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January 13, 2014

The McKnight Brain Research Foundation
c/o Ms. Melanie Cianciotto
Vice President for Foundations and Endowments
SunTrust Bank
200 South Orange Avenue
SOAB 10th Floor
Orlando, Florida 32801

Dear Ms. Cianciotto,

It is my pleasure to present this year's stewardship report for the period ending September 30, 2013, to the Evelyn F. McKnight Brain Research Foundation on behalf of the Evelyn F. McKnight Brain Institute at UAB. The enclosed report contains information regarding the incredible work done by the Institute in the past year and adheres to the standards provided to us.

I am happy to inform you that the Department of Neurobiology and the McKnight Brain Institute at UAB continue to surpass expectations, and we are excited about the progress being made.

The Foundation's leadership in this important area of research is extraordinary and we are very grateful for your generosity and partnership with UAB, which remains invaluable.

If you have any questions or need additional information, please do not hesitate to call Daphne B. Powell, Sr. Director of Stewardship and Donor Relations, at (205) 934-1807. Please express my immense gratitude to all of the trustees of the Evelyn F. McKnight Brain Research Foundation.

Best regards,

Shirley Salloway Kahn, Ph.D.
Vice President for Development,
Alumni and External Relations

SSK/sm

Enclosure

UAB THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Knowledge that will change your world

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UAB EVELYN F. MCKNIGHT BRAIN INSTITUTE

DEPARTMENT of NEUROBIOLOGY

Annual Report

2013

J. David Sweatt, Ph.D.
Professor
Evelyn F. McKnight Endowed Chair, Department of Neurobiology
Director, Evelyn F. McKnight Brain Research Institute

University of Alabama at Birmingham
Shelby Interdisciplinary Biomedical Research Building
1825 University Boulevard
Birmingham, Alabama
35294

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McKnight Brain Research Foundation
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Institution: The Evelyn F. McKnight Brain Institute
At the University of Alabama at Birmingham

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INSTITUTE DIRECTOR'S OVERALL REPORT

ANNUAL REPORT

McKnight Brain Research Foundation
Report for Evelyn F. McKnight Brain Institute
University of Alabama at Birmingham
October 2012 – September 2013

This report was prepared by Dr. J. David Sweatt as Director of the Evelyn F. McKnight Brain Institute (MBI) and holder of the Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging at the University of Alabama at Birmingham (UAB).

This report provides an overview and summary of the activities and accomplishments for 2013 of the UAB MBI as a whole. The format is as follows. The first section is an executive summary prepared according to the suggested 17-point format provided by the McKnight Brain Research Foundation (MBRF). The second section is an overall list of the Investigators of the UAB MBI. In the third section each UAB MBI Investigator with an appointment at the faculty level has prepared his or her own individual annual report for 2013, which is in a shortened and abbreviated format and includes scientific achievements, publications, awards, and collaborations. I also have presented my own individual scientific report as Evelyn F. McKnight Endowed Chair in the final section. The appendices include copies of documents referred to in the summary.

Overview

We are of course deeply grateful that the MBRF has partnered with UAB to provide the most recent five-year commitment to the Institute, establishing a permanent endowment to support the Institute.

Highlights for the past year for the UAB MBI include:

- Overall, McKnight Investigators hold appointments across three academic schools (Medicine, Optometry and Arts & Sciences) and seven departments (Neurobiology, Neurology, Vision Science, Psychiatry & Behavioral Neurobiology, Physical Medicine & Rehabilitation, Molecular Cellular & Developmental Biology, and Psychology). A full listing of the investigators is available in Section 3.
- McKnight Investigator Dr. Lori McMahon, Jarman F. Lowder Professor of Neuroscience at UAB, was appointed as the new Associate Director of the UAB MBI. Dr. McMahon is also the Associate Director of the UAB Comprehensive Center for Healthy Aging and Director of the UAB Comprehensive Neuroscience Center. I would like to express my sincere appreciation for the prior service of Dr. John Hablitz in the Associate Director role. Dr. Hablitz served ably for seven years before retiring from the position this year. Dr. Hablitz remains as Vice Chair of Neurobiology, a McKnight Investigator, and Professor of Neurobiology.
- Dr. Selwyn Vickers, former Chair of the Surgery Department at the University of Minnesota and IOM member, was recruited as the new Dean of the School of Medicine at UAB. Dr. Sweatt served as co-chair of the search committee that recruited Dr. Vickers. Dr. Vickers' continues UAB's strong commitment to the MBI. The Dean's office has recently committed $750,000 for a new McKnight recruitment specifically in the area of cognitive epigenetics. The search for the new McKnight Investigator in this area is ongoing, with Dr. Hablitz serving as the chair of the search committee.

