/psychology (PNP) program, which I direct, investigates the foundations of cognitive science. Recent research has addressed issues in language processing, the problem of consciousness, and the role of body and environment in supporting adaptive behaviors. My research centers on connectionist models of cognitive function, with special emphasis on the issue of learning flexible, multi-purpose behaviors. I am currently working on adaptive behavior which requires real-time interactions between simple, embodied agents and the world, and on the implications of dynamic systems models for cognitive science.

Clark, A. (1997) Being There: Putting Brain, Body and World Together Again. Bradford Books, MIT Press.

Clark, A (1998) "Where Brain, Body and World Collide" Daedalus: J Am Acad Arts & Sci 127:2: Spring 1998 p.257-280

Clark, A. (1997) "The Dynamical Challenge" Congitive Science 21:4:461-481

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John Clark, Ph.D.
Professor
Physics

My research involves theoretical studies of dynamical behavior, computation, learning, and memory in natural and artificial neural networks. Methods applied include nonlinear dynamics, statistical mechanics, information theory, Bayesian probability theory, and computer simulation. Current efforts are focused on probabilistic descriptions of neural computation based on population coding.

Clark, J. W. (1991) Neural network modeling. Physics in Medicine and Biology 36: 1259-1317.

Clark, J. W. (1999) Neural networks: new tools for modeling and data analysis in science. In: Scientific Applications of Neural Nets. J. W. Clark, T. Lindenau, and M. L. Ristig, eds, Springer-Verlag, Berlin, pp. 1-96.

Clark, J. W., Gernoth, K. A., Dittmar, S., and Ristig, M. L. (1999) Higher-order probabilistic perceptrons as Bayesian inference engines. Physical Review E.

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David B. Clifford, M.D.
Professor and Vice Chair
Neurology & Neurological Surgery (Neurology)

My current research focuses HIV induced neurologic complications including motor-cognitive disorder and peripheral neuropathy. My group also is working on new treatments for progressive multifocal leukoencephalopathy, CNS Lymphoma, HTLV-1 associated myelopathy. Approaches include neuropsychologic testing, quantitative sensory testing, skin biopsy and morphologic peripheral nerve analysis, CSF PCR testing, and quantitative viral load studies.

Hall CD, Dafni U, Simpson D, Clifford D, Wetherill PE, Cohen B, McArthur J, Hollander H, Yiannoutsoso C, Eajor E, Millar, Timpone J and the ACTG 243 Team. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with human immunodeficiency virus infection. N Engl J Med 1998;338: 1345-51.

Navia BA, Dafni U, Simpson D, Tucker T, Singer E, McArthur JC, Yiannoutsos C, Zaborski L, Lipton SA and the AIDS Clinical Trial Group. A Phase I/II Trial of Nimodipine for HIV-related neurologic complications. Neurology 1998;51:221-228.

Clifford DB and Simpson D. Targeting HIV therapy for the brain. HIV:Advances in Research and Therapy 1998;8 10-17.

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Anne M. Connolly, M.D.
Assistant Professor
Neurology & Neurological Surgery (Neurology); Pediatrics

In my laboratory, we study autoantibodies and work to characterize specific autoantigens in a variety acquired and inhereted neurologic diseases affecting children. These diseases include immune mediated neuropathies, opsoclonus myoclonus syndrome, acquired epileptic aphasia, autism and muscular dystrophies.

Connolly, AM, Pestronk, A., Mehta, S. Yee, WC, Green, B.J., Fellin, C. Olney, R.K., Miller, R.G., Devor, W.N. Serum IgM monoclonal autoantibody binding to the 301-314 amino acid epitope of b-tubulin: Clinical association with slowly progressive demyelinating polyneuropathy. Neurology 1997,49:243-248.

Connolly, AM, Pestronk, A. Mehta, S, Pranzatelli, M.R., and Noetzel, MJ. Serum autoantibodies in childhood opsoclonus-myoclonus syndrome: an analysis of antigenic targets in Neural tissues. J. Pediatr. 1997, 130:878-84.

Connolly, AM, Pestronk, A. Mehta, S. and Al-Lozi, M. Case of the month: Primary a-sarcoglycan (adhalin) deficiency responsive to immunosuppression over three years. 1998, Muscle Nerve 21: 1549-1553.

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Maurizio Corbetta, M.D.*
Assistant Professor
Neurology; Radiology; Anatomy & Neurobiology

My research uses functional brain scanning methods (fMRI and PET) to map areas important for vision and attention in the normal human brain. A more clinical line of research focusses on the neural basis of recovery after brain injury. We use functional imaging to track changes in the pattern of brain activation of patients with brain injury during recovery.

Corbetta M., Akbudak E., Conturo T.E., Drury H.A., Linenweber M., Ollinger J.M., Petersen S.E., Raichle M.E., Van Essen D.C., Snyder A.Z., Shulman G.L. (1998) A common fronto-parietal cortical network for attention and eye movements. Neuron 21, 761-773.

Corbetta M. and Shulman G.L. (1998). Human cortical mechanisms of attention during visual orienting and search. Philosophical Transactions of the Royal Society (London) 353: 1353-1362.

Corbetta, M. (1998). Functional anatomy of visual attention in the human brain: studies with positron emission tomography. Parasuram Raya, editor "The Attentive Brain", MIT press, Cambridge, MA.

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Douglas F. Covey, Ph.D.*
Professor
Molecular Biology & Pharmacology

We are interested in the design, synthesis and evaluation of allosteric modulators of ion channel function. Currently, most of our research involves studying allosteric modulators of GABAA receptors. We have prepared two different classes of compounds having unique pharmacological properties at GABAA receptors. The compounds are of interest as investigational tools for physiological studies of ion channel function, and as potential drugs having anticonvulsant, anxiolytic, sedative, hypnotic and anesthetic activity.

Hu Y., Wittmer L.L., Kalkbrenner M., Evers A.S., Zorumski C.F., and Covey D.F. Neurosteroid Analogues. 5. Enantiomers of neuroactive steroids and benz[e]indenes: total synthesis, electrophysiological effects on GABAA receptor function and anesthetic action in tadpoles. J. Chem. Soc., Perkin Trans. I, 3665-3671 (1997).

Canney D.J., Lu H.-F., McKeon A.C., Yoon K.-W., Xu K., Holland K.D., Rothman S.M., Ferrendelli J.A., and Covey D.F. Structure-activity studies of fluoroalkyl-substituted g-butyrolactone and g-thiobutyrolactone modulators of GABAA receptor function. Biomed. Chem., 6, 43-55 (1998).

Nilsson, K. R., Zorumski, C. F., and Covey, D. F. Neurosteroid Analogues. 6. The Synthesis and GABAA Receptor Pharmacology of Enantiomers of Dehydroepiandrosterone Sulfate, Pregnenolone Sulfate, and (3a,5b)-3-Hydroxypregnan-20-one Sulfate. J. Med. Chem., 41, 2604-2613 (1998).

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Ann Marie Craig, Ph.D.*
Associate Professor
Anatomy & Neurobiology

We study cellular and molecular mechanisms of synaptogenesis and synaptic plasticity. Using a dissociated hippocampal cell culture system, we are determining the steps of assembly of molecular components of the two major synapse types in the mammalian brain: excitatory glutamatergic synapses and inhibitory GABAergic synapses. We are currently focusing on the molecular mechanisms underlying subcellular targeting of glutamate receptors, including cis-acting targeting signals, interacting proteins, and modulation by synaptic activity.

Rao, A., and A.M. Craig (1997) Activity regulates the synaptic localization of the NMDA receptor in hippocampal neurons. Neuron, 19:801-812.

Allison, D.W., I. Spector, V.I. Gelfand, and A.M. Craig (1998) Role of actin in anchoring postsynaptic receptors in cultured hippocampal neurons: Differential attachment of NMDA versus AMPA receptors. J. Neurosci. 18:2423-2436.

Craig, A.M. (1998) Activity and synaptic receptor targeting: the long view. Neuron, 21:459-462.

Rao, A., E. Kim, M. Sheng, and A.M. Craig (1998) Heterogeneity in the molecular composition of excitatory postsynaptic sites during development of hippocampal neurons in culture. J. Neurosci. 18:1217-1229.

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Dorothy Anne H. Cross, M.D.
Associate Professor - Neurology & Neurological Surgery (Neurology)

The goal of our research is to understand the mechanisms involved in pathogenesis of CNS inflammation and demyelination in the central nervous system. Our studies primarily employ a murine model for the human disease multiple sclerosis, known as experimental autoimmune encephalomyelitis (EAE). 1) Studies of the role of soluble immune mediators in demyelination. 2) Studies indicating a key role for T cell co-stimulation molecules in EAE and ongoing studies to determine which CNS cells express co-stimulation molecules and what factors induce expression.

Cross, A.H., Misko, T.P., Lin, R.F., Hickey, W.F., Trotter, J.L., and Tilton, R.G. (1994) Aminoguanidine, an inhibitor of inducible nitric oxide synthase, ameliorates experimental autoimmune encephalomyelitis in SJL mice. J. Clin. Invest. 93:2684-2690.

Cross, A.H., Girard, T.J., Giacoletto, K.S., Evans, R.J., Keeling, R.M.., Lin, R.F., Trotter, J.L., and Karr, R.W. (1995) Long-term inhibition of murine experimental autoimmune encephalomyelitis using CTLA-4-Fc supports a key role for CD28 costimulation. J. Clin. Invest. 95:2783-2789.

Cross, A.H., Manning, P.T., Keeling, R.M, Schmidt, R.E., and Misko, T.P. (1998) Peroxynitrite formaiton within the cnetral nervous system inactive multiple sclerosis. J. Neuroimmunol. 88:45-56

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Michael Crowder, M.D., Ph.D.*
Assistant Professor - Anesthesiology; Molecular Biology & Pharmacology

We are interested in the machinery controlling behavior and anesthetic-induced disruption of behavior in the nematode, Caenorhabditis elegans. We have identified genes that determine the sensitivity of C. elegans to clinical concentrations of general anesthetics. Through molecular genetic approaches, we are defining the role of the gene products in anesthetic action. Ultimately, we should learn the mechanisms of anesthesia in C. elegans and, perhaps, how anesthetics produce unconsciousness, amnesia, and analgesia in humans.

Crowder CM, Shebester LD, Schedl TS. Behavioral effects of volatile anesthetics in Caenorhabditis elegans, Anesthesiology 85:901-12, 1996

Van Swinderen B, Ebert RH, Shook DR, Cherkasova VA, Johnson TE, Shmookler Reis RJ, and Crowder CM. Quantitative trait loci controlling halothane sensitivity in Caenorhabditis elegans, Proc Natl Acad Sci USA 94:8232-37, 1997

CM Crowder. Mapping Anesthesia Genes: Why and How? Anesthesiology 88:293-96, 1998.

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John G. Csernansky, M.D.*
Professor
Psychiatry; Anatomy & Neurobiology

Our clinical research is focused on investigating relationships between brain structural and functional abnormalities and specific elements of psychopathology. Additional goals of these studies are to develop improved methods of diagnosis using neuroimaging technologies and to find new psychotropic drugs that have fewer neurological side effects and are effective in a greater proportion of patients. Our preclinical research is focused on improving understanding of neural circuits connecting cortical and subcortical areas (e.g. hippocampus and nucleus accumbens), with particular attention to the functional consequences of corticolimbic neuropathy caused by excitotoxic drugs in both younger and older animals.

Bardgett, M.E., Salaris, S.L., Jackson, J.L., Harding, J., Csernansky, J.G. The effects of kainic acid lesions on dopaminergic responses to haloperidol and clozapine. Psychopharmacology 133:142-151, 1997.

Csernansky, J.G., Bardgett, M.E. Limbic-cortical neuronal damage and the pathophysiology of schizophrenia. Schizophrenia Bull. 24:231-248, 1998.

Csernansky, J.G., Joshi, S., Wang, L.E., Haller, J.W., Gado, M., Miller, J.P., Grenander, U., Miller, M.I. Hippocampal morphometry in schizophrenia via high dimensional brain mapping. Proc. Natl. Acad. Sci. 95:11406-11411, 1998.

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Ralph G. Dacey, M.D.
Professor and Head (Neurological Surgery)
Neurology & Neurological Surgery (Neurosurgery)

Our research centers on the cellular physiology of the cerebral microvasculature. We studythe role of radial and longitudinal cell to cell communication in microvascular regulation. Experimental studies focus on an examination of the heterogeneous responsiveness of isolated and cannulated intracerebral arterioles to vasoactive substances affecting the endothelial and smooth muscle cell layers of the vascular wall.

Dietrich, H. H., Y. Kajita, and R. G. Dacey, Jr.. Local and conducted vasomotor responses in isolated rat cerebral arterioles. Am. J. Physiol. Heart Circ. Physiol. 271:H1109-16., 1996.

Kajita, Y., M. Takayasu, Y. Mori, H.H. Dietrich, and R. G. Dacey, Jr. Role of nitric oxide in autoregulatory response in rat intracerebral arterioles. Neurosurgery 42: 834-842, 1998.

Kajita, Y., H. H. Dietrich, and R. G. Dacey, Jr. Basic fibroblast growth factor induces dilation of isolated intracerebralarterioles in rats: Role of membrane hyperpolarization. J. Cereb. Blood Flow Metab. submitted 1999.

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Gregory DeAngelis, Ph.D.*
Assistant Professor
Anatomy & Neurobiology

My laboratory studies cortical circuits that mediate visual perception and visually guided behavior. Single- and multi-neuron recordings are obtained from alert monkeys while they perform visual discrimination tasks. Microstimulation and reversible inactivation are used to establish causal links between physiology and perception. Current research interests include depth perception, 3D object representation, and visual feature integration.

DeAngelis GC, Cumming BG, Newsome WT (1998) Cortical area MT and the perception of stereoscopic depth. Nature 394: 677-80.

DeAngelis GC, Ohzawa I, Freeman RD (1995) Receptive-field dynamics in the central visual pathways. Trends in Neurosciences 18: 451-8.

DeAngelis GC, Ohzawa I, Freeman RD (1991) Depth is encoded in the visual cortex by a specialized receptive field structure. Nature 352: 156-9.

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Colin P. Derdeyn, M.D.
Assistant Professor
Mallinckrodt Institute of Radiology

My research is on the hemodynamic and metabolic effects of different cerebrovascular diseases on the brain, and the effects of medical or endovascular treatment of these disorders on cerebral blood flow, autoregulatory vasodilation, and oxygen extraction. These measurements primarily utilize PET. One of my studies is on the effect of upregulation in the expression of endothelial nitric oxide synthase on cerebral hemodynamics in people with atherosclerosis. Another study is underway to develop techniques using MRI to provide similar regional and quantitative measurements of blood flow, blood volume and oxygen extraction that are currently only obtainable with PET. My research closely parallels my clinical interests, the diagnosis and treatment of cerebrovascular disease. My specialty is the endovascular (within the blood vessels) treatment of cerebral aneurysms, arteriovenous malformations, embolic stroke, and atherosclerotic stenoses of the vessels of the head and neck.

Selected References:

Derdeyn CP, Videen TO, Fritsch SM, Yundt KD, Carpenter DA, Grubb RL, Powers WJ. Compensatory mechanisms to chronic hypoperfusion in patients with carotid occlusion. Stroke 1999:30:1019-1024.

Derdeyn CP, Videen TO, Simmons NR, Yundt KD, Fritsch SM, Grubb RL, Powers WJ. Count-based PET method for predicting stroke in patients with symptomatic carotid occlusion. Radiology 1999;212:449-506.

Derdeyn CP, Grubb RL, Powers WJ. Cerebral hemodynamic impairment: methods of measurement and association with stroke risk. Neurology 1999;53:251-259.