- The appointment last year of McKnight Investigator and former Neurology Chair Dr. Watts to the UAB President's position, and McKnight Investigator Dr. David Standaert to the Neurology Chair position, continues to promote the strategic emphasis on developing the neurosciences at UAB.
- Neuroscience has been identified as one of six strategic pillars for continued investment and expansion as part of the UAB SOM five-year strategic plan, which is in its third year of funding and implementation this year.
- Dr. Sweatt served as a member of the search committee for the new Chair of the Biology Department in the College of Arts and Sciences, helping identify and recruit the newly named Chair, Dr. Steven Austad. Dr. Austad comes to UAB from the University of Texas Health Science Center at San Antonio, where he served as professor in the Department of Cellular and Structural Biology and interim director of the Barshop Institute for Longevity and Aging Studies. Dr. Austad is a leader in aging studies; beginning January 1, 2014, he will serve as the scientific director for the American Federation for Aging Research. He also serves on the initial review board for aging grants for the Ellison Medical Foundation, the external advisory committee at the Mayo Clinic Kogod Center on Aging, and the public policy committee for the Gerontological Society of America. He received a bachelor's degree in English literature from the University of California, Los Angeles; a bachelor's degree in biology from California State University, Northridge; and a Ph.D. in biological sciences from Purdue University. Austad also writes "On Aging," a biweekly column for the San Antonio Express-News. Dr. Austad will be offered a McKnight Investigator position at UAB once he is here and settled in.
- The Civitan International Research Center based in the Department of Neurobiology continues to receive approximately $500K - $600K per year in spendable support. Much of this is used to support the Civitan research fMRI facility, which is used by several McKnight Investigators.
- This year McKnight Investigator Dr. David Sweatt received approximately $2,000,000 in additional new grant funding from DARPA, the Defense Advanced Research Projects Agency. This alternative source of research funding is especially important in today's environment with increased difficulty in obtaining traditional NIH R01 support. The project specifically funds an innovative new nanotechnology and bioinformatics-based approach to developing cognitive enhancers relevant to memory improvement in aging-related cognitive decline.
- The McKnight Institute co-sponsored a Grant Acceleration Retreat held off campus, which brought together 16 young faculty members with 15 of their senior colleagues to provide intensive mentoring and feedback on planned R01 grant applications. Dr. Steve Kaminsky, Director of the Rett Syndrome Foundation, was the keynote speaker.
- Neuroimaging is highly relevant to studies of cognitive aging, and UAB and Auburn University have initiated a collaboration to facilitate large-scale neuroimaging projects using Auburn's 7T magnet. UAB also has acquired a new state-of-the-art cyclotron to enable new PET imaging modalities related to CNS dysfunction.
- The MBI-based T32 Training Grant in Cognition and Cognitive Disorders was renewed for five years by the NIH/NINDS.
- The UAB MBI helped catalyze the establishment of the new McKnight Inter-Institutional Bioinformatics Core, now funded by the MBRF.
- A Neurodegeneration Symposium was held at UAB March 29, 2013. Five outside speakers and a number of local MBI Investigators participated in the Symposium. In addition, aging researcher Dr. Carl Cotman visited UAB this year, hosted by McKnight Investigator Dr. Erik Roberson.

1. Summary of Scientific Achievements since Last Report

As mentioned above, individual McKnight Investigator's scientific accomplishments are noted in a separate section. The next few paragraphs highlight a few of the principal discoveries from the Institute this year.

McKnight Investigator Dr. Harry Sontheimer published studies that demonstrate a role for ion channels in regulating the generation of new neurons in the adult CNS, a rapidly emerging subfield of great relevance to cellular aging. His laboratory found that the potassium channel KCa3.1 modulates neuroblast migration along the rostral migratory stream (RMS) in vivo. In the subventricular zone of the CNS, neuronal precursor cells (NPCs), called neuroblasts, migrate through the RMS to become interneurons in the olfactory bulb. Ion channels regulate neuronal migration during development, yet their role in migration through the adult RMS was unknown. To address this question, the Sontheimer lab utilized genetically engineerd mice to fluorescently label neuroblasts in the adult. Time-lapse confocal microscopy in situ showed inhibiting the potassium channel KCa3.1 prolonged the stationary phase of neuroblasts' saltatory migration, reducing migration speed by over 50%. Both migration and KCa3.1 currents could also be inhibited by blocking Ca2+ influx via transient receptor potential (TRP) channels, which, together with positive immunostaining for transient receptor potential canonical 1 (TRPC1), suggest that TRP channels are an important Ca2+ source modulating KCa3.1 activity. These studies identified a previously unrecognized role for ion channels in migration of adult NPCs. These studies, which were published in *Cerebral Cortes*, indicate that manipulation of ion channel activity may offer a strategy to minimize the decline of neurogenesis associated with aging.

McKnight Investigators Drs. Jacques Wadiche and Linda Overstreet-Wadiche collaboratively published their discovery of an important new mechanism for regulating synaptic function in the cerebellum, a finding which has significant implications for synaptic plasticity in the CNS. Their paper describing these results was published in one of the top journals in the field of neuroscience, *Neuron*. In their studies they focused on synaptic function at synapses at Purkinje neurons and discovered that "spillover"-mediated feedforward inhibition functionally segregates inhibitory interneuron activity. Neurotransmitter "spillover" represents a novel form of neural transmission not restricted to morphologically defined synaptic connections. Their data demonstrates how glutamate release from single neurons modulates excitability of neighboring cells, thus expanding the influence of certain types of neurons on cerebellar cortical activity in a manner not predicted by anatomical connectivity. Overall, these mechanisms help to regulate the gating of information into and out of the cerebellar cortex, an area critically important for certain types of long-term memory formation.

Finally, McKnight Investigator Dr. Erik Roberson published a novel finding this year in the *Journal of Neuroscience* related to the cognitive disorder frontotemporal dementia. Frontotemporal dementia (FTD) is an aging-related neurodegenerative disease with hallmark deficits in social and emotional function. Heterozygous loss-of-function mutations in GRN, the progranulin gene, are a common genetic cause of the disorder, but the mechanisms by which progranulin haploinsufficiency causes neuronal dysfunction in FTD are unclear. The Roberson lab investigated progranulin heterozygous (Grn(+/-)) mice, which model progranulin haploinsufficiency. They found that Grn(+/-) mice developed age-dependent social and emotional deficits potentially relevant to FTD. However, unlike Grn(-/-) mice, behavioral deficits in Grn(+/-) mice occurred in the absence of gliosis or increased expression of tumor necrosis factor-α. Instead, we found neuronal abnormalities in the amygdala, an area of selective vulnerability in FTD, in Grn(+/-) mice. Their findings indicate that FTD-related deficits resulting from progranulin haploinsufficiency can develop in the absence of detectable gliosis and neuroinflammation, thereby

dissociating microglial activation from functional deficits and suggesting an important effect of progranulin deficiency on neurons.

2. Publications in Peer Reviewed Journals

Investigators at the UAB MBI published a total of 93 research papers, reviews and commentaries in peer-reviewed journals. The journals in which these papers were published included many of the leading scientific journals in the discipline of neuroscience: *Nature Neuroscience, Neurobiology of Aging, Journal of Neuroscience, Neuron, J. Neurochemistry,* etc.

3. Publications (Other)

- **Books**

  Dr. David Sweatt was lead Editor on a book in 2013: *Epigenetic Regulation in the Nervous System; Basic Mechanisms and Clinical Impact.* The volume was published by Elsevier in February 2013.

  Dr. Farah Lubin is Co-editing the book "Epigenetics and Neuroplasticity: Evidence and Debate. This volume will be published by Elsevier in 2014.

  Dr. Robin Lester is Co-editing the book "Nicotinic Receptors", which will be published by Springer in 2014.

- **Book Chapters**

  Investigators at the UAB MBI published a total of nine book chapters.

4. Presentations at Scientific Meetings (Also Includes Invited Research Seminars)

Investigators at the UAB MBI presented a total of 73 scientific presentations. UAB MBI Investigators presented their work at numerous prestigious institutions including: Univ. of Michigan, Vanderbilt, Northwestern, Washington Univ., the American College of Neuropsychopharmacology, three Gordon Conferences and DARPA. MBI Investigators also presented their work at prominent national meetings including those sponsored by the Society for Neuroscience, the Molecular and Cellular Cognition Society, the American Epilepsy Society, and the American Speech-Hearing Association.

Please note that the UAB MBI sponsored a number of prominent scientists to come visit UAB and the MBI and give research presentations concerning their own work. A list of MBI-sponsored speakers for 2013 is appended to this report.

5. Presentations at Public (Non-Scientific) Meetings or Events

Investigators at the UAB MBI presented 12 public-forum presentations in 2013. Dr. David Sweatt was interviewed for NPR's *All Things Considered*, where he discussed the role of epigenetic mechanisms in memory and memory dysfunction.