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Aaron DiAntonio, M.D., Ph.D.*
Assistant Professor
Molecular Biology & Pharmacology

The primary interest in our laboratory is the regulation of synaptic strength during development. In particular, we focus on the role of postsynaptic activity in the regulation of presynaptic structure and function. We use the Drosophila neuromuscular junction as a model system because of the ease with which genetic, molecular, anatomical, and electrophysiological techniques can be combined. A second focus of the laboratory is the molecular mechanisms underlying synapse formation and growth. During larval development the average neuromuscular junction has a ten fold increase in the number of synaptic boutons and a hundred fold increase in the number of active zones. We have generated genetic tools that disrupt normal growth control, leading to hyperinnervation and impaired synaptic function. This provides the basis for interacting genetic screens that may identify molecules that regulate synaptic growth during development.

DiAntonio, A., Petersen, S.A., Heckmann, M. and Goodman, C.S. (1999) Glutamate Receptor Expression Regulates Quantal Size and Quantal Content at the Drosophila Neuromuscular Junction. J. Neuroscience 19: 3023-3032.

Davis, G.W., DiAntonio, A, Petersen, S.A., and Goodman, C.S. (1998) Postsynaptic PKA Controls Quantal Size and Reveals a Retrograde Signal that Regulates Presynaptic Transmitter Release in Drosophila. Neuron 20: 305-315.

Petersen, S.A., Fetter, R.D., Noordermeer, J.N., Goodman, C.S., and DiAntonio, A. (1997) Genetic Analysis of Glutamate Receptors in Drosophila Reveals a Retrograde Signal Regulating Presynaptic Transmitter Release. Neuron 19: 1237-1248.

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J. David Dickman, Ph.D.*
Associate Professor
Central Institute for the Deaf

Our research addresses issues related to the sensory processing of movement information, as well as the influence of gravity upon developing neural systems. Our work encompasses a multidisciplinary approach, where anatomical, cellular, electrophysiological, and behavioral techniques are used to characterize the neural mechanisms that comprise vestibular system function.

Dickman, J.D. Spatial orientation of the semicircular canals and their innervating afferents in pigeons. Exp. Brain Res., 1996, 111, 8-20.

Dickman, J.D. and Fang, Q. Differential central projections of vestibular afferents in pigeons. J. Comp. Neurol., 1996, 367, 110-131.

Si, X., Angelaki, D.E., and Dickman, J.D. Response properties of pigeon otolith afferents to linear acceleration. Exp. Brain Res., 1997, 117, 242-250.

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Alex Dromerick, M.D.
Assistant Professor
Neurology
Occupational Therapy

Our group focuses on recovery of function after acquired brain injury in humans. We use a busy clinical service as a laboratory to support and execute clinical trials of rehabilitation techniques, natural history studies, and brain structure-function studies.

Dromerick A.W. and MJ Reding: Functional outcome for patients with hemiparesis, hemihypesthesia, and hemianopsia. Does lesion location matter? Stroke 1995; 26:2023-2026

Hanlon R.E., Mattson D., Demery J.A., and A.W. Dromerick: Axial movements of aphasic patients with ideomotor apraxia. Cortex, 34: 731-741, 1999.

Hanlon R.E., Lux W.E., and A.W. Dromerick Global aphasia without hemiparesis: language profiles and lesion distribution. Journal of Neurology, Neurosurgery, and Psychiatry, 66:365- 369, 1999.

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Laura L. Dugan, M.D.*
Assistant Professor
Neurology & Neurological Surgery (Neurology)

My laboratory studies free radicals, generated by mitochondria and other sources, as signaling molecules and mediators of excitoxic and apoptotic cell death in the CNS, using fluorescence confocal microscopy, EPR, and biochemical/molecular biology techniques. We are also exploring the chemistry, free radical biology, and neuroprotective properties of the novel anti-oxidants, C60 (buckminsterfullerene) derivatives.

Dugan, L.L., Sensi, S.L., Canzoniero, L.M.T, Handran, S.D., Rothman, S.M., Lin, T.T., Goldberg, M.P., and Choi, D.W. (1995) Mitochondrial production of reactive oxygen species in cortical neurons following exposure to N-methyl-D-aspartate. J. Neurosci. 15:6377-6388.

Dugan LL, Turetsky DM, Du C, Lobner D, Wheeler M, Almli R, Shen CKF, Luh TY, Choi DW and Lin TS. (1997) Carboxyfullerenes as Neuroprotective Agents. Proc. Natl. Acad. Sci. U.S.A. 94:9434- 9439.

Dugan, LL, Creedon, DJ, Johnson, EM, and Holtzman, DM. (1997) Rapid suppression of free radical formation by NGF involves the MAPK pathway. Proc. Natl. Acad. Sci. U.S.A. 94:4086-4091.

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Alex S. Evers, M.D.*
Professor and Head (Anesthesiology)
Anesthesiology; Internal Medicine
Molecular Biology & Pharmacology

The focus of my laboratory is to identify and characterize the protein binding sites with which anesthetic molecules interact in the central nervous system. Our approach is to develop anesthetic molecules that can function as photoaffinity labeling reagents, and to use them to label anesthetic binding proteins. We are currently focusing on the identification and characterization of anesthetic steroid binding sites.

Wittmer LL, Hu Y, Kalkbrenner M, Evers AS, Zorumski CF and Covey DF, Enantioselectivity of steroid-induced GABAA receptor modulation and anesthesia. Mol. Pharmacol. 50:1581-1586, (1996).

Evers AS, Dubois BW and Burris KE. Saturable binding of volatile anesthetics to proteins studied by 19F-NMR spectroscopy and photoaffinity labeling. Progress in Anesthetic Mechanisms 3:151-157, (1995).

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Stanley Finger, Ph.D. Professor
Psychology

I am interested in the history of neuroscience, especially the relationship between brain and behavior as perceived by scientists in earlier time periods. I am also interested in the history of treatments and recovery from brain damage. At the present time, my major project is a book dealing with neuroscientists from different cultures and time periods. I hope to show how these men (e.g., Galen, Vesalius, Broca) took us one step closer to understanding the brain as the organ of mind. I am also working on a number of historical papers, such as the discovery of Tourette syndrome.

Finger, S. 1994. The Origins of Neuroscience: A History of Explorations into Brain Function. NY:: Oxford University Press.

Finger, S. 1998. "A happy state of mind": An Early history of mild elation, denial of disability, optimism, and laughing in multiple sclerosis. Archives of Neurology, 55, 241-250

Finger, S., and Law, M. B. 1998. Karl August Weinhold and his "science" in the era of Mary Shelley's Frankenstein: Experiments on electricity and the restoration of life. Journal of the History of Medicine and Allied Sciences, 53, 161-180.

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N. Gautam, Ph.D.*
Associate Professor - Anesthesiology; Genetics

A particular hormone or neurotransmitter always evokes a specific physiological response and yet many receptors, effectors and G protein subunit types are present in a single cell. The long-term aim of research in our laboratory is to identify the molecular mechanisms underlying specificity in G protein mediated signaling.

Gautam, N., Downes, G., Yan, K. and Kisselev, O. (1998) The G protein __ complex. Cell. Signalling 10: 447-455.

Kisselev, O., Fann, Y.C., Kao, J., Ponder, J. W., Gautam, N. and Marshall G.R. (1998) Light-activated rhodopsin induces structural binding motif in G-protein alpha subunit. Proc. Natl. Acad. Sci.USA 95:4270-4275.

Downes, G.B., Copeland, N.G., Jenkins, N.A., Gautam, N. (1998) Structure and mapping of the G protein _3 subunit gene and a divergently transcribed novel gene, Gng3lg. Genomics, 57:173-176.

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Jeffrey M. Gidday, Ph.D.*
Assistant Professor
Neurology & Neurological Surgery (Neurosurgery)
Cell Biology & Physiology; Ophthalmology & Visual Sciences

Research in our laboratory focuses on understanding the mechanisms underlying vascular regulation and dysfunction in the brain and retina under the conditions of ischemia, trauma, and diabetes. This includes elucidating the roles of oxygen- and nitrogen-based free radicals, cytokines, and other inflammatory mediators on leukocyte-endothelial interactions, vascular permeability, and vascular injury in response to these stimuli, as well as evaluating vascular reactivity and vascular control mechanisms in these CNS tissues.

Gidday, J.M., T.S. Park, E.R. Gonzales, J.W. Beetsch. CD18−dependent leukocyte adherence and vascular injury in the pig cerebral circulation following ischemia. *Am. J. Physiol*. 272: H2622-2629, 1997.

Gidday, J.M., Y. Zhu. Endothelium-dependent changes in retinal blood flow following ischemia. *Curr. Eye Res*. 17: 798-807, 1998

Gidday, J.M., T.S. Park, A.R. Shah, E.R. Gonzales. Modulation of basal and postischemic leukocyte-endothelial adherence by nitric oxide. *Stroke* 29: 1423-1430, 1998.

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Jonathan Gitlin, M.D. *
Professor
Pediatrics; Pathology

Our laboratory is interested in the molecular basis of inherited neurologic disease. Current studies are focused on the role of copper in the pathogenesis of neurodegeneration in disorders such as amyotrophic lateral sclerosis. This work utilizes a variety of transgenic murine models as well as neuronal cell cultures.

Culotta VC, Klomp LWJ, Strain J, Casareno RLB, Krems B and Gitlin JD. The copper chaperone for superoxide dismutase. J Biol Chem 1997; 272:23469-23472.

Hung IH, Casareno RLB, Labesse G, Mathews FS and Gitlin JD. HAH1 is a copper binding protein with distinct amino acid residues mediating copper homeostasis and antioxidant defense. J Biol Chem 1998; 273:1749-1754.

Payne AS, and Gitlin JD. Functional expression of the Menkes disease protein reveals common biochemical mechanisms among the copper-transporting P-type ATPases. J Biol Chem 1998; 273: 3765- 3770.

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Alison Goate, BSc Hons D. Phil.* (Oxon)
Professor
Psychiatry; Genetics

We are using a genetic approach to understand the pathogenesis of Alzheimer's disease (AD) and related dementias. Initial studies focussed upon families showing Mendelian inheritance of dementia. This has resulted in the identification of mutations in four genes. In vitro studies are underway to determine the pathogenic effects of mutations in these genes. A genome-wide screen is being performed to identify genetic risk factors for late onset AD.

Bullido, MJ, Artiga, MJ, Recuero,et al., A polymorphism (-491A/T) in the transcriptional regulatory region of apolipoprotein E gene associated with risk for dementia of the Alzheimer type Nature Genetics (1998) 18: 69-71.

Hutton M., Lendon, C.L., Rizzu, et al. Association of missense and 5'-splice-site mutations in tau with inherited dementia FTDP-17 Nature (1998) 393: 702-705.

Wu, W., Holmans, P., Wavrant-DeVrieze, et al. Failure to confirm a locus at chromosome 12p11-12 in late onset Alzheimer's disease. JAMA (1998) 280: 619-622.

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Mark Goldberg, M.D.*
Associate Professor
Neurology & Neurological Surgery (Neurology) Anatomy & Neurobiology

Our research focuses on cellular mechanisms of brain cell damage following stroke and trauma, using culture systems from mouse cortex. The laboratory emphasizes microscopy techniques, including digital fluorescence imaging of intracellular ion concentrations and confocal microscopy. Please see our web page (see below) for additional information about the lab

McDonald JW, Althomsons SP, Hyrc KL, Choi DW, Goldberg MP. Oligodendrocytes from forebrain are highly vulnerable to AMPA/kainate receptor-mediated excitotoxicity. Nat Med 1998 4:291-297.

Faddis BT, Hasbani MJ, Goldberg MP. Calpain activation contributes to dendritic remodeling after brief excitotoxic injury in vitro. J Neurosci 1997 17:951-959.

Hyrc K, Handran SD, Rothman SM, Goldberg MP. Ionized intracellular calcium concentration predicts excitotoxic neuronal death: observations with low-affinity fluorescent calcium indicators. J Neurosci 1997 17:6669-6677.

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David I. Gottlieb, Ph.D.*
Professor
Anatomy & Neurobiology

The focus of my laboratory is the genetic control of the pathway from progenitor cell to CNS neuron. To facilitate analysis, we have developed a new model system utilizing genetically normal mouse embryonic stem (ES) cells. Large numbers of ES cells in tissue culture are synchronously differentiated into neurons expressing the most diagnostic phenotypes including synapse formation. The new culture system allows us to utilize genetics, cell culture and biochemistry to study neuronal differentiation. Our aim is to identify genes that orchestrate differentiation and find out how they work.

Bain, G., Kitchens, D., Yao, M., Huettner, J., and Gottlieb, D.I. (1995) Embryonic stem cells express neuronal properties in vitro. Devel. Biol. 168:342-357.

Bain, G. Ray,W., Yao, M, and Gottlieb, DI (1996) Retinoic acid promotes neural and represses mesodermal gene expression in mouse embryonic stem cells in culture. BBRC 223: 691

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Robert Grubb, Jr., M.D.
Professor
Neurology & Neurological Surgery (Neurosurgery): Radiology

Positron emission tomography (PET) measurements of cerebral blood flow, blood volume, oxygen metabolism, and oxygen extraction fraction are used to investigate the role of cerebral hemodynamic factors in the pathogenesis of stroke in patients with symptomatic carotid artery occlusion and the role of cerebral ischemia in patients with severe closed head injuries.

Yundt, KD, Grubb, RL Jr., Diringer, MN, Powers, WJ: Autoregulatory vasodilation of parenchymal vessels is impaired during cerebral vasospasm. J.Cereb Blood Flow Metab. 18:419-424, 1998.

Derdeyn, CP, Yundt, KD, Videen, TO, Grubb, RL Jr., Carpenter, DA, Powers, WJ: Increased oxygen extraction is associated with prior ischemic events in patients with carotid occlusion. Stroke 29:754-758, 1998.

Derdeyn, CP, Powers, WJ, Grubb, RL Jr.: Hemodynamic effects of middle cerebral artery stenosis and occlusion. Am.J.Neuroradiol. 19:1463-1469, 1998.

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David Gutmann, M.D., Ph.D.*
Associate Professor
Neurology & Neurological Surgery (Neurology); Genetics; Pediatrics

Our laboratory is interested in the function of central nervous system (CNS) tumor suppressor genes and their protein products. Tumor suppressor genes comprise a family of genes whose protein products are important for the normal regulation of the balance between cell growth and differentiation. Dysfunction of these proteins predisposes to uncontrolled cell proliferation and to tumor formation.

Gutmann DH, Geist RT, Xu HM, Kim JS, Saporito-Irwin S. Defects in neurofibromatosis 2 protein function can arise at multiple levels. Hum Mol Genetics 1998 7:335-345.

Xu MH, Gutmann DH. Merlin differentially Associates with the microtubule and actin cytoskeleton. J Neurosci Res 1998 51:403-415.

Gutmann DH, Saporito-Irwin S, DeClue JE, Weinecke R, Guha A. Alterations in the rap1 signaling pathway are common in human gliomas. Oncogene 1997 15:1611-1616.

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David A. Harris, M.D., Ph.D.*
Associate Professor
Cell Biology & Physiology

We are interested in the cellular and molecular biology of prion diseases. These fatal neurodegenerative disorders are caused by a conformationally altered host protein (PrP) that is infectious in the absence of nucleic acid. We have developed experimental systems for studying prion formation in the test tube, in cultured cells, and in transgenic mice. A second major interest of the laboratory is Alzheimer's disease, in particular the presenilin and amyloid precursor proteins.

Daude, N., Lehmann, S., and Harris, D.A. Identification of intermediate steps in the conversion of a mutant prion protein to a scrapie-like form in cultured cells. J. Biol. Chem. 272: 11604-11612, (1997).

Lehmann, S., Chiesa, R., and Harris, D.A. Evidence for a six- transmembrane domain structure of presenilin 1. J. Biol. Chem. 272:12047-12051, (1997).