6. Awards and Honors

Investigators at the UAB MBI received several national-level awards and honors in 2013. Dr. Sweatt was the recipient of the Civitan International Research Center Outstanding Scientist Award. Dr. Sweatt was also featured in the 25th Anniversary issue of the journal *Neuron* for having the most highly cited paper in that journal for the year 2007. Dr. Harald Sontheimer was honored with an invitation to give a major

public lecture at the Society for Neuroscience Annual Meeting. Vlad Parpura was elected as a Fellow of the Academy Europea. Ten MBI faculty served on NIH Study Sections, and six faculty members served as journal editors or on editorial boards.

7. Faculty

Three new faculty members joined the MBI in 2013. Dr, Paul Gamlin moved to the MBI from the School of Optometry, where he was previously the Chair of Vision Sciences. Paul investigates the systems neuroscience of vision and vision disorders. We also recruited Dr. Kazu Nakazawa from the NIMH. Dr. Nakazawa works on epigenetics and cognitive function and is Associate Professor in the Department of Psychiatry. Based in the Neurology Department, Dr. Erobogene Ubogu, M.D., Professor and Director, Division of Neuromuscular Disorders, also joined the MBI last year. All three of these Investigators are based on the 11th floor of the Shelby Building.

As a result of philanthropic gifts to the institution, there are two vacant endowed chairs that are currently housed in the Department of Psychiatry & Behavioral Neurobiology, the *Geropsychiatry Research Chair* and the *F. Cleveland Kinney Endowed Chair in Geriatric Psychiatry.* The market share of each endowment exceeds $1.5 million, and both are available for the recruitment of senior level, star-quality faculty engaged in the investigation and treatment of memory disorders in the elderly. The department's chair and members of the UAB MBI steering committee have agreed to utilize proceeds from both endowments and future memory research-related endowments in Neurology and Psychiatry for future UAB-MBI recruitments. Recruited faculty will receive joint appointments in Psychiatry and Neurology and will also be appointed McKnight Investigators. The two searches for the Kinney Chair and the Geropsychiatry Chair are currently ongoing.

In the important area of brain imaging, an emerging UAB/Auburn neuroimaging collaboration continues to be an important and critical opportunity for growth. This collaboration provides an unprecedented opportunity to facilitate large scale neuroimaging projects using Auburn's 7T magnet. The two UAB/Auburn retreats in 2012 and 2013 led to at least eight NIH/NSF grant submissions and the first collaborative publication that likely will have high impact in the field of autism research (Deshpande G, Libero LE, Sreenivasan KR, Deshpande HD, Kana RK. Identification of neural connectivity signatures of autism using machine learning. *Front Hum Neurosci.* 2013*).* Efforts are underway to develop an Alabama Imaging Consortium spear headed by the neuroscience community together with Auburn, with anticipated additional membership with UAH, Univ of South AL., and eventually with institutions in neighboring states. An opportunity exists to be the major imaging network in the South. The success of this consortium will be largely dependent upon securing a new research only fMRI scanner to replace the aging facility in the Civitan International Research Center. This scanner will support the research of investigators across many UAB schools and several McKnight Investigators.

In the area of Radiology and brain imaging, Dr. Bob Kessler, a clinician-scientist, neuro-radiologist and PET imager from Vanderbilt, has joined UAB as a Professor in the Radiology Department. In addition, Dr. Mark Bolding, a nuclear physics and imaging specialist, has joined Radiology this past year as well. Moreover, in the Neurology Department search committees have been working on endowed chairs in PD and AD (Strain and Warren Chairs, respectively), and it is anticipated that at least one of these slots will be filled with an clinical neuroimaging specialist.

Ongoing Primary Recruitment based in the MBI:

As already mentioned, as part of the new Strategic Plan for the School of Medicine, the Dean approved an additional new recruitment as part of the MBI endeavor in 2013. Thus we are undertaking a targeted recruitment in the area of neuro-epigenetics and cognitive function and plan to recruit an assistant professor, NIH-funded investigator for this position. The Dean's office has committed $750,000 for a new McKnight recruitment specifically in the area of cognitive epigenetics. The search for the new McKnight Investigator in this area is ongoing, with Dr. Hablitz serving as the Chair of the search committee. The lab space for this recruit will be on the 9th floor of the Shelby Building.