Lehmann, S., and Harris, D.A. Mutant and infectious prion proteins display common biochemical properties in cultured cells. J. Biol. Chem. 271:1633-1637, (1996).

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M. Rosario Hernandez, DDS
Associate Professor
Ophthalmology; Anatomy & Neurobiology

Investigations are on the cellular and molecular mechanisms involved in retinal ganglion cell loss and optic nerve head remodeling in human glaucoma. We focus on the role of astrocytes in the pathogenesis of glaucoma and on defining astrocyte responses to elevated intraocular pressure and to hypoxia. Our studies are conducted in human optic nerve heads with glaucoma using morphological and molecular techniques adapted for our samples.

Hernandez, MR, Pena JDO. The optic nerve head in glaucomatous optic neuropathy. Arch Ophthalmol 1997; 115:389-395.

Varela HJ, Hernandez MR. Astrocyte responses in human optic nerve head with primary open angle glaucoma. J Glaucoma, 1997;6:303-313.

Kobayashi S, Vidal I, Pena JDO, Hernandez MR. Expression of neural cell adhesion molecule (NCAM) characterizes a subpopulation of type 1 astrocytes in human optic nerve head. Glia 1997; 20:262-273

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John Heuser, M.D.*
Professor
Cell Biology & Physiology

Electron microscopic visualization of everything from whole cells to individual molecules is the work of this laboratory. Special emphasis is given to developing new methods of sample preparation that will achieve a more natural, life-like appearance of samples in the microscope. To accomplish this, we have developed what is now called the "quick-freeze, deep-etch" technique for electron microscopy and have disseminated the equipment and procedures needed to carry out this technique throughout the field.

Rothberg, K.G., Heuser, J.E., Donzell, W.C., Ying, Y-S., Glenney, J.R., and Anderson, R.G.W. (1992) Caveolin, a protein subunit of caveolar membrane coats. Cell 68:673-682.

Castellino, F., Heuser, J., Marchetti, S., Bruno, B. ,and Luini, A. (1992) Glucocorticoid stabilization of actin filaments: A possible mechanism for inhibition of ACTH release. Proc. Natl. Acad. Sci. USA 89:3775-3779.

Westervelt, P., Henkel, T., Trowbridge, D., Orenstein, J., Heuser, J., Gendelman, H., and Ratner, L. (1992) Dual regulation of silent vs. productive HIV-1 infection in primary monocytes by distinct genetic determinants. J. Virol. 66:3925-3931.

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Stephen M. Highstein, M.D., Ph.D.*
Professor - Otolaryngology; Anatomy & Neurobiology

We study the role of the brainstem and cerebellum in the accomplishment of motor learning and memory in alert primates. We employ single cell neuronal recording and marking techniques. We rely heavily upon computers for the analysis of data and for the generation of mathematical models of this form of learning.

Partsalis, A. M., Zhang, Y., and Highstein, S. M. (1995) Dorsal Y-group in the squirrel monkey. I. Neuronal responses during rapid and long-term modifications of the vertical VOR. J. Neurophysiol. 73:615-631.

Highstein, S. M., Partsalis, A. M., and Arikan, R. (1997) Role of the Y-group of the vestibular nuclei and flocculus of the cerebellum in motor learning of the vertical vestibulo-ocular reflex. Progress in Brain Research, 114:383-397.

Highstein, S. M., Rabbitt, R., D., and Boyle, R. (1996) Determinants of semicircular canal afferent response dynamics in the toadfish, Opsanus tau. J. Neurophysiol. 75:575-596.

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David Holtzman, Ph.D.*
Assistant Professor
Neurology & Neurological Surgery (Neurology); Molecular Biology & Pharmacology;

The E4 allele of apoE is a strong risk factor for Alzheimer's disease (AD).We are utilizing transgenic, neurobiological, and cell biological approaches to study interactions of apoE with receptors and other proteins which contribute to its actions in the normal, injured, and AD brain. Another interest is in understanding mechanisms of cell death following neonatal hypoxic-ischemic injury and the role of growth factors and reactive oxygen species in this process.

Cheng Y, Deshmukh M, D'Costa A, Gidday J, DeMaro J, Shah A, Jacquin M, Johnson EM Jr., Holtzman DM. Prominent apoptosis in neonatal hypoxia-ischemia: Caspase inhibitor treatment affords neuroprotection with delayed administration. J. Clin. Invest. 1998;101:1992-1998.

Sun Y, Wu S, Bu G, Onifade M, Patel S, LaDu MJ, Fagan AM, Holtzman DM. GFAP-apoE transgenic mice: Astrocyte specific expression and differing biological effects of astrocyte-secreted apoE3 and apoE4 lipoproteins. J. Neuroscience 1998; 18:3261-3272.

Bu G, Sun Y, Schwartz AL, Holtzman DM. NGF induces both rapid and long term changes in cell surface and total cellular expression of LRP, an endocytic receptor for both apoE/lipoproteins and amyloid precursorprotein. J. Biol. Chem. 1998; 273:13359-13365.

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Chung Y. Hsu, M.D., Ph.D.
Professor - Neurology & Neurological Surgery (Neurology)

We conduct basic and clinical research on vascular mechanism of ischemic and traumatic injuries. Current ongoing research projects include: 1) alteration of gene regulation and DNA damage-repair after cerebral ischemia-reperfusion; and 2) molecular mechanisms of inflammatory apoptosis in cerebral endothelial cells after ischemic insult.

Yeh H-J, He YY, Xu J, Hsu CY, Deuel TF: Upregulation of pleiotrophin (ptn) gene expression in microvasculature, macrophage, and astrocyte on acute ischemic brain injury in the rat. J Neurosci 18:3699-3707, 1998.

Jan Xu J, Yeh CH, Chen SW, He L, Sensi SL, Canzoniero LMT, Choi DW, Hsu CY: Involvement of de novo ceramide biosynthesis in TNF-a/cycloheximide-induced cerebral endothelial cell death. J Biol Chem 273:16521-16526, 1998.

Hsu CY (ed.): Cerebral Ischemia: From basic mechanisms to clinical trials, Karger, AG, Basel, 1998.

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Jim Huettner, Ph.D.*
Associate Professor
Cell Biology & Physiology

My laboratory studies the ion channels gated by glutamate receptors. Our goal is to understand how neurons communicate at excitatory synapses and how glutamate receptors contribute to normal brain function and pathology. We also study the in vitro differentiation of embryonic stem (ES) cells into neurons. Using this system, we hope to learn how neurons acquire their unique cellular properties.

Finley, M.F.A., Kulkarni, N., and Huettner, J.E. Synapse formation and establishment of neuronal polarity by P19 embryonic carcinoma cells and embryonic stem cells. J. Neurosci. 16:1056-65, (1996).

Wilding, T.J. and Huettner, J.E. Antagonist pharmacology of kainate- and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-preferring receptors. Mol. Pharmacol. 49:540-46, (1996).

Wilding, T.J. and Huettner, J.E. Activation and desensitization of hippocampal kainate receptors. J. Neurosci. 17:2713-2721, (1997).

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Mark Jacquin, Ph.D.
Professor
Neurology & Neurological Surgery (Neurology)

The long-term aim of our research is fourfold: 1) to determine the cellular circuitry responsible for the functional organization of sensory systems; 2) to uncover cellular and molecular principles controlling development of the mammalian peripheral and central nervous systems; 3) to assess the structural and functional consequences of peripheral and central nervous system injury; 4) to isolate effective strategies for repair of injured neural tissue. The rodent somatosensory system is being used as a model because of its stereotyped normal organization which lends itself to quantification, its known susceptibility to injury, and its clinical applications.

Golden, J.P., J.A. DeMaro, P.L. Robinson & M.F. Jacquin. Development of terminals and synapses in laminae I and II of the rat medullary dorsal horn after infraorbital nerve transection at birth. J. Comp. Neurol. 383:339-348, 1997

Glazewski, S., M. McKenna, K. Fox & M.F. Jacquin. Experience-dependent depression of vibrissae responses in adolescent rat barrel cortex. Europ. J. Neurosci. 10:2107-2116, 1998.

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Eugene M. Johnson, Jr., Ph.D.*
Professor
Neurology; Molecular Biology & Pharmacology

Our primary interests are in the biology of neurotrophic factors and the molecular mechanisms of neuronal programmed cell death. We also are studying the physiology and pharmacology of novel neurotrophic factors, which we isolated and cloned in collaboration with the lab of Dr. J. Milbrandt in the Dept. of Pathology. A variety of cellular, morphological, biochemical and genetic methods are utilized. Our long range goal is to contribute to the amelioration of neuronal degenerative processes.

P. T. Kotzbauer, P. A. Lampe, R. O. Heuckeroth, J. P. Golden, D. J. Creedon, E. M. Johnson, Jr, and J. Milbrandt, Neurturin, a relative of glial-cell-derived neurotrophic factor, Nature, 384, 467-470 (1996)

R. M. Easton, T. L. Deckwerth, A. Sh. Parsadanian, and E. M. Johnson, Jr., Analysis of the mechanism of loss of trophic factor dependence Associated with neuronal maturation: A phenotype indistinguishable from BAX deletion, J. Neurosci., 17, 9656-9666 (1997)

J. Milbrandt, F. deSauvage, T. L. Fahrner, R., et al,. and E. M. Johnson, Jr., Persephin, a novel neurotrophic factor related to GDNF and neurturin, Neuron, 20, 245-253 (1998)

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Henry J. Kaplan, M.D.*
Professor - Ophthalmology & Visual Sciences

The major cause of blindness over age 55 is age-related macular degeneration. A new surgical operation has been developed to operate beneath the macula (i.e. retina) in man and remove abnormal scar tissue and damaged retinal pigment epithelium. The next step in restoration of lost vision in these patients is transplantation of retinal pigment epithelium and/or photoreceptors. An experimental model of retinal transplantation has been developed in the micropig. We are studying the functional fate of retinal transplants within the normal pig including the antigenicity of the transplant, the immune responsiveness of the host and the histologic integrity of the transplant.

Del Priore LV, Kaplan HJ, Hornbeck R, et al.: Retinal pigment epithelial debraidement as a model for the pathogenesis and treatment of macular degeneration. Am J Ophthalmol 1996;122:629-643.

Tezel TH, Del Priore LV, Kaplan HJ: Harvest and storage of adult human retinal pigment epithelial sheets. Curr Eye Res 1997;16:802-809.

Tezel TH, Del Priore LV, Kaplan HJ: Reattachment to a substrate prevents apoptosis of human reinal pigment epithelium. Graefe's Arch Clin Exp Ophthalmol 1997;235:41-47.

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Raphael Kopan, M.D.*
Associate Professor - Medicine; Molecular Biology & Pharmacology

Our lab focuses on a tissue culture approach to elucidate the biochemical steps and molecules involved in signal transduction by Notch. Proteins of the Notch family are large, ligand-activated transmembrane receptors (1). Ligand binding induces proteolytic release of the Notch intracellular domain (NICD) (2), which translocates to the nucleus where it binds to and activates members of the CSL family of DNA binding proteins (3). We are now using genetic and biochemical means to characterize the pathway further and to test for the existence of processing- independent Notch signaling.

R. Kopan, Eric H. Schroeter Harold Weintraub and Jeffrey S. Nye. Signaltransduction by activated mNotch: Importance of proteolytic processing andits regulation by the extracellular domain.(1996) PNAS. 93, 1683-1688.

Jarriault, S., Brou, C., Logeat, F., Schroeter, E. H., Kopan, R. andIsraël, A: An activated form of murine Notch stimulates transcription ofthe HES-1 gene through the DNA-binding protein KBF2/RBP-Jk. (1995). Nature. 377, 355-358.

J. Nye, R. Kopan and R. Axel: An activated Notch suppresses neurogenesis and myogenesis but not Gliogenesis in mammalian cells. (1994). Development. 120: 2421-2430.

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David A. Leib, Ph.D.*
Associate Professor
Ophthalmology & Visual Sciences; Molecular Microbiology

The marked neurotropism of herpes simplex virus (HSV) and adeno-associated virus (AAV) in vivo make them plausible vectors for the delivery of foreign genes into mammalian neurons. Work ongoing in our laboratory is using HSV and AAV-derived vectors to deliver and drive the expression of therapeutic genes in a variety of neuronal tissues. Such vectors may be ultimately used for gene therapy.

Olivo, P.D. and Leib, D.A.(1993) Gene delivery to neurons: Is herpes simplex virus the right tool for the job? 15:547-554.

Pepose, J.S. and Leib, D.A. (1994). Herpes simplex viral vectors for therapeutic gene delivery to ocular tissues. Investigative Ophthalmology and Visual Science 34, 2662-2665.

Walker, J. Laycock, K.A., Pepose, J.S., and Leib, D.A. (1998). Postexposure vaccination with a virion host shutoff defective mutant reduces UV-B radiation-induced ocular herpes simplex virus shedding in mice. Vaccine, 16: 6-8.

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Jeff W. Lichtman, M.D., Ph.D.*
Professor
Anatomy & Neurobiology

My laboratory studies the ways in which experience modifies neuronal connections especially those kinds of changes that persist for long periods and thus may provide insight into the mechanisms of memory and learning. We have focussed particularly on the competitive interactions between neurons that occur in normal development that cause some synaptic connections to be permamnently lost while competing synapses are stably maintained.

Gan, W-B., and Lichtman JW, Synaptic segregation at the developing neuromuscular junction. Science 1998 Nov 20; 282: 1508-1511.

Nguyen QT, Parsadanian AS, Snider WD, Lichtman JW, Hyperinnervation of neuromuscular junctions caused by GDNF overexpression in muscle. Science 1998 Mar 13;279(5357):1725-9

Colman H, Nabekura J, Lichtman JW, Alterations in synaptic strength preceding axon withdrawal.Science 1997 Jan 17;275(5298):356-61

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Maurine Linder, Ph.D.*
Assistant Professor
Cell Biology & Physiology

Our research explores the biology and enzymology of protein palmitoylation in signal transduction. Association of signaling proteins with membranes and their functional activities require the covalent attachment of lipids, including reversible acylation with palmitate. Our goal is to understand how regulated palmitoylation affects subcellular location and protein-protein interactions of signaling proteins. We also study the role of palmitoylation in the function, regulation, and trafficking of proteins that participate in synaptic vesicle exocytosis.

Dunphy JT, Greentree WK, Manahan CL, and Linder, ME; G-protein palmitoyltransferase activity is enriched in plasma membranes. J. Biol. Chem. (1996) 271:7154-7159.

Gonzalo S and Linder ME; SNAP-25 palmitoylation and plasma membrane targeting require a functional secretory pathway. Mol. Biol. Cell (1998) 9:585-597.

Srinivasa SP, Bernstein LS, Blumer KJ, and Linder ME; Plasma membrane localization is required for RGS4 function in S. cerevisiae. Proc. Natl. Acad. Sci. (1998) 95:5584-5589.

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Chris Lingle, Ph.D.*
Professor - Anesthesiology; Anatomy & Neurobiology

Calcium-dependent potassium channels, which are abundantly expressed in almost all excitable cells, couple changes in intracellular calcium concentrations to changes in cellular electrical excitability. Using methods of electrophysiology and molecular biology, we are interested in the physiological roles of these channels, how channel structure determines channel function, and how Ca^{2+}-dependent channels may be selectively activated by positioning at sites of Ca^{2+} influx.

Prakriya, M., Solaro, C.R. and Lingle, C.J. (1996). $[Ca^{2+}]i$ elevations detected by BK channels during Ca^{2+} influx and muscarine-induced release of Ca^{2+} from intracellular stores in rat chromaffin cells. Journal of Neuroscience 16:4344-4359.

Solaro, C.R., Ding, J.P., Li, Z.W., and Lingle, C.J. (1997) The cytosolic inactivation domains of BKi channels do not behave like simple, open-channel blockers. Biophysical Journal 73:819-830.