8. Trainees, Post Doctoral, Pre-Doctoral, Other

A. The labs of MBI faculty currently involve the training of 31 graduate students and 18 post-doctoral fellows.

B. Recruiting Initiatives for 2013

As described above we will continue ongoing searches for senior-level MBI Investigators, several with an endowed chair position, in 2014. In addition, as described above as part of the new Strategic Plan for the School of Medicine, the Dean has approved an additional new recruitment as part of the MBI endeavor for 2014. We are undertaking a targeted recruitment in the area of neuro-epigenetics and cognitive function and plan to recruit an assistant professor, NIH-funded investigator for this position.

9. Clinical/Translational Programs

A. New Programs

The new initiatives in Neuroimaging were described above, so they will not be reiterated here.

In addition, Dr. Sweatt's new DARPA project is translational, relating to the identification of novel constructs for cognitive enhancement.

B. Update on Existing Clinical Studies

Not applicable

C. New Treatments

Not applicable

D. Drug Trials, Future Research and/or Clinical Initiatives

Dr. Harry Sontheimer's laboratory is executing a new clinical trial for the use of sulfasalazine in glioblastoma-related epileptogenesis, funded by the UAB CCTA. This exciting new avenue of clinical research is based on Sontheimer's recent discovery of the utility of this approach in animal studies, which were published last year (2012) in *Nature Medicine*.

10. Technology

A. Patent Applications

Dr. Sweatt's laboratory filed a provisional patent application for histone H2A.Z as a novel target for memory enhancement.

B. Revenue Generated from Technology
Not applicable

11. Budget Update

A full financial report is included as Section 2.

12. Educational Programs Focusing on Age Related Memory Loss

A. Scientific
The MBI was instrumental in establishing the new undergraduate honors Neuroscience major at UAB. It is the only program like it in the country—a joint offering between the undergraduate College of Arts and Sciences and the School of Medicine. This will be a recruiting platform for future medical and graduate students interested in memory research. For example, several of our 2013/2014 graduates from this program are currently in (or applying to) medical school or MD/PhD programs at UAB.

B. Public
Not applicable

13. Collaborative Programs with other McKnight Institutes, Institutions and Research Programs

UAB MBI Investigators have identified a total of 10 inter- and intra-MBI collaborations, representing all three other MBIs. More details on these collaborations are noted in the section with the individual investigators' data.

14. Collaborative Programs with Non McKnight Institutes, Institutions and Research Programs

UAB MBI Investigators have identified a total of 78 inter- and intra-institutional collaborations locally, nationally and internationally.

15. Were any funds used for a Prohibited Purpose during the report period?

No

16. Do you recommend any modification to the Purpose or mandates in the Gift Agreement?

None

17. Did all activities during the report period further the Purpose?

Yes

18. Briefly describe your progress compared to the original goals.

The UAB MBI is progressing in accordance with the original strategic plan for the Institute, which was outlined to the Board when the UAB MBI was approved for renewed funding in 2009. We have focused on recruiting new faculty members as was originally proposed. The quality of the new

investigators has been uniformly excellent. The current membership of the UAB MBI comprises 30 Investigators, with a nicely diverse distribution of assistant, associate, and full professors including five current or former department chairs. Approximately two-thirds (21/30) of the Investigators are new appointees to the Institute since 2006, an exceptional expansion given the state of the economy over that timeframe.

Another exciting development over the 2013 funding period was that the President, Dr. Ray Watts, was recruited from within UAB, and this ensures continuity of UAB programmatic initiatives. Dr. Watts has assured me that all UAB commitments to the UAB MBI will be honored and upheld throughout the transition and beyond. Dr. Watts is a strong supporter of the Institute and plans to continue to emphasize the Neurosciences as a strategic priority for the School of Medicine, and as described above, he was previously Chair of the Neurology Department and Dean of the School of Medicine at UAB.

As described above, as part of the new Strategic Plan for the School of Medicine, new SOM Dean Selwyn Vickers has approved an additional new recruitment as part of the MBI endeavor for 2014. We are undertaking a targeted recruitment in the area of neuroepigenetics and cognitive function, and plan to recruit an NIH-funded investigator for this position.

We also are progressing nicely in developing our research infrastructure as planned. The 11th floor of the Shelby building, i.e., the final third of the MBI physical plant, was completed and we have begun occupancy with Drs. Roberson, Lubin, Gamlin, Nakazawa, and Ubogu occupying new labs there. Both the Neurology and Psychiatry Departments are undertaking collaborative recruitments with the MBI to recruit additional new MBI-relevant professors into the MBI 11th floor. Two important Core laboratories, the *MBI Mouse Behavioral Assessment Core* and the *McKnight Rodent Physiological Assessment Core*, are in operation and provide an excellent platform for inter-Institute collaborations. These two Cores provide excellent opportunities for expanded expertise among UAB MBI Investigators in utilizing cutting-edge genetically engineered mouse models relevant to cognitive aging. In addition, these two cores capitalize on scientific strengths of the UAB MBI and allow for collaborative opportunities with the other MBIs, which in general are not historically strong in the area of mouse genetic engineering. Finally, as already mentioned, the new McKnight Inter-Institute Epigenetics and Bioinformatics Initiative provides a powerful platform for collaboration and cross-fertilization in the area of the epigenetics of cognitive aging.