Ding, J.P., Li, Z.W., and Lingle, C.J. 1998. (1998) Inactivating BK channels in rat chromaffin cells may arise from hetero-multimeric assembly of distinct inactivation- competent and noninactivating subunits. Biophysical Journal 74:268-289.

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Arthur D. Loewy, Ph.D.*
Professor - Anatomy & Neurobiology

Basic life processes are controlled by the autonomic nervous system--a diffuse collection of peripheral nerves that innervate all the tissues of the body. This neural network is regulated by specific brain regions. Our research is concerned with localizing these higher control centers and studying their chemical architecture. One major tool is the viral transneuronal tracing method, which has been used to study the neuroanatomical and chemoarchitecture of visceral motor systems. In addition, the central command neurons that regulate the fight-or-flight response have been discovered and current research is directed at studying the higher brain sites that modulate these command neurons.

Jansen, A.S.P., Nguyen, X.V., Karpitskiy, V., Mettenleiter, T.C., and Loewy, A.D. (1995) Central command neurons of the sympathetic nervous system: basis of the fight-or-flght response,
Science 270: 644-646.

Farkas, E., Jansen, A.S.P., and Loewy, A.D. (1998) Periaqueductal gray matter input to cardiac-related sympathetic premotor neurons, Brain Research 792: 179-192.

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Peter D. Lukasiewicz, Ph.D.*
Associate Professor
Ophthalmology & Visual Sciences; Anatomy & Neurobiology

The vertebrate retina is ideally suited for studying synaptic interactions. It is an accessible part of the central nervous system and it can be stimulated physiologically with light. The roles of neurotransmitters in synaptic transmission are studied by making whole-cell patch recordings from morphologically identified neurons in the retinal slice preparation. These studies will help define the neuronal circuitry used to process different forms of visual information in the retina.

Lukasiewicz, P.D. and Shields, C.R. (1998) Different combinations of GABAA and GABAC receptors confer distinct temporal properties to retinal synaptic responses. Journal of Neurophysiology, 79:3157-3167.

Cook, P.B., Lukasiewicz, P.D. and McReynolds, J.S. (1998) Transient lateral inhibition in retinal ganglion cells is mediated by glycine and requires action potentials. Journal of Neuroscience 18:2301-2308.

Lukasiewicz, P.D. and Shields, C.R. (1998) A diversity of GABA receptors in the retina. Seminars in Cell & Developmental Biology, 9: 293-299.

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Kathleen McDermott, Ph.D.
Assistant Professor
Radiology; Psychology

I use both neuroimaging and behavioral methods to explore human memory. Using fMRI, I have been examining the neural correlates of human memory encoding and retrieval and how they interact. I'm also interested in identifying factors that cause false memories and in how false memories can enhance our understanding of memory processing in general.

McDermott, K.B., Ojemann, J.G., Petersen, S.E., Ollinger, J.M., Snyder, A.Z., Akbudak, E., Conturo, T.E., & Raichle, M.E. (1999). Direct comparison of episodic encoding and retrieval of words: An event-related fMRI study. Memory (special issue on neuroimaging).

McDermott, K.B. (1996). The persistence of false memories in list recall. Journal of Memory and Language, 35, 212-230.

McDermott, K.B. (1997). Priming on perceptual implicit memory tests can be achieved through presentation of Associates. Psychonomic Bulletin & Review, 4, 582-586.

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John McDonald, M.D., Ph.D.
Assistant Professor
Neurology & Neurological Surgery (Neurology)

Work in our laboratory is directed toward elucidating the molecular mechanisms underlying spinal cord injury and developing effective treatments. The focus of our research is in three areas: 1) mechanisms of white matter injury, specifically excitotoxic oligodendrocyte death, 2) mechanisms of remyelination, and 3) transplantation of embryonic stem cells.

Liu XZ, Xu XM, Hu R, Du C, McDonald JW, et al. Neuronal and glial apoptosis after traumatic spinal cord injury. J. Neurosci., 17:5395-5406, 1997.

McDonald JW, Althomsons SP, Hyrc KL, Choi DW and Goldberg MP. Oligodendrocytes are highly vulnerable to AMPA/kainate receptor-mediated excitotoxicity. Nature Med., 4:291-297, 1998.

McDonald JW, Levine JM and Qu Y. Multiple classes of the oligodendrocyte lineage are highly vulnerable to excitotoxicity. NeuroReport, 9:2757-2762, 1998.

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Steve Mennerick, M.D., Ph.D.*
Assistant Professor
Psychiatry; Anatomy & Neurobiology

The broad aim of my research is to understand control of excitation and inhibition by neurotransmitters in the central nervous system. This is an important goal because neurotransmitter actions can be double-edged, underlying both normal transmission and neurotoxicity. In one project we are exploring the cellular mechanisms by which certain anticonvulsant drugs selectively depress synaptic glutamate release (an excitatory neurotransmitter) relative to GABA release (an inhibitory neurotransmitter) from hippocampal neurons. In another project, we are examining the role of astrocytes and glutamate transporters in altering neuronal excitability. In a third project, we are investigating the mechanisms by which chronic overinhibition causes death of immature neurons. This latter project may be important for understanding the effects of ethanol and other drugs on the immature nervous system. For all of these studies we use electrophysiological, molecular, and imaging techniques applied to simple *in vitro* systems of neurons in culture and to heterologous expression systems.

Mennerick S, Shen W, Xu W, Benz A, Tanaka K, Shimamoto K, Isenberg KE, Krause JE, Zorumski CF (1999) Substrate turnover by transporters curtails synaptic glutamate transients. J Neurosci. 19:9242-51.

Mennerick S, Jevtovic-Todorovic V, Todorovic SM, Shen W, Olney JW, Zorumski CF. (1998) Effect of nitrous oxide on excitatory and inhibitory synaptic transmission in hippocampal cultures. J Neurosci. 18:9716-26.

Mennerick S, Matthews G. (1996) Ultrafast exocytosis elicited by calcium current in synaptic terminals of retinal bipolar neurons. Neuron. 17:1241-9.

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Jeffrey Milbrandt, M.D., Ph.D.*
Professor
Pathology; Medicine

Our laboratory studies the biological function of neurturin, persephin and GDNF, closely related neurotrophic factors that promote survival of multiple neuronal populations including dopaminergic neurons, which degenerate in Parkinson's disease, and motor neurons, which are affected in Lou Gehrig's disease. These factors signal through a receptor complex comprised of the Ret tyrosine kinase and members of a family of GPI-linked co-receptors termed GFRa receptors.

Milbrandt J, Sauvage FJ, Fahrner TJ, et al. Persephin, a novel neurotrophic factor related to GDNF and neurturin. Neuron 1998 20:245-253.

Baloh RH, Tansey MG, Golden JP, et al. TrnR2, a novel receptor which mediates neurturin and GDNF signaling through Ret. Neuron 1997 18:793-802.

Araki T, Milbrandt J. Ninjurin, a novel adhesion molecule, is induced by nerve injury and promotes axonal growth. Neuron 1996 17:353-361.

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Jonathan Mink*, M.D., Ph.D.
Assistant Professor
Neurology & Neurological Surgery (Neurology); Anatomy & Neurobiology; Pediatrics

My research interest is the role of the basal ganglia in the control of movement. We hypothesize that a primary function of the basal ganglia is to select and inhibit competing movements or behaviors. To test the hypothesis, we record basal ganglia neurons in trained monkeys during movement, perform focal pharmacologic manipulations of the basal ganglia output, and do quantitative analysis of normal and abnormal movement.

Mink, J.W., and Thach, W.T. (1991) Basal ganglia motor control. III. Pallidal ablation: normal reaction time, muscle cocontraction, and slow movement. J. Neurophysiol. 65:330-351.

Mink, J.W., and Thach, W.T. (1993) Basal ganglia intrinsic circuits and their role in behavior. Curr. Opinion Neurobiol. 3:950-957.

Mink JW. (1996) The Basal Ganglia: Focused Selection and Inhibition of Competing Motor Programs. Prog. Neurobiol. 50:381-425.

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Stanley Misler, M.D., Ph.D.*
Professor
Medicine; Cell Biology & Physiology

Mechanisms of Ca induced exocytosis from excitable endocrine cells (insulin-secreting pancreatic islet cells and adrenal chromaffin cells) investigated by single cell assays of exocytosis (membrane capacitance measurements, electrochemical amperometry and membrane bound fluorescent dyes). Modulation of exocytosis by other second messengers and by the excitatory neurotoxin alpha-latrotoxin from the black widow spider

Liu, J and Misler S (1998) alpha-latrotoxin alters spontaneous and depolarization-evoked quantal release from rat adrenal chromaffin cells: evidence for multiple modes of action. J. Neuroscience 18:6113-6125.

Barnett DW and Misler S. (1997) An optimized approach to membrane capacitance estimation using dual frequency excitation. Biophysical J. 72:1641-1658.

Zhou Z, Misler S. (1996) Amperometric detection of quantal secretion from patch-clamped rat pancreatic beta-cells. J. Biol. Chem. 271:270-277.

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Stephen M. Moerlein, Ph.D.*
Associate Professor
Radiology; Biochemistry & Molecular Biophysics

Imaging techniques such as positron emission tomography (PET), single photon emission tomography (SPECT) and g-scintigraphy offer unique opportunities for biomedical research. Because the in vivo tissue distribution of radiotracers is reconstructed by imaging equipment, this methodology permits the noninvasive study of physiological function (metabolism, pharmacology) rather than anatomical structure only, as is the case for MRI or CAT scanning. Moreover, due to the noninvasive nature of these modalities, application to human subjects is possible, and serial studies can be repeated on the same individual.

Moerlein SM, Perlmutter JS, Cutler PD, Welch MJ. Radiation dosimetry of $^{[18F]}$(N-methyl)benperidol as determined by whole-body PET imaging of primates. Nucl Med Biol 1997 24:311-318.

Moerlein SM, Perlmutter JS, Markham J, Welch MJ. In vivo kinetics of $^{[18F]}$(N-methyl)benperidol: a novel PET tracer for assessment of dopaminergic D2-like receptor binding. J Cereb Blood Flow Meta 1997 17:833-845.

Perlmutter JS, Stambuk MK, Markham J, et al. Decreased $^{[18F]}$spiperone binding in putamen in idiopathic focal dystonia. J Neurosci 1997 17:843-859.

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John C. Morris, M.D. Professor
Neurology & Neurological Surgery (Neurology) Pathology (Neuropathology)

Investigations from our programs focus on the behavioral, neurological, and pathologic distinctions between aging and dementia. We explore the phenomenology of Alzheimer's disease through longitudinal studies employing clinical, neuropsychiatric, and neuroimaging techniques. The clinical and pathological phenotypes of inherited dementias are Characterized to facilitate identification of causative mutations. Translational research studies include treatment trials of novel Antidementia compounds.

Lendon CL, Lynch T, Norton J, McKeel DW, Busfield F, Craddock N, Chakraverty S, Gopalakrishnan G, Shears SD, Grimmett W, Wilhelmsen KC, Hansen L, Morris JC, Goate AM. Hereditary dysphasic disinhibition dementia. A frontotemporal dementia linked to 17q21-22. Neurology 1998;50:1546-1555.

Price JL, Morris JC. (1999) Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. Annals of Neurology 45: 358-368.

Hong M, Zhukareva V, Vogelsber-Ragaglia V, Wszolek Z, Reed L, Miller BL, Geschwind DH, Bird TD, McKeel D, Goate A, Morris JC, Wilhelmsen KC, Schellenberg GD, Trojanowski JQ, Lee V M-Y. (1998) Mutation-specific functional impairments in distinct tau isoforms of hereditary FTDP-17. Science 282: 1914-1917.

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Louis Muglia, M.D., Ph.D.*
Assistant Profesor
Pediatrics; Molecular Biology & Pharmacology; Obstetrics & Gynecology

Our research efforts center on defining the role of neuropeptides produced by the hypothalamus in the stress response, reproduction, and behavior. Through the analysis of murine transgenic and gene inactivation models, we have characterized essential in vivo functions of corticotropin-releasing hormone (CRH), oxytocin (OT), and adenylyl cyclase type VIII (AC8).

Muglia LJ, Jacobson L, Dikkes P, Majzoub JA. Corticotropin-releasing hormone deficiency reveals major fetal but not adult glucocorticoid need. Nature 1995; 373:427-432.

Muglia, L., Jacobson, L., Weninger, S. C., Luedke, C. E., Bae, D. S., Jeon K.-H., and Majzoub, J.A. Impaired diurnal adrenal rhythmicity restored by constant infusion of corticotropin releasing hormone in CRH-deficient mice J. Clin. Invest. 1997; 99:2923-2929.

Gross, G., Imamura, T., Luedke, C., Vogt, S. K., Olson, L. M., Nelson, D. M., Sadovsky, Y., and Muglia, L. J. Opposing actions of prostaglandins and oxytocin determine the onset of murine labor. Proc. Natl. Acad. Sci. USA 1998; 95: 11871-11875.

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Jeff Neil, M.D., Ph.D.*
Assistant Professor
Neurology & Neurological Surgery (Neurology); Pediatrics; Anatomy & Neurobiology

Our research group is interested in evaluating brain injury and development through magnetic resonance (MR) imaging methods. We are evaluating diffusion tensor imaging (DTI) in animal models to determine the underlying biophysical basis for the unique sensitivity of this method to brain injury. We are also applying DTI to newborn human infant brain to obtain insight into the timing and localization of injury in newborns who eventually develop cerebral palsy.

Neil J (1997) Measurement of water motion (apparent diffusion) in biological systems. Concepts Magn. Reson. 9:385-401.

Neil J, Shiran SI, McKinstry RC, Schefft GL, Snyder AZ, Almli CR, Akbudak E, Aaronovitz JA, Miller JP, Lee BCP, and Conturo TE (1998) Normal brain in human newborns: Apparent diffusion coefficient and diffusion anisotropy measured using diffusion tensor imaging. Radiology 209:57-66.

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Jeanne M. Nerbonne, Ph.D.*
Professor
Molecular Biology & Pharmacology

The goal of our research is to define the molecular mechanisms controlling the regulation, modulation and functional expression of voltage-gated K^+ channels in mammalian cardiac myocytes and cortical neurons. Electrophysiological, biochemical, immunohistochemical and molecular techniques are exploited to characterize K^+ channel properties and distributions. Novel transgenic strategies are being used to manipulate K^+ channel expression in vivo, and the functional consequences of these manipulations are being explored.

Locke, R.E., and Nerbonne, J.M. (1997) Role of voltage-gated K+ currents in mediating the regular-spiking phenotype of callosal-projecting at visual cortical neurons. J. Neurophysiol. 78: 2321-2223.

Barry, D.M., Xu, H., Schuessler, R.B., and Nerbonne, J.M. (1998). Functional knockout of the transient outward current, long QT syndrome, and cardiac remodelling in mice expressing a dominant-negative Kv4 alpha subunit. Circ. Res., 85:560-567.

Nerbonne, J.M. (1998). Regulation of voltage-gated K+ channel expression in the developing mammalian myocardium. J. Neurobiol., 37:37-59.

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John Newcomer, M.D.
Assistant Professor
Psychiatry; Psychology

This laboratory investigates neurochemical regulators of memory performance in human subjects. Our work has primarily focused on the adverse effects of glucocorticoids, memory facilitating effects of glucose and insulin, and memory impairments induced by NMDA receptor antagonists. Most recently we have begun studying treatments which may block memory and other behavioral effects of NMDA antagonists as a treatment model relevant to schizophrenia and other neuropsychiatric diseases.

Newcomer, J.W., Craft, S., Hershey, T., Askins, K., and Bardgett, M.E. (1994) Glucocorticoid-induced impairment in declarative memory performance in adult humans. J. Neurosci. 14:2047-2053.

Newcomer, J.W., Farber, N.B., Jevtovic-Todorovic, V., Selke, G., Melson, A.K., Hershey, T., Craft, S., Olney, J.W. (1999) Ketamine-Induced NMDA Receptor Hypofunction as a Model of Memory Impairment and Psychosis. Neuropsychopharmacology, 20:106-118.

Newcomer, J.W., Craft, S., Fucetola, R., Moldin, S.O., Selke, G., Paras, L., Miller, R. (1999) Glucose-Induced Increase in Memory Performance in Patients with Schizophrenia. Schizophr Bull, 25:321-325.

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Colin G. Nichols, Ph.D.*
Associate Professor
Cell Biology & Physiology

Research in my laboratory is focused on the molecular and cellular regulation of potassium channels, in particular those that link metabolism to electrical activity. We are developing a detailed understanding of the regulation of inwardly rectifying channels and the structural basis of channel activity, using various molecular biological, genetic and biophysical approaches.

Nichols CG, Lopatin AN. Inward rectifier potassium channels. Ann Rev Physiol 1997 59:171-191.

Nichols CG, Shyng S-L, Nestorowicz A, et al. ADP as the intracellular regulator of insulin secretion. Science 1996 272:1785-1787.

Aguilar-Bryan L, Nichols CG, Wechsler SW, et al. Cloning of the b-cell high affinity sulfonylurea receptor: a regulator of insulin secretion. Science 1995 268:423-426.

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Bruce Nock, Ph.D.*
Associate Professor
Psychiatry; Anatomy & Neurobiology

Our research is principally concerned with morphine-stress-glucocorticoid interactions and is based on our discovery that chronic exposure to morphine upregulates corticosteroid-binding globulin in blood and, thereby, reduces physiologically active glucocorticoid. Glucocorticoids exert both permissive and suppressive actions to protect the body against stress. Morphine appears to suppress both mechanisms. This is likely to adversely affect both mental and physical health over the long run and may contribute to the maintenance of drug abuse.

Nock, B., Wich, M. and Cicero, T. J.: Chronic exposure to morphine increases corticosteroid-binding globulin. J. Pharmacol. Exp. Ther. 1997, 282:1262-1268.

Nock, B., Cicero, T.J. and Wich, M.(1998): Chronic exposure to morphine decreases physiologically active corticosterone in both male and female rats but by different mechanisms. J. Pharmacol. Exp. Ther. 286:875-82..

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Michael L. Nonet, Ph.D.*
Assistant Professor
Anatomy & Neurobiology

My laboratory studies the presynaptic nerve terminal using the nematode Caenorhabditis elegans. Utilizing a combination of classical genetic, reverse genetic and cell biology techniques, we are identifying and characterizing molecules that are involved in regulating synaptic release. Additionally, we are interested in how the presynaptic terminal develops and are exploring how proteins target to the presynaptic terminal and to synaptic vesicles using GFP as a marker.

Iwasaki, K., Staunton, J., Saifee, O., Nonet, M. L. and Thomas J . aex-3 encodes a novel regulator of presynaptic activity in C. elegans. Neuron 18:613-622. 1997.

Nonet, M. L., Saifee, O., Zhao, H., Rand, J. B. and Wei, L. Synaptic transmission deficits in C. elegans synaptobrevin mutants. J. Neurosci. 18: 170-180. 1998.

Saifee, O. Wei, L. and Nonet, M. L. The C. elegans unc-64 gene encodes a syntaxin that interacts genetically with synaptobrevin. Mol. Biol. Cell 9: 1235-1252. 1998.

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John Olney, M.D.*
Professor
Psychiatry; Pathology

Our research focuses on excitatory neurotransmitters, including acetylcholine and glutamate. These common substances serve vitally important metabolic, neurotrophic and neurotransmitter roles in the CNS, but also harbor treacherous neurotoxic (excitotoxic) potential. We study excitotoxic mechanisms and the role these mechanisms may play in neuropsychiatric disorders including Alzheimer's, Huntington's and Parkinson's diseases, schizophrenia, epilepsy, stroke and cerebral palsy.

Olney JW, Farber NB. Glutamate receptor dysfunction and schizophrenia. Arch Gen Psychiatry 52, 998-1007, 1995.

Olney JW, Wozniak DF, Farber NB. Excitotoxic neurodegeneration in Alzheimer's disease: new hypothesis and new therapeutic strategies. Arch Neurol 54 (10), 1234-1240, 1997.

Ikonomidou C, Bosch F, Miksa M, Vockler J, Bittigau P, Pohl D, Dikranian K, Tenkova T, Turski L, Olney JW. Blockade of glutamate receptors triggers apoptotic neurodegeneration in the developing brain. Science 283:70-74, 1999.

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Karen L. O'Malley, Ph.D.*
Professor
Anatomy & Neurobiology

My laboratory is interested in the molecular and cellular bases of neurological and neuropsychiatric disorders. Because atypical dopaminergic function is associated with these disorders we are using animal models and cell culture techniques in pursuit of these interests.

Liu, J., Merlie, J.P., Todd, R.D. and O'Malley, K.L. Identification of cell type specific promoter elements associated with the rat tyrosine hydroxylase gene using transgenic founder analysis. Mol. Brain Res. 50:33-42 (1997).

Yamaguchi, I., Harmon, S.K., Todd, R.D., and O'Malley, K.L. The rat D4 dopamine receptor couples to cone transducin to inhibit forskolin-stimulated cAMP accumulation. J. Biol. Chem. 272:16599-16602 (1997).

Lotharius, J., Dugan, L., and O'Malley, K.L. Distinct mechanisms underlie neurotoxin-mediated cell death in cultured dopamine neurons. J. Neurosci. 19:1284-1293 (1999).

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T.S. Park, M.D.*
Professor
Neurology & Neurological Surgery (Neurosurgery); Pediatrics ; Anatomy & Neurobiology

Accumulating evidence indicates that neutrophils contribute to the mediation of brain injury following focal ischemic stroke. Our research is directed at elucidation of the biochemical mechanisms underlying neutrophil-mediated ischemic brain injury. We are pursuing the overall hypothesis that particular reactive oxygen and nitrogen metabolites (NO, superoxide anion, and peroxynitrite), elastase, and myeloperoxidase-derived oxidants collectively mediate neutrophil-endothelial cell adherence and neutrophil-mediated microvascular and parenchymal injury following focal ischemia.

Gidday JM, Park TS, Shah AR, Gonzales ER: Modulation of basal and postischemic leukocyte-endothelial adherence by nitric oxide. Stroke 1998; 29:1423-1430

Park TS, Gonzales ER, Gidday JM: Platelet-activating factor mediates ischemia-induced leukocyte-endothelial adherence in newborn pig brain. J Cereb Blood Flow Metab, 1999; 19:417-424.

Beetsch JW, Park TS, Shah AR, Gidday JM: Xanthine oxidase-derived superoxide causes anoxia/reoxygenation injury of cerebral endothelial cells. Brain Res 1998; 786:89-95.

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Alan L. Pearlman, M.D.*
Professor
Neurology & Neurological Surgery (Neurology); Cell Biology & Physiology

We are interested in how the mammalian cerebral cortex is formed in embryonic life, and how this process goes wrong to produce abnormalities of human cortical development. We study these mechanisms in an organotypic cortical slice preparation in which neuronal migration and axon growth can be observed and perturbed experimentally. We make extensive use of mutant and transgenic mice in these studies. Current projects focus on the role of neurotrophins and of extracellular matrix molecules and their receptors.

Sheppard, A. M., and A. L. Pearlman (1997). Abnormal reorganization of preplate neurons and their associated extracellular matrix: an early manifestation of altered neocortical development in the reeler mutant mouse. J. Comp. Neurol. 378:173-179.

Brunstrom, J. E., M.R. Gray-Swain, P. A. Osborne, and A. L. Pearlman (1997) Neuronal heterotopias in the developing cerebral cortex produced by neurotrophin-4. Neuron 18:505-517.

Pearlman, A.L., P.M. Faust, M.E. Hatten and J.E. Brunstrom (1998). New directions for neuronal migration. Curr. Opin. Neurobiol. 8:45-54,

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Jay S. Pepose, M.D., Ph.D.*
Professor - Ophthalmology and Visual Sciences; Pathology

My research focuses on viral diseases of the eye. One broad area deals with herpes simplex virus, which establishes latency in the sensory and autonomic ganglia and then later reactivates. Reactivation can be the cause of a variety of ocular conditions, including herpes keratitis, iritis and Bell's palsy. We have developed an animal model of HSV reactivation in mice, achieving 70% reactivation by exposure to UV-B. The model has been useful in evaluating vaccines, antivirals and putative anti-reactivation drugs. We are using knockout mice to further define the role of specific cytokines in herpes reactivation and keratitis formation.

Keadle TL, Laycock KA, Miller JK, et al. Efficacy of a recombinant glycoprotein D subunit vaccine on the development of primary and recurrent ocular infection with herpes simplex virus type 1 in mice. J Infect Dis 1997 176:331-338.

Miller JK, Laycock KA, Umphress JA, et al. A comparison of recurrent and primary herpes simplex keratitis in NIH inbred mice. Cornea 1996 15:497-504.

Blatt AN, Laycock KA, Brady RH, Krogstad DJ, Pepose JS. Prophylactic acyclovir effectively reduces herpes simplex virus type 1 reactivation following exposure of latently infected mice to ultraviolet B. Invest Ophthal Vis Sci 1993 34:3452-3465.

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Julio Perez-Fontan, M.D. Professor
Pediatrics; Anesthesiology

Work in my laboratory analyzes the organization and function of the brain stem and intrinsic airway parasympathetic networks. We combine physiological, immunohistochemical, and molecular methods to study the relationships of preganglionic neurons and airway ganglia, with special emphasis on the effects of preganglionic denervation on the phenotype of denervated ganglion cells.

Pérez Fontán, J.J. and C.R. Velloff. Neuroanatomic organization of the parasympathetic bronchomotor system in developing sheep. Am. J. Physiol. 1997; 273: R121-R133.

Carver, T.W., Jr., S.K. Srinathan, C.R. Velloff,, and J.J. Pérez Fontán. Increased type I procollagen mRNA in airways and pulmonary vessels after vagal denervation in rats. Am. J. Resp. Cell Mol. Biol. 1997; 17: 691-701.

Pérez Fontán, J.J., L.P. Kinloch, and D.F. Donnelly. Integration of ventilatory and bronchomotor responses during chemoreceptor stimulation in developing sheep. Respir. Physiol. 1998; 111: 1-13.

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David H. Perlmutter, M.D.*
Professor
Pediatrics; Cell Biology & Physiology

We study the regulation of α1- antitrypsin and its role in tissue injury and inflammation, including studies of a novel cell surface receptor, SEC-R, which recognizes α1-AT and mediates feedback regulation of α1-AT gene expression. SEC-R recognizes a highly conserved pentapeptide in the α1-AT sequence and a serendipitously discovered homologous sequence in the amyloid-beta peptide and the tachykinins. SEC- R is expressed by neurons and mediates endocytosis and catabolism of soluble amyloid-beta peptide. We also study the cellular biochemistry of a genetic deficiency of α1-AT deficiency in which an abnormal protein is retained in the endoplasmic reticulum and causes liver injury in infants.

Molmenti E, Perlmutter DH, Rubin D. Cell-specific expression of the alpha-1-antitrypsin gene in human intestinal epithelum. J Clin Invest 1993; 92:2022-2034.

Perlmutter DH. Metabolic liver disease in children. In: Seminars in Gastrointestinal Disease (Sleisenger MH, Fordtran JS, eds), WB Saunders:Philadelphia 1994; 5:54-64.

Sippel CJ, McCollum MJ, Perlmutter DH. Bile acid transport by the rat liver canalicular bile acid transport/ecto-ATPase protein is dependent on ATP but not on its own ecto-ATPase activity. J Biol Chem 1994; 269:2820-2826.

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Joel S. Perlmutter, M.D.*
Associate Professor
Neurology & Neurological Surgery (Neurology); Radiology

The primary interest of my research is to investigate basal ganglia physiology, pharmacology and pathophysiology. The research particularly emphasizes the study of abnormalities associated with involuntary movement disorders such as dystonia and Parkinson's disease as well as to investigate the effects of chronic medication and surgical interventions on basal ganglia function. For these studies, positron emission tomography (PET) and magnetic resonance imaging (MRI) are used to measure regional brain function including radioligand-receptor binding, regional cerebral blood flow, and responses to physiological and pharmacological stimulation.

Hershey T, Black KJ, Stambuk MK, Carl JL, McGee-Minnich L, Perlmutter JS: Altered thalamic response to levodopa in Parkinson's disease patients with dopa-induced dyskinesias. Proc Natl Acad Sci. 95:12016-12021, 1998.

Perlmutter JS, Tempel LW, Black KJ, Parkinson D, Todd RD: MPTP induces dystonia & parkinsonism: clues to the pathophysiology of dystonia. Neurology 49:1432-1438, 1997.

Feiwell RJ, Black KJ, McGee-Minnich LA, Snyder AZ, MacLeod AK, Perlmutter JS (1999) Diminished regional blood flow response to vibration in patients with blepharospasm. Neurology 52:291-297.

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Steven Petersen, Ph.D.*
Associate Professor
Neurology & Neurological Surgery (Neurology)
Radiology; Anatomy & Neurobiology; Psychology

We use behavioral and functional neuroimaging techniques (PET, fMRI) to study the neural mechanisms underlying attention, language, learning and memory. We have also extended our research interests in the area of rehabilitation following brain injury. Our current focus has been on two aspects of memory: episodic memory and procedural learning.

Shulman, G. L., Corbetta, M., Buckner, R.L., Raichle, M.E., Fiez,J.A., Miezin, F.M., and Petersen, S.E. (1997) Top-down modulation of early sensory cortex. Cerebral cortex 7:193-206.

Petersen, S.E., van Mier, H., Fiez, J.A., and Raichle, M.E. (1998) The effects of practice on the functional anatomy of task performance. Proc. Nat. Acad. Sci. 95:853-860.

Kelley, B.M., Miezin, F. M., Mc Dermott, K.B., Buckner, R. L., Raichle, M.E., Cohen, N.J., Ollinger, J.M. and Petersen, S.E. (1998) Hemispheric asymmetry in human dorsal frontal cortex and medial temporal lobe for verbal and nonverbal memory encoding. Neuron 20:927-936.

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William J. Powers, M.D.
Professor
Neurology & Neurological Surgery (Neurology); Radiology

My research is primarily concerned with studying the changes in cerebral hemodynamics and metabolism that occur in human subjects, both during normal physiological activity and in neurological and other diseases. We use positron emission tomography (PET) and short-lived radioactive chemicals to produce physiologic images of the brain showing cerebral blood flow, cerebral blood volume, cerebral metabolic rate of oxygen and cerebral metabolic rate of glucose.

Powers, W.J., Boyle, P.J., Hirsch, I.B., Cryer, P.E. (1993) Unaltered cerebral blood flow during hypoglycemic activation of the sympathochromaffin system in humans. Am J. Physiol., 265:R883-R887.

Powers, W.J., Hirsch, I.B., Cryer, P.E. (1995) Effect of stepped hypoglycemia on the regional cerebral blood flow response to physiological brain activation. Am. J. Physiol.).

Powers, W.J., Dagogo-Jack, S., Markham, J., Larson, K.B., Dence, C.S. (1995) Cerebral transport and metabolism of 1-11C-D-glucose during stepped hypoglycemia. Ann. Neurol. 38:599-609.

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Joseph L. Price, D. Phil.*
Professor
Anatomy & Neurobiology

The goal of my laboratory is to analyze the organization of the limbic forebrain in humans and experimental animals, and its relation to neurological or psychiatric disorders, particularly Alzheimer's Disease and mood disorders. The research has focused on the amygdala, related parts of the thalamus and basal ganglia, and the prefrontal cortex, as components of an interconnected system involved in both visceral function and emotional and cognitive behavior.