19. Please describe any negative events (loss of personnel, space, budget, etc.) that occurred during the report period and the possible impact on carrying out the Gift Agreement.

None

20. Please provide any general comments or thoughts not covered elsewhere – a response is not required. Please respond only if you would like to add something not otherwise covered elsewhere.

No additional comments.

21. Signature, date, and title of person submitting report

1/7/14

J. David Sweatt, Ph.D.
Professor
Evelyn F. McKnight Endowed Chair
Director, Evelyn F. McKnight Brain Institute
Chairman, Department of Neurobiology
UAB School of Medicine

Date

FINANCE

McKnight Brain Research Foundation

Financial Summary Format:

(Institute) and/or (Endowed Chair)

Summary for 12 months ended 09/30/13

Account Name: Evelyn F. McKnight Brain Institute Endowed Support Fund

	Beginning Balance on 10/01/2012	$ 3,106,315
B.	Investment Growth	$ 370,353
C.	Distributions	$ 188,781
D.	Additional Contribution	$ 1,000,000
E.	Ending Balance on 09/30/2013	$ 4,287,887

DEFINITIONS

DISTRIBUTION is the money transferred from the account to the spendable/operating account for the designated use.

BALANCE is the market value of the account as of the first or last day of the reporting year.

ADDITIONAL CONTRIBUTION is additional contribution by MBRF, the reporting institution, match etc.

INVESTMENT GROWTH (Loss) is the total undistributed interest, dividends, and realized and unrealized gains and losses.

BALANCE is the value of the account's corpus including all contributions, and applicable state match monies as of the date indicated.

McKnight Brain Research Foundation

Financial Summary Format:

(Institute) and/or (Endowed Chair)

Summary for 12 months ended 09/30/13

Account Name: Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging

	Beginning Balance on 10/01/2012	$ 1,438,744
B.	Investment Growth	$ 133,587
C.	Distributions	$ 69,969
D.	Additional Contribution	$ 0
E.	Ending Balance on 09/30/2013	$ 1,502,362

DEFINITIONS

DISTRIBUTION is the money transferred from the account to the spendable/operating account for the designated use.

BALANCE is the market value of the account as of the first or last day of the reporting year.

ADDITIONAL CONTRIBUTION is additional contribution by MBRF, the reporting institution, match etc.

INVESTMENT GROWTH (Loss) is the total undistributed interest, dividends, and realized and unrealized gains and losses.

BALANCE is the value of the account's corpus including all contributions, and applicable state match monies as of the date indicated.

MCKNIGHT BRAIN INSTITUTE AT UAB
2013 ANNUAL REPORT
FINANCIAL SUPPLEMENT

In compliance with Section 6.3 of the gift agreement between the Evelyn F. McKnight Brain Research Foundation (MBRF) and UAB, this income and distributions report is provided as a supplement to the annual report on the McKnight Brain Institute (MBI) at UAB.

In compliance with Sections 9.2.1.2 and 10.3 of said gift agreement, UAB ensures that the contributions from the MBRF and the distributions from the endowed chair have been used solely for the purpose of promoting research and investigation of the brain in the fundamental mechanisms that underlie the neurobiology of memory with a clinical relevance to the problems of age-related memory loss.

In compliance with Sections 7, and 9.1.5.3, of said gift agreement, UAB ensures that no portion of the contributions received from the MBRF or distributions from the endowed chair were used directly or indirectly to construct, purchase, improve, or maintain real property; to pay overhead or indirect costs; or for anything other than direct expenditures in furtherance of the purpose of the fund.

Fiscal Year	Item	MBRF Deposits	MBRF Chair, Gift and Endowment Distributions **	MBRF Funds Expended or Encumbered	Matching Funds Expended or Encumbered Endowment Distributions	Matching Funds Expended or Encumbered
Grand Totals	**MBRF Prior Agreement**	**$ 6,000,000**	**$ 598,150**	**$ 5,911,757**	**$ -**	**$ 12,357,436**
2010	**MBRF New Agreement**	**$ 1,000,000**		$ 1,000,000		
		$ 500,000				
	Sweatt Salary			$ 81,617		
	Rumbaugh Salary			$ 26,966		
	L.Wadiche Salary			$ 72,485		
	J. Wadiche Salary			$ 78,526		
	V. Parpura Salary			$ 156,829		
	K. Visscher Salary			$ 117,192		
	R. Lester Salary			$ 12,594		
	F. Lubin Salary			$ 11,677		
	J. Hablitz Salary			$ 30,723		
	K. Speed Salary			$ 24,455		
	V. Hixon Salary			$ 6,734		
	I. Rivera Salary			$ 4,851		
	M. Kilgore Salary			$ 26,245		
	One Pilot Project			$ 25,000		
	Evelyn F. McKnight Interdisciplinary Retreat			$ 10,808		$ 4,000
	V. Hixon and M. Kilgore Travel			$ 2,833		
	M. Olsen Start Up Package					$ 756,000
	G. King Start Up Package			$ 35,000		$ 665,000
	F. Cleveland Kinney Endowed Chair in Geriatric Psychiatry*				$ 74,014	$ 1,500,050
	Geropsychiatry Research Chair*				$ 102,544	$ 1,222,896
	Patsy W. and Charles A. Collat Scholar in Neuroscience - D. Geldmacher					$ 500,000
	Dixon Scholar in Neurology - M. Gray					$ 245,000

MCKNIGHT BRAIN INSTITUTE AT UAB
2013 ANNUAL REPORT
FINANCIAL SUPPLEMENT

Fiscal Year	Item	MBRF Deposits	MBRF Chair, Gift and Endowment Distributions **	MBRF Funds Expended or Encumbered	Matching Funds Expended or Encumbered Endowment Distributions	Matching Funds Expended or Encumbered
	Parpura Start Up Package			$ 40,000		
	F. Lubin Start Up Package			$ 8,750		
	J. Wadiche Start Up Package			$ 55,000		
	L. Wadiche Start Up Package			$ 10,000		
	MBRF Chair Spendable Earnngs		$ 83,499			
	MBRF Gift Earnings **		$ 61,169			
	MBRF Institute Spendable Earnings		$ 55,984			
	Previous MBRF Agreement Residual		$ 409,277			
FY 10 Totals		**$ 1,500,000**	**$ 609,929**	**$ 1,838,285**	**$ 176,558**	**$ 4,892,946**
2011	**MBRF New Agreement**	**$ 1,000,000**		$ 1,000,000		
		$ 500,000				
	Sweatt Salary			$ 74,605		
	L.Wadiche Salary			$ 74,297		
	J. Wadiche Salary			$ 80,489		
	V. Parpura Salary			$ 156,829		
	K. Visscher Salary			$ 103,503		
	F. Lubin Salary			$ 55,208		
	J. Hablitz Salary			$ 30,723		
	K. Speed Salary			$ 12,505		
	V. Hixon Salary			$ 6,532		
	S. Hyman Salary			$ 4,924		
	G. Kass Salary			$ 12,469		
	S. Ewell Salary			$ 6,417		
	Evelyn F. McKnight Interdisciplinary Retreat			$ 10,483		$ 5,000
	F. Cleveland Kinney Endowed Chair in Geriatric Psychiatry *				$ 67,724	
	Geropsychiatry Research Chair*				$ 93,795	
	Warren Family Scholar					$ 600,000
	Patsy W. and Charles A. Collat Scholar in Neuroscience - D. Geldmacher					$ 300,000
	S. Phillips Development Grant					$ 10,000
	SOM Additional Support					$ 50,000
	Parpura Start Up Package			$ 25,000		
	J. Wadiche Start Up Package			$ 11,760		
	L. Wadiche Start Up Package			$ 13,290		
	A. Theibert - Support			$ 15,000		
	R. Lester - Support			$ 20,000		
	MBRF Chair Spendable Earnings		$ 79,969			
	MBRF Gift Earnings **		$ 59,606			
	MBRF Institute Spendable Earnings		$ 100,316			
	Previous MBRF Agreement Residual		$ 317,881			
FY 11 Totals		**$ 1,500,000**	**$ 557,772**	**$ 1,714,034**	**$ 161,519**	**$ 965,000**