Price, JL, Carmichael, ST Drevets WC. Networks Related to the Orbital and Medial Prefrontal Cortex. A substrate for emotional behavior? Prog Brain Res. 1996; 107: 523-536.

Drevets, WC, Price, JL, Simpson, JR, Todd, R, Reich, T, Vannier, M, Raichle, M. Subgenual prefrontal cortex abnormalities in mood disorders. Nature, 1997, 386:824-827.

Price JL: Diagnostic Criteria for Alzheimerís Disease. Neurobiology of Aging 1997; 18:S67-S70.

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Madelon T. Price, Ph.D.
Research Professor
Psychiatry

My laboratory is interested in the role of neurotransmitters in neurotoxic mechanisms. Excitotoxic transmitters are involved in inducing brain damage in epilepsy, stroke, head trauma, Alzheimer's disease, schizophrenia and many other psychiatric and neurological disorders. We are especially interested in developing agents to prevent and/or ameliorate these conditions.

Price MT, Romano C, Fix AS, Tizzano JP, Olney JW. Blockade of the second messenger functions of the glutamate metabotropic receptor is associated with degenerative changes in the retina and brain of immature rodents. Neuropharmacology 1995; 34(8):1069-1079.

Romano C, Price MT, Almli, T and Olney JW. Excitotoxic neurodegeneration induced by oxygen/glucose deprivation in isolated retina. Invest Ophthal & Visual Sci: 39, 416-423, 1998.

Chen, Q. Olney, J.W. Price, M.T. and Romano C. Biochemical and morphological analysis of non-NMDA receptor mediated excitotoxicity in chick embryo retina. Visual Neuroscience 6:131-139, 1999.

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Marcus E. Raichle, M.D.*
Professor
Radiology; Neurology & Neurological Surgery (Neurology)
Anatomy & Neurobiology

Our work uses short-lived (i.e., 2-110 minute half-life) cyclotron-produced, positron-emitting radionuclides with positron emission tomography (PET) and functional Magnetic Resonance Imaging (f MRI) for the in vivo study of the central nervous system of humans and non-human primates.

MacLeod A-M, Buckner RL, Miezin FM, Petersen SE, Raichle ME. Right prefrontal cortex activation during semantic monitoring. NeuroImage 1998 7:41-48.

Ojemann JG, Neil JM, MacLeod A-M, et al. Increased functional vascular response in the region of a glioma. J Cereb Blood Flow Metab 1998 18:148-153.

Yablonskiy DA, Neil JJ, Raichle ME, Ackerman JH. Homonuclear J coupling effects in volume localized NMR spectroscopy: pitfalls and solutions. Magn Reson Med 1998 39:169-178.

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Yi Rao, Ph.D.*
Assistant Professor
Anatomy & Neurobiology

We are interested in signaling mechanisms underlying vertebrate neural development. In one project, we have found that eye development begins as a single morphogenetic field, which segregate into two distinct eyes. We are further pursuing studies of dorsal/ventral patterning within the retina. In a second project, we are studying a new family of developmental regulators encoded by the vertebrate fringe genes. We are investigating how Fringe proteins modulate the Notch signaling pathway.

Wu, W., Wong, K., Chen, J. H., Jiang, Z. H., Dupuis, S., Wu, J. Y., and Rao, Y. (1999). Directional guidance of neuronal migration in the olfactory system by the concentration gradient of the secreted protein Slit. Nature 400:331-336.

Zhu, Y., Li, H. S., Zhou, L., Wu, J. Y., and Rao, Y. (1999). Cellular and molecular guidance of GABAergic neuronal migration from an extra-cortical origin to the neocortex. Neuron 23: 473-485.

Li, H. S., Chen, J. H., Wu, W., Fagaly, T., Yuan, W. L., Zhou, L., Dupuis, S., Jiang, Z., Nash, W., Gick, C., D. Ornitz, Wu, J. Y., and Rao, Y. (1999). Vertebrate Slit, a Secreted Ligand for the Transmembrane Protein Roundabout, is a Repellent for Olfactory Bulb Axons. Cell 96, 807-818.

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Keith M. Rich, M.D.*
Associate Professor
Neurology & Neurological Surgery (Neurosurgery)
Anatomy & Neurobiology

Our primary area of investigation is apoptosis in human brain tumors. We are specifically investigating the regulation of individual members of the bcl-2 gene family and p53 in modulating the sensitivity of malignant gliomas to treatment with DNA-damaging agents. Studies on human brain tumor will be prospectively correlated molecular changes in expression of p53 and bcl-2 gene family members with the clinical response to therapy strategies.

Tong, J.X., Vogelbaum, M.A., and Rich, K.M., Radiation-induced apoptosis in dorsal root ganglions, Journal of Neurocytology 26:771-777, 1997.

Vogelbaum, M.A., Tong, J.X., Higashikubo, R., Gutmann, D.H., Rich, K.M., Transfection of C6 glioma cells with the bax gene results in increased sensitivity to treatment with cytosine arabinoside, Journal of Neurosurgery 88(1):99-105, 1998.

Vogelbaum, M.A., Tong, J.X., Rich, K.M., Developmental regulation of apoptosis in dorsal root ganglion neurons, Journal of Neuroscience 18(21):8929-8935, 1998.

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Henry Roediger, Ph.D.
Professor and Department Head (Psychology)
Psychology; Philosophy

My research is concerned with learning and memory in human adults. Programs of research include study of memory illusions and the development of false memories, priming on implicit memory tests and the relation to explicit memory, effects of repeatedly testing memory; and effectiveness of retrieval cues in accessing seemingly forgotten information.

Rajaram, S. & Roediger, H.L. (1997). Remembering and knowing as states of consciousness during retrieval. In J.D. Cohen & J.W. Schooler (Eds.), Scientific Approaches to Consciousness. (pp. 213-240). Hillsdale, NJ.

Goff, L.M. & Roediger, H.L. (1998). Imagination inflation for action events: repeated imaginings lead to illusory recollections, Memory & Cognition, 26, 20-33.

Srinivas, K., Rajaram, S., & Roediger, H.L. (in press). A transfer-appropriate processing account of context effects in word fragment completion, Journal of Experimental Psychology: Learning, Memory and Cognition.

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Carmelo Romano, Ph.D.*
Associate Professor
Ophthalmology & Visual Sciences Anatomy & Neurobiology

Most of the work in our lab concerns neurotransmitter receptors, especially those for glutamate. We use biochemical, immunochemical, pharmacological and molecular techniques to examine the properties, distribution and functioning of these receptors in the retina and brain. We are especially interested in pathological consequences of glutamate receptor activation; both in vitro and in vivo models of retinal excitotoxic and ischemic damage are used for this purpose.

Chen, Q., Olney, J.W., Lukasiewicz, P.D., Almli, T. and Romano, C. Ca^{2+}-independent excitotoxic neurodegeneration in isolated retina, an intact neural net: A role for Cl- and inhibitory transmitters. Mol. Pharmacol. 1998, 53: 564-572

Romano, C. Chen, Q. and Olney, J.W. The intact isolated (ex vivo) retina as a model system for the study of excitotoxicity. Prog. Retina Eye Res. 1998.

Romano, C., Yang, W-L., and O'Malley, K.L. The metabotropic glutamate receptor mGluR5 is a disulfide-linked dimer. J. Biol. Chem. 1996; 271: 28612-28616

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Kevin A. Roth, M.D., Ph.D.*
Associate Professor
Pathology (Neuropathology); Molecular Biology & Pharmacology

Our research is focused on the cellular and molecular regulation of neuronal apoptosis, Apoptosis is a catastrophic consequence of many neuropathological processes including Alzheimer's disease and stroke, however, it is also a normal component of nervous system development. We have defined an apoptotic pathway involving an interaction between Bax and Bcl-XL, whereby an increased intracellular ratio of Bax:Bcl-XL leads to Caspase-3 activation and neuronal death. Future in vivo and in vitro studies with Apaf-1, Caspase-3, Caspase-9, and other Bcl-2 family gene-disrupted mice will further define the apoptotic pathways activated during nervous system development and in neuropathological conditions.

Motoyama, N., Wang, F., Roth, K.A., Sawa, H., Nakayama, K.I., Nakayama, K., Negishi, I., Senju, S., Zhang, Q., Fujii, S., and Loh, D.Y. (1995) Massive cell death of immature hematopoietic cells and neurons in Bcl-x deficient mice. Science 267:1506-1510.

Roth, K.A., Motoyama, N., Loh, D.Y. (1996) Apoptosis of bcl-x deficient telencephalic cells in vitro. J. Neurosci. 16:1753-1758.

Shindler, K.S., Latham, C.B., Roth, K.A. (1997) bax deficiency prevents the increased cell death of immature neurons in bcl-x-deficient mice. J. Neurosci. 17:3112-3119.

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Steven Rothman, M.D.* Professor
Neurology & Neurological Surgery (Neurology)
Pediatrics; Anatomy & Neurobiology

My colleagues and I are interested in using the techniques of modern cellular neurobiology to learn more about the pathophysiology and treatment of two serious and often devastating neurological diseases: stroke and epilepsy. Our most current experiments are examining the physiological alterations associated with aborted apoptosis, the activation of caspases in human brain slices deprived of oxygen and glucose, and the utility of rapid cooling to terminate epileptic bursting.

Hill MW, Reddy PA, Covey DF, Rothman SM. Contribution of subsaturating GABA concentrations to IPSCs in cultured hippocampal neurons. J Neurosci 18:5103-5111, 1998.

Hyrc K, Handran SD, Rothman SM, Goldberg MP. Ionized intracellular calcium concentration predicts excitotoxic neuronal death: observations with low-affinity fluorescent calcium indicators. J Neurosci 17:6669-6677, 1997

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Carl M. Rovainen, Ph.D.*
Professor
Cell Biology & Physiology

Our research is on brain blood vessels and ministrokes. Drs. Tom Woolsey and Ling Wei and I use in vivo videomicroscopy to image local blood flow by transits of intravascular fluorescein through arterioles and venules and to map neural functions by intrinsic optical signals in barrel cortex during whisker stimulation. Our goal is to test neural and vascular plasticity as potential mechanisms to aid recovery from stroke.

Wang, D.-B., Blocher, N.S., Spence, M.E., Rovainen, C.M., and Woolsey, T.A. (1992) Development and remodeling of cerebral blood vessels and their flow in postnatal mice observed with in vivo videomicroscopy. J. Cereb. Blood Flow Metab. 12:935-946.

Wei, L., Rovainen, C.M. and Woolsey, T.A. (1995) Ministrokes in rat barrel cortex. Stroke 26: 1459-1462

Woolsey, T.A., Rovainen, C.M., Cox, S.B., Henegar, M.H., Liang, G.E., Liu, D., Moskalenko, Y.E., Sui, J., and Wei, L. (1996) Neuronal units linked to microvascular modules in cerebral cortex: response elements for imaging the brain. Cerebral Cortex 6: 647-660

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Eugene H. Rubin, M.D., Ph.D.
Professor
Psychiatry

I am involved in several clinical studies of dementia of the Alzheimer type (DAT). Areas of emphasis include the psychopathology of DAT, defining and studying very mild forms of DAT, atypical dementias, and pharmacologic trials in DAT. I am also involved in a multi-year study being conducted by investigators from the Center for Mental Health Services Research in the GW Brown School of Social Work at Washington University entitled "Service Use of Depressed Elders after Acute Care."

Tariot PN, Mack JL, Patterson MB, Edland SD, Weiner MF, Fillenbaum G, Blazina L, Teri L, Rubin E, Mortimer JA, Stern Y, The Behavior Rating Scale for Dementia (BRSD) of the Consortium to Establish a Registry for Alzheimer's Disease. Am J Psychiatry 1995;152:1349-1357

Rubin EH, Storandt M, Miller JP, Kinscherf DA, Grant EA, Morris JC, Berg L: A prospective study of cognitive function and onset of dementia in cognitively healthy elders. Archives of Neurology 1998;55:395-401

Berg L, McKeel DW, Miller JP, Storandt M, Rubin EH, Morris JC, Baty J, Coats M, Norton J, Goate AM, Price JL, Gearing M, Mirra SS, Saunders AM: Clinicopathologic studies in cognitively healthy aging and Alzheimer's Disease: Relation of histologic markers to dementia severity, age, sex, and APOE genotype. Archives of Neurology 1998;55:326-335

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Lawrence B. Salkoff, Ph.D.*
Professor
Anatomy & Neurobiology; Genetics

Genome sequencing projects are rapidly changing the pace, perspectives and techniques of modern biological science. We are focusing on exploiting the newly available resources of the C. elegans genome sequencing project, as well as DNA sequencing projects from mammalian species to ion channel biology. With more than half of the C. elegans genome sequenced, an intriguing picture of the diversity of potassium channels in this organism has emerged. The number of genes encoding potassium channels is far greater than expected (there may be as many as 100 in the C. elegans genome).

Schreiber M, Wei A, Yuan A, et al. Slo3, a novel pH-sensitive K+ channel from mammalian spermatocytes. J Biol Chem 1998 273:3509-3516.

Johnstone D, Wei A, Butler A, Salkoff L, Thomas J. Behavioral defects in C. elegans egl-36 mutants result from potassium channels shifted in voltage-dependence of activation. Neuron 1997 19:151-164.

Schreiber M, Salkoff L. A novel calcium-sensing domain in the BK channel. Biophys J 1997 73:1355-1363.

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Joshua R. Sanes, Ph.D.*
Professor
Anatomy & Neurobiology

We are interested in identifying the molecules and structures that regulate synapse formation and account for its specificity. We concentrate on the neuromuscular junction because it is simple and accessible. Recently, however, we have begun to extend our analysis to the more complicated but perhaps even more interesting synapses of the brain. To learn which molecules are functionally critical, we combine studies of synapse formation in vitro with molecular genetic analysis of "knockout mice" in vivo.

Gautam, M, Noakes, PG, Moscoso, L, Rupp, F, Scheller, RH, Merlie, JP and Sanes, JR: Defective neuromuscular synaptogenesis in agrin-deficient mutant mice. Cell 1996; 85:525-535.

Inoue, A and Sanes, JR: Lamina-specific connectivity in the brain: Roles for N-cadherin, neurotrophins, and glycoconjugates. Science 1997; 276:1428-1431.

Patton, BL, Chiu, AY and Sanes, JR: Synaptic laminin prevents glial entry into the synaptic cleft. Nature 1998; 393:698-701.

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Robert E. Schmidt, M.D., Ph.D.*
Professor
Pathology

Interference with the normal function of peripheral nerve underlies a variety of neurologic diseases and provides a window for the elucidation of basic mechanisms of axonal function. Research interests involve the determination of the mechanisms underlying the response of the peripheral nervous system to various forms of toxic, infectious, immunologic, and metabolic injury. We have developed and characterized an animal model of diabetic autonomic neuropathy involving rats with streptozotocin-induced diabetes using biochemical, immunohistochemical, physiologic, and ultrastructural techniques.

Schmidt, R.E., Plurad, S.B., Parvin, C.A., and Roth, K.A. (1993) Effect of diabetes and aging on human sympathetic autonomic ganglia. Am. J. Pathol. 143:143-153.

Schmidt, R.E., Dorsey, D.A., Beaudet, L.N., Plurad, S.B., Parvin, C.A. and Bruch, L.A. (1998) Vacuolar neuritic dystrophy in aged mouse superior cervical ganglia is strain-specific. Brain Research 806:141-151.

Schmidt, R.E., Beaudet, L.N., Plurad, S.B., Snider, W.D., and Ruit, K.G. (1995) Pathologic alterations in pre- and postsynaptic elements in aged mouse sympathetic ganglia. J. Neurocytol. 24:189-206.

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Alan L. Schwartz, M.D., Ph.D.*
Professor and Department Head (Pediatrics)
Pediatrics; Molecular Biology & Pharmacology

Our laboratory focuses on the molecular biology of cell surface receptor structure and function in the areas of endocytosis and protein targeting and turnover. Two principal areas are currently being investigated: molecular regulation of endocytosis mediated by the multi-functional receptor, LRP, and the role of the ubiquitin system in intracellular protein turnover. These studies involve an integrated molecular, cellular, biochemical and morphological approach. Examples include the role of LRP in the biology of apolipoprotein E effects on neurons and the role of LRP in the regulation of plasminogen activator biology.

Govers R, van Kerkhof P, Schwartz AL, Strous GJ: Di-leucine-mediated internalization of ligand by a truncated growth hormone receptor is independent of the ubiquitin conjugation system. J Biol Chem 1998; 273: 16426-16433.

Ho G, Broze GJ Jr, Schwartz AL: Role of heparan sulfate proteoglycans in the uptake and degradation of tissue factor pathway inhibitor-coagulation factor Xa complexes. J Biol Chem 1997; 272: 16838-16844.

Bu G, Schwartz AL: RAP, a novel type of ER chaperone. Trends Cell Biol 1998; 8:272-276.

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Yvette Sheline, M.D.
Assistant Professor
Psychiatry; Radiology

My research focuses on characterizing limbic structures such as hippocampus, amygdala, and medial prefrontal cortex using 3-D MRI studies of volumes and PET studies of 5-HT2A receptor binding in subjects with major depression. Correlations of structural and functional variables with clinical variables such as age, duration of illness, treatment response, cortisol levels, and neuropsychological status are currently in progress.

Sheline Y.I., Wang P.W., Gado M.H., Csernansky J.G., Vannier M.W. Hippocampal Atrophy in Recurrent Major Depression. Proc. Nat'l Academy of Sciences USA 93:3908-3913, 1996.

Sheline Y.I., Gado M.H, Price J.L. Amygdala core nuclei volumes are decreased in recurrent major depression. NeuroReport 9: 2023-2028, 1998.

Uzunova V, Sheline Y, Davis J, Rasmusson A, Usunov D, Costa E, Guidotti A. Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. PNAS 95: 3239-3244, 1998.

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Dwayne Simmons, Ph.D.*
Research Associate Professor
Central Instutute for the Deaf; Anatomy & Neurobiology; Otolaryngology

My laboratory investigates the mechanisms of axon guidance, target selection and synaptogenesis in auditory pathways within the cochlea and brainstem. We employ a variety of anatomical, biochemical and molecular techniques to study how synapses are formed. Our overall goal is to provide insight on how fundamental developmental mechanisms contribute to the maturation of cochlear function.

Simmons, D.D., C. Bertolotto, J.H. Kim, J. Raji-Kubba, and N.B. Mansdorf (1998). Choline acetyltransferase expression during a putative developmental waiting period. Journal of Comparative Neurology. 397:281-295.

Simmons, D.D. and B.J. Morley (1998) Differential expression of the a9 nicotinic acetylcholine receptor subunit in the neonatal and adult cochlea. Molecular Brain Research. 56:287-292.

Simmons, D.D., H.D. Moulding, and D. Zee (1996). Olivocochlear innervation of inner and outer hair cells during postnatal maturation: An immunocytochemical study. Developmental Brain Research 95:213-226.

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Lawrence H. Snyder, M.D., Ph.D.*
Assistant Professor
Anatomy & Neurobiology

We study the processing of spatial information in the cerebral cortex of primates. Monkeys are trained to play video games in which they must look at and reach for various colored spots of light. We then record brain activity to determine how the locations of those spots of light, and the motor intentions of the animal, are coded and processed by individual neurons. Issues of interest include attention, sensor fusion, and eye-hand coordination.

Snyder, L.H., Grieve, K.L., Brotchie, P., and Andersen,R.A. Separate body- and world-referenced representations of visual space in parietal cortex. Nature, 394:887-891, 1998.

Snyder, L.H., Batista, A.B., and Andersen, R.A. Coding of intention in the posterior parietal cortex. Nature 386:167-170, 1997.

Snyder, L.H. and King, W.M. Behavior and physiology of the macaque vestibulo-ocular reflex response to sudden off-axis rotation: computing eye translation. Brain Research Bulletin, 40:293-302, 1996

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Mitchell Sommers, Ph.D.
Assistant Professor
Psychology

My research focuses on behavioral and computational approaches to understanding hearing and speech perception in older adults and Alzheimer's patients. We are particularly interested in relating specific anatomical deficits in these two populations to changes in communication abilities. The lab has also recently started to examine hearing and speech perception in pediatric cochlear implant patients.

Sommers,M. S. and Gehr, S. (1998). Auditory frequency selectivity and suppression in younger and older adults. Journal of the Acoustical Society of America, 103, 1067-1075.

Sommers,M. S. and Amano, S. (1998). Lexical competition in spoken word recognition by younger and older adults: A comparison of the rime cognate, neighborhood, and cohort. Journal of the Acoustical Society of America, 608-611.

Sommers,M.S. (1998). Spoken word recognition in individuals with Dementia of the Alzheimer,s type: Changes in talker normalization and lexical discrimination. Psychology and Aging, 13):631-646.

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Paul S.G. Stein, Ph.D.*
Professor
Biology

Neural circuits in the spinal cord produce patterns of motor output responsible for specific behaviors. We study the physiology of spinal cord circuits that generate three types or "forms" of scratching and two forms of swimming in the turtle. We test a hypothesis of spinal cord motor pattern generation, the "Bilateral Shared Core" hypothesis (Stein et al., 1995).

Stein, P.S.G., McCullough, M.L., and Currie, S.N. Reconstruction of flexor/extensor alternation during fictive rostral scratching by two-site stimulation in the spinal turtle with a transverse spinal hemisection. J. Neurosci. 18:467-479, (1998).

Field, E.C. and Stein, P.S.G. Spinal cord coordination of hindlimb movements in the turtle: interlimb temporal relationships during bilateral scratching and swimming. J. Neurophysiol. 78:1404-1413, (1997).

Stein, P.S.G., Victor, J.C., Field, E.C., and Currie, S.N. Bilateral control of hindlimb scratching in the spinal turtle: contralateral spinal circuitry contributes to the normal ipsilateral motor pattern of fictive rostral scratching. J. Neurosci. 15:4343-4355, (1995).

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Joe Henry Steinbach, Ph.D.*
Professor
Anesthesiology; Anatomy & Neurobiology

Nerve cells communicate with neurons and effector cells by releasing neurotransmitters, which bind to and activate receptors on the post-synaptic cells. I want to understand how transmitter gated ion channels function, and to identify regions of the receptor protein which are involved in the binding of activators and modulators.

Maconochie DJ, Steinbach JH. The channel opening rate of adult and fetal type mouse muscle nicotinic receptors, activated by acetylcholine. J Physiol 1998 506:53-72.

Ueno S, Bracamontes J, Zorumski C, Weiss DS, Steinbach JH. Bicuculline and gabazine are allosteric inhibitors of channel opening of the GABAA receptor. J Neurosci 1997 17:625-634.

Ueno S, Zorumski C, Bracamontes J, Steinbach JH. Endogenous subunits can cause ambiguities in the pharmacology of exogenous GABAA receptors expressed in HEK293 cells. Mol Pharmacol 1996 50:931-938.

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Martha Storandt, Ph.D.
Professor
Psychology; Neurology

My research deals with aging. A major goal is understanding the distinction between normal aging and Alzheimer's disease, especially the very early stages of the disease, and how each affects cognitive function. Most of the research involves administering standard and experimental psychometric tests to healthy older people as well as those with dementia. This work is done through the Alzheimer's Disease Research Center. I also am interested in strategies healthy older people can use to compensate for age-related changes in memory.

>Storandt, M. and VandenBos, G. (1994) Neuropsychological Assessment of Dementia and Depression in Older Adults: A Clinician's Guide. Am. Psychological Assoc., Washington, D.C.

Rubin, E. H., Storandt, M., Miller, J. P., Kincherf, D. A., Grant, E. A., Morris, J. C., & Berg, L. (1998). A prospective study of cognitive function and onset of dementia in cognitively healthy elders. Archives of Neurology, 55, 395-401.

Storandt, M., Kaskie, B., & Von Dras, D. D. (1998). Temporal memory for remote events in healthy aging and dementia. Psychology and Aging, 13, 4-7.

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Nobuo Suga , Ph.D.*
Professor - Biology

Many species of bats (which account for about 20% of all mammalian species) use sounds for biosonar and communication. We study electrophysiologically, anatomically and behaviorally the questions: How does the bat's auditory system extract the information necessary for biosonar and communication from species-specific complex sounds? Does the auditory system have subsystems or subdivisions devoted to processing either biosonar signals or communication sounds. How does the auditory system interact with the vocal system anatomically and physiologically?

Suga, N. (1990) Biosonar and neural computation in bats. Sci. Am. June vol: pp. 60-68.

Suga, N. (1992) Philosophy and stimulus design for neuroethology of complex-sound processing. Trans. Roy. Soc. London B336:423-428.

Edamatsu, H. and Suga, N. (1993) Differences in response properties of neurons between two delay-tuned areas in the auditory cortex of the mustached bat. J. Neurophysiol. 69:1700-1712.

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Paul H. Taghert, Ph.D.*
Associate Professor
Anatomy & Neurobiology

We study the neural basis of behavior in Drosophila by focusing on the functions of neuropeptide transmitters. We study transcriptional mechanisms that regulate neuropeptide gene expression and study the enzymes that are specifically required for their biosynthesis and processing. This information is used to analyze behavior by manipulating neuropeptide expression in vivo using techniques of Drosophila molecular genetics.

Kolhekar, AS, Roberts, MS, Jiang, N, Johnson, R, Mains, RE, Eipper, BA and Taghert, PH: Neuropeptide amidation in Drosophila: separate genes encode the two enzymes catalyzing amidation. J. Neurosci. 1997, 17: 1363-1376.

O'Brien, MA and Taghert, PH: A peritracheal neuropeptide system in Drosophila: release of myomodulin-like neuropeptides at ecdysis. J. Exp. Biol 1998, 201, 193-209.

Hewes, RE, Snowdeal, E, Saitoe, M and Taghert, PH: Functional redundancy of the FMRFamide-related neuropeptides at the larval neuromuscular junction of Drosophila. J. Neurosci. 1998, 18: 7138-7151.

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William Thomas Thach, Jr., M.D.*
Professor
Anatomy & Neurobiology
Neurology & Neurological Surgery

The research in my laboratory is on the neural control of posture and movement. We are especially interested in: (1) the specific roles played by different parts of the central nervous system in health; (2) the specific disabilities caused by damage of these parts; and (3) the patterns of recovery of function following damage.

Bastian AJ, Mink JW, Kaufman BA, Thach WT. Posterior vermal split syndrome. Ann Neurol 1998 Forthcoming.

Miall RC, Keating JG, Malkmus M, Thach WT. Simple spike activity predicts occurrence of complex spikes in cerebellar Purkinje cells. Nat Neurosci 1998 Forthcoming.

Keating JG, Thach WT. No clock signal in the discharge of neurons in the deep cerebellar nuclei. J Neurophysiol 1997 77:2232-2234.

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Richard D. Todd, M.D., Ph.D.*
Professor
Psychiatry; Genetics

My research interests can be divided into three broad, overlapping areas: (1) studies of genes and gene products that have a high likelihood of being involved in neuropsychiatric disorders; (2) linkage studies of familial forms of psychiatric disorders; and (3) twin studies of children at high familial/genetic risk for psychiatric disorders. Most of these studies are collaborative ventures which attempt to integrate and apply molecular, imaging and clinical approaches to specific disorders.

Drevets WL, Price JL, Simpson JR Jr, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997 386:824-827.

Lobos EA, Todd RD. Cladistic analysis of disease association with tyrosine hydroxylase: application to manic-depressive disease and alcoholism. Am J Med Genet (Neuropsychiatr Genet) 1997 74-289-295.

Todd RD, Carl J, Harmon S, O'Malley KL, Perlmutter JS. Dynamic changes in striatal dopamine D2 and D3 receptor protein and mRNA in response to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) denervation in baboons. J Neurosci 1996 16:7776-7782.

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Lawrence Tychsen, M.D.*
Associate Professor
Ophthalmology & Visual Sciences; Pediatrics; Anatomy & Neurobiology

How do infants learn to keep their eyes straight? Why do approximately 5% of children develop crossed eyes (strabismus) and poor binocular vision? My laboratory studies development of binocular vision and eye movements in cross-eyed monkeys and humans. The experiments involve perceptual testing (binocular stereovision and motion vision), electrophysiological recordings (visually-evoked potentials), recording of vergence and pursuit eye movements, and, in collaboration with A. Burkhalter, examination of visual cortex circuits using neuronal tracers and histochemical labels.

Tychsen, L., Burkhalter, A. and Boothe, R.G., Neural mechanisms in infantile esotropia: What goes wrong? Amer. Orthoptic J. 46:18-28, 1996.

Zhai, H.F., Anteby, I. and Tychsen, L.: Asymmetric motion VEPs in infantile strabismus are not an artifact of latent nystagmus. Invest. Ophthalmol. Vis. Sci. 38:S994, 1997.

Tychsen, L.: Infantile esotropia and current neurophysiologic concepts. In: Rosenbaum, A.L., Santiago, A.P. ed. Clinical Strabismus Management. W.B. Saunders, 1999:.

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David C. Van Essen, Ph.D.*
Professor and Head - Anatomy & Neurobiology

We use a combination of physiological, anatomical and computational approaches to study information processing in the primate visual system. Our work focuses on the macaque monkey, but we are increasingly involved in collaborative studies on human visual cortex. Anatomical studies aim to identify specific pathways and characterize connectivity patterns among the dozens of visual areas known to exist in the cerebral cortex. Physiological studies address the interrelated issues of pattern recognition, visual attention and figure-ground segregation. Studies on visual attention test for changes in neural response profiles according to where attention is directed relative to the cell's receptive field.

Van Essen DC, Drury HA, Joshi S, Miller MI. Functional and structural mapping of human cerebral cortex: solutions are in the surfaces. Proc Natl Acad Sci USA 1998 95:788-795.

Connor CE, Preddie DG, Gallant JL, Van Essen DC. Spatial attention effects in macaque area V4. J Neurosci 1997 17:3201-3214.

Van Essen DC. A tension-based theory of morphogenesis and compact wiring in the central nervous system. Nature 1997 385:313-318.

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Tom O. Videen, Ph.D.
Research Assistant Professor
Neurology & Neurological Surgery (Neurology); Radiology

Our laboratory studies functional activation of the brain and changes in brain function and neuroreceptor binding properties accompanying disease or other pathophysiology. We use PET, MRI and CT to study both human and non-human primates. My primary interests are developing and evaluating methodologies for visualization and quantitative analyses of these data.

Videen TO, Perlmutter JS, Mintun MA, Raichle ME (1988) Regional correction of positron emission tomography for the effects of cerebral atrophy. J. Cerebral Blood Flow and Metabolism, 8:662-670.

Black KJ, Gado MH, Videen TO, Perlmutter JS (1997) Baboon basal ganglia stereotaxy using internal MRI landmarks: validation and application to PET imaging. J. Computer Assisted Tomography, 21:881-886.

Grubb RL, Derdeyn CP, Fritsch SM, Carpenter DA, Yundt KD, Videen TO, Spitznagel EL, Powers WJ (1998) The importance of hemodynamic factors in the prognosis of of symptomatic carotid occlusion. J. Am. Medical Association, 280:1055-1060.

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Mark Warchol, Ph.D.*
Assistant Research Scientist
Central Institute for the Deaf; Anatomy & Neurobiology; Otolaryngology

We study the cellular mechanisms that regulate the survival and regeneration of sensory hair cells in the inner ear. Of particular interest are the influences of cytokines and extracellular matrix molecules in sensory regeneration. Additional studies focus on the role of macrophages and other leukocytes in the maintenance of hair cell sensory epithelia.