MCKNIGHT BRAIN INSTITUTE AT UAB
2013 ANNUAL REPORT
FINANCIAL SUPPLEMENT

Fiscal Year	Item	MBRF Deposits	MBRF Chair, Gift and Endowment Distributions **	MBRF Funds Expended or Encumbered	Matching Funds Expended or Encumbered Endowment Distributions	Matching Funds Expended or Encumbered
2012	**MBRF New Agreement**	**$ 1,000,000**		$ 1,000,000		
	Sweatt Salary			$ 74,432		
	L.Wadiche Salary			$ 77,984		
	J. Wadiche Salary			$ 81,004		
	V. Parpura Salary			$ 153,611		
	K. Visscher Salary			$ 89,463		
	F. Lubin Salary			$ 93,245		
	J. Hablitz Salary			$ 30,092		
	K. Speed Salary			$ 13,601		
	V. Hixon Salary			$ 6,528		
	G. King Salary			$ 33,836		
	S. Ewell Salary			$ 14,917		
	Evelyn F. McKnight Interdisciplinary Retreat			$ 11,938		$ 3,062
	F. Cleveland Kinney Endowed Chair in Geriatric Psychiatry*				$ 65,269	
	Geropsychiatry Research Chair*				$ 90,396	
	Warren Family Scholar*				$ 39,775	$ 1,000,000
	Jarman F. Lowder Endowed Professorship in Neuroscience - L. McMahon*				$ 25,723	$ 505,519
	Virginia B. Spencer Endowed Professorship in Neuroscience - E. Roberson*				$ 24,041	$ 500,000
	Patsy W. and Charles A. Collat Scholar in Neuroscience - D. Geldmacher*				$ 14,125	
	L. Dobrunz - CCTS Pilot Project					$ 15,000
	SOM Additional Support					$ 50,000
	Evelyn F. McKnight Advertisement			$ 4,463		
	L. Dobrunz - Pilot Project			$ 52,000		
	A. Theibert - Support			$ 10,000		
	R. Lester - Support			$ 5,000		
	D. Sweatt - Travel			$ 771		
	V. Hixon - Travel			$ 1,214		
	MBRF Chair Spendable Earnngs		$ 73,369			
	MBRF Gift Earnings **		$ 6,546			
	MBRF Institute Spendable Earnings		$ 145,708			
	Previous MBRF Agreement Residual		$ 174,079			
FY 12 Totals		**$ 1,000,000**	**$ 399,702**	**$ 1,754,099**	**$ 259,329**	**$ 2,073,581**

MCKNIGHT BRAIN INSTITUTE AT UAB
2013 ANNUAL REPORT
FINANCIAL SUPPLEMENT

Fiscal Year	Item	MBRF Deposits	MBRF Chair, Gift and Endowment Distributions **	MBRF Funds Expended or Encumbered	Matching Funds Expended or Encumbered Endowment Distributions	Matching Funds Expended or Encumbered
2013	**MBRF New Agreement**	**$ 1,000,000**		**$ 1,000,000**		
	Sweatt Salary			$ 75,262		
	L.Wadiche Salary			$ 56,980		
	J. Wadiche Salary			$ 81,979		
	V. Parpura Salary			$ 88,679		
	K. Visscher Salary			$ 79,244		
	J. Hablitz Salary			$ 30,233		
	K. Speed Salary			$ 11,311		
	V. Hixon Salary			$ 6,531		
	Evelyn F. McKnight Interdisciplinary Retreat			$ 11,043		$ 4,500
	F. Cleveland Kinney Endowed Chair in Geriatric Psychiatry*				$ 66,963	
	Geropsychiatry Research Chair*				$ 92,742	
	Warren Family Scholar*				$ 75,495	
	Jarman F. Lowder Endowed Professorship in Neuroscience - L. McMahon*				$ 26,395	
	Virginia B. Spencer Endowed Professorship in Neuroscience - E. Roberson *				$ 24,664	
	Patsy W. and Charles A. Collat Scholar in Neuroscience - D. Geldmacher *				$ 19,400	
	SOM Additional Support					$ 275,000
	SOM McKnight Recruitment					$ 750,000
	L. Dobrunz - Pilot Project			$ 7,000		
	A. Theibert - Support			$ 35,000		
	V. Hixon - Travel			$ 1,084		
	MBRF Chair Spendable Earnngs		$ 69,969			
	MBRF Gift Earnings **		$ 3,741			
	MBRF Institute Spendable Earnings		$ 188,781			
	Previous MBRF Agreement Residual		$ 10,000			
FY 13 Totals		**$ 1,000,000**	**$ 272,491**	**$ 1,484,346**	**$ 305,659**	**$ 1,029,500**
Grand Totals		**$ 5,000,000**	**$ 1,839,894**	**$ 6,790,764**	**$ 903,065**	**$ 8,961,027**
	*denotes encumbered endowment match					
	**Original MBRF gift