M.E. Warchol (1997) Macrophage Activity in the Avian Cochlea: Demonstration of a Resident Population and Recruitment to Sites of Hair Cell Lesions. Journal of Neurobiology. 33: 724-734.

J. Kil, M.E. Warchol, and J.T. Corwin (1997) Normal and Aminoglycoside-Induced Cell Death in the Avian Vestibular Sensory Epithelia. Hearing Research. 114: 117-126.

M.E. Warchol and J.T. Corwin (1996) Regenerative Proliferation in Organ Cultures of the Avian Cochlea: Identification of the Initial Progenitors and Determination of the Latency of the Proliferative Response. Journal of Neuroscience 16: 5466-5477.

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Ling Wei, M.D.
Research Assistant Professor
Cell Biology & Physiology

Using ischemia/stroke models of adult and young animals and combined with functional optical imaging, videomicroscopy, and quantitative autoradiography, we investigate alterations in local blood flow, blood brain barrier, neuronal/vesicular plasticity, and their relationship to cell death (necrosis and apoptosis), angiogenesis and long-term functional recovery.

Wei, L., Rovainen, C.M. and Woolsey, T.A. Ministroke in rats barrel cortex. Stroke 26: 1459-1462, 1995.

Fenstermacher, J.D. and Wei, L. Measuring local cerebral capillary permeability-surface area products by quantitative autoradiography. In: An Introduction To The Blood-brain Barrier: methodology, biology and pathology. Ed. By WiliiaM.Pardridge, pp. 122-132; Cambridge University Press, Cambridge, UK, 1998.

Wei, L., Craven, K., Erinjeri, J., Liang, G.E., Bereczki, D., Rovainen, C.M., Woolsey, T.A., and Fenstermacher, J.D. Local cerebral blood flow during the first hour following acute ligation of multiple arterioles in rat whisker barrel cortex. Neurobiol. Dis. 5: 142-150, 1998.

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Desiree White, Ph.D.
Assistant Professor
Psychology

The prefrontal cortex subserves an executive control system that permits the integration and organization of information across a range of cognitive domains. In my laboratory we investigate the contributions of executive control to learning and memory in children (e.g., phenylketonuria, epilepsy) and adults (e.g., cerebrovascular disease) with prefrontal brain damage.

White, D. A., Craft, S., Hale, S., & Park, T. S. (1994). Working memory and articulation rate in children with spastic diplegic cerebral palsy. Neuropsychology, 8, 180-186.

Chapman, L., White, D. A., & Storandt, M. (1997). Prose recall in individuals with dementia: Effects of delay interval. Archives of Neurology, 54, 1501-1504.

White, D. A., Taylor, M., Butters, N., Salmon, D., Mack, C., Heaton, R., Peavy, G., Ryan, L., Atkinson, J. H., McCutchan, J. A., Grant, I., & the HNRC Group. (1997). Memory for verbal information in individuals with HIV-associated dementia complex. Journal of Clinical and Experimental Neuropsychology, 19, 357-366.

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Mark Willard, Ph.D.*
Professor
Anatomy & Neurobiology
Biochemistry & Molecular Biophysics

Our laboratory is investigating the process of infection of cells by viruses that rely upon axonal transport for delivery to the cell bodies of neurons. We hope to learn how individual components of these viruses behave during the course of infection, and the mechanism of viral axonal transport.

Soppet, D.R., Beasly, L.L., and Willard, M.B. (1992) Evidence for unequal crossing over in the evolution of the neurofilament polypeptide H. J. Biol. Chem., 267: 17354-17361.

Spencer, S.A., Schuh, S.M., Liu, W., and Willard, M.B. (1992) Identification of three sites in the neuronal growth-associated protein GAP-43 that are phosphorylated in living systems. J. Biol. Chem., 267: 9059-9064.

Xu, Z. Liu, W., And Willard, M.B. (1992) Identification of six phosphorylation sites in the COOH-terminal tail region of the rat neurofilament protein M. J. Biol Chem., 267: 4467-4471.

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Rachel O.L. Wong, Ph.D.*
Assistant Professor
Anatomy & Neurobiology

Neuronal connectivity is highly organized at maturity. We are primarily interested in how neurons of the visual system form and maintain appropriate connections during development. In particular, we are investigating how a unique pattern of neural activity, generated before vision, sculpts connections between the retina and its brain targets. In addition, we are studying how circuits within the retina itself form during development, using a combination of electrophysiology and optical (calcium and two-photon) imaging techniques.

Wong, R.O.L. (1997) Patterns of correlated spontaneous bursting activity in the developing mammalian retina. Sem. Cell and Dev. Biol. 8: 5-12.

Fischer, K.F., Lukasiewicz, P.D. and Wong, R.O.L. (1998) Age-dependent and cell-class specific modulation of retinal ganglion cell bursting activity by GABA. J. Neurosci. 18: 3767-3778.

Wong, R.O.L. (1999) Retinal waves and visual system development. Annu. Rev. Neurosci.

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Thomas A. Woolsey, M.D.*
Professor
Neurology & Neurological Surgery (Neurosurgery)
Anatomy & Neurobiology
Cell Biology & Physiology

We study CNS structure, function, development and disease models, and the dynamic regulation of the blood supply in the whisker/barrel system of rodents. Current work concerns: 1) the role of neuronal activity in map pattern formation; 2) processing sensory information by cortical neurons; and 3) dynamics of the cerebral microcirculation .

Boero, J., J. Ascher, A. Arregui, C. Rovainen and T.A. Woolsey, 1999 Increased brain capillaries in chronic hypoxia,. J. Appl. Physiol., 86:1211-1219.

Hanaway, J., T.A. Woolsey, M.H. Gado and M.P. Roberts, Jr. 1998 The Brain Atlas: A Visual Guide to the Human Nervous System. Fitzgerald Science Press, Inc., Bethesda. 250 pp.

McCasland, J.S., L.S. Hibbard, R.W. Rhoades and T.A. Woolsey 1997 Activation of a wide-spread network of inhibitory neurons in barrel cortex. Somatosens. Motor Res., 14:138-147.

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Jane Wu, M.D., Ph.D.*
Assistant Professor
Pediatrics; Molecular Biology & Pharmacology

We are interested in understanding molecular mechanisms of mammalian gene expression and pathogenetic mechanisms underlying neurodegenerative diseases. We are studying alternative pre-mRNA splicing and its role in regulating genes involved in programmed cell death. We are investigating biological function of presenilin genes and their role in Alzheimer's disease.

Zhang W-J and Wu JY. Sip1, A Novel RS domain-containing Protein Essential for pre-mRNA Splicing. Mol. Cell. Biol.18:676-684, 1998

Zhang W-J, Han S-W, McKeel DW, Goate A and Wu JY. Interaction of Presenilins with the Filamin Family of Actin-Binding Proteins. J. Neurosci. 18 (3): 914-922, 1998

Jiang Z-H, Zhang W-J, Rao Y and Wu JY. Regulation of Ich-1 pre-mRNA alternative splicing and apoptosis by mammalian splicing factors Proc. Natl. Acad. Sci. USA 95:9155-9160, 1998

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Ling-Gang Wu, Ph.D.
Assistant Professor
Anesthesiology; Anatomy & Neurobiology

We are interested in basic cellular mechanisms of synaptic transmission in the central nervous system. Focus is on 1) the function and modulation of presynaptic calcium channels, 2) vesicle exocytosis and endocytosis, and 3) mechanisms of synaptic plasticity, such as short-term synaptic depression and paired-pulse facilitation. We use the calyx-type synapse in the medial nucleus of the trapezoid body in the auditory brainstem of the rat. This synapse is ideally suited for studying synaptic transmission, because simultaneous voltage clamp recordings of the presynaptic terminal and the postsynaptic neuron, together with optical imaging of presynaptic Ca^{2+} concentrations, can be made at single synapses in the brain slice preparation. In addition to these advanced techniques, we are currently applying a technique using the activity-dependent styryl dyes (e.g., FM1-43) to image the vesicle recycling process in brainstem slices.

Kay, A.R., Alfonso, A., Alford, S, Cline, H.T., Holgado, A.M., Sakmann, B., Snitsarev, V.A., Stricker, T.P., Takahashi, M., Wu, L.G. Imaging synaptic activity in intact brain and slices with FM1-43 in c. elegans, lamprey, and rat. Neuron 24:809–817, 1999.

Wu, L.G. and Borst, J.G.G. The reduced release probability of releasable vesicles during recovery short-term synaptic depression. Neuron 23:821-832, 1999.

Wu, L.G, Borst, J.G.G., and Sakmann, B. R-type Ca^{2+} currents evoke transmitter release in a rat central synapse. Proceedings of National Academy of Science 95:4720-4725, 1998.

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Kelvin A. Yamada, M.D.
Assistant Professor
Neurology & Neurological Surgery (Neurology); Pediatrics

We use electrophysiological recording techniques to study synaptic transmission between neurons in culture and in brain slices. My research interests include axonal mechanisms that can contribute to synaptic plasticity, long term potentiation in hippocampi following ischemic or seizure induced injury, and short term effects of seizure activity upon synaptic plasticity in an in vitro seizure model.

Yamada, KA, Covey, DF, Hsu, CY, Hu, R, Hu, Y, He, YY: The diazoxide derivative IDRA 21 enhances ischemic hippocampal neuron injury, Annals of Neurology, 1998, 43: 664-669.

Yamada, KA, Hill, MW, Hu, Y, Covey, DF: The diazoxide derivative 7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine-S,S-dioxide (IDRA 21) augments AMPA and GABA mediated synaptic responses in cultured hippocampal neurons, Neurobiology of Disease, 1998, 5: 196-205.

Yamada, KA: Modulating excitatory synaptic neurotransmission: Potential treatment for neurological disease? Neurobiology of Disease, 1998, 5: 67-80.

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Shan Ping Yu, M.D., Ph.D.
Research Assistant Professor
Neurology & Neurological Surgery (Neurology)

Investigation in our lab is to understand the ionic mechanisms related to excitotoxicity and degeneration in the central nervous system. Modulations of NMDA and non-NMDA receptors are one of our major interests. Other studies include voltage-gated ion channels and membrane transporters such as Na+, Ca^{2+} and K+ channels and Na+-Ca^{2+} exchanger. Ion channels are studied at whole-cell and single-channel level using patch-clamp and internal perfusion techniques on primary cultured neurons and DNA transfected cell lines.

Yu, S.P. & Choi, D.W. Na+-Ca^{2+} exchanger currents in cortical neurons: concomitant forward and reverse operation and effect of glutamate. Eur. J. Neurosci. 9: 1273 - 1281, 1997.

Yu, S.P., Yeh, C-H., Sensi, S.L., Gwag, B., Canzoniero, L.M.T., Farhangrazi, Z.S., Ying, H.S., Tian, M., Dugan, L.L. & Choi, D.W. Mediation of neuronal apoptosis by enhancement of outward potassium current. Science 278: 114-117, 1997.

Yu, S.P. and Kerchner, G.A. Endogenous Voltage-gated Potassium Channels in Human Embryonic Kidney (HEK293) Cells. J. Neurosci. Res. 52, 612-617, 1998.

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Min Zhuo, Ph.D.*
Assistant Professor
Anesthesiology
Anatomy & Neurobiology

We are interested in the cellular mechanisms of excitatory synaptic transmission and plasticity in the brain (e.g., spinal cord, hippocampus and cingulate cortex) and functional implications of such plastic changes. These mechanisms will help us to understand how pain is perceived/modulated and how pain-related memory is stored in the brain.

Kavalali, E.T., Zhuo, M., Bito, H., Tsien, R.W. Dendritic calcium channels characterized by recordings from isolated hippocampal dendritic segments. Neuron 18:651-663 (1997).

Li, P. and Zhuo, M. Silent glutamatergic synapses and nociception in mammalian spinal cord. Nature 393:695-698 (1998).

Li, P., Wilding, T.J., Kim, S.J., Calejesan, A.A., Huettner, J.E. and Zhuo, M. Kainate receptor-mediated sensory synaptic transmission in mammalian spinal cord. Nature, 397: 161-164 (1999).

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Charles F. Zorumski, M.D*
Professor and Head (Psychiatry)
Psychiatry; Anatomy & Neurobiology

Our laboratory is interested in the physiology and pharmacology of glutamate and GABA with emphasis on the participation of these transmitters in synaptic function and synaptic plasticity. Our studies use a variety of electrophysiological methods to record from cell cultures, brain slice preparations and cells expressing recombinant receptors.

Izumi Y, Benz AM, Katsuki H, Zorumski CF: Endogenous monocarboxylates sustain hippocampal synaptic function and morphological integrity during energy deprivation. J. Neuroscience 1997; 17: 9448-9457.

Jevtovic-Todorovic V, Todorovic SM, Mennerick S, Powell S, Dikranian K, Benshoff N, Zorumski CF, Olney JW: Nitrous oxide (laughing gas) is an NMDA antagonist, neuroprotectant and neurotoxin. Nature Medicine 1998; 4: 460-463.

Mennerick S, Dhond RP, Benz A, Xu W, Rothstein JD, Danbolt NC, Isenberg KE, Zorumski CF: Neuronal expression of the glutamate transporter GLT-1 in hippocampal microcultures. J. Neuroscience 1998; 18: 4490-4499.

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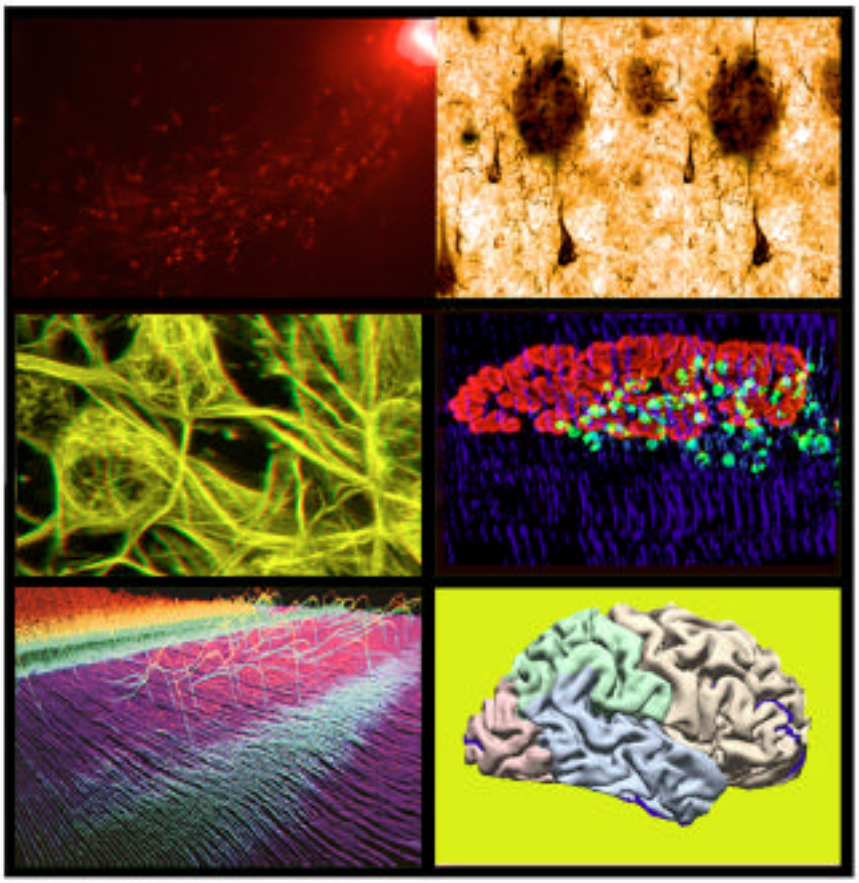

Program in Neuroscience

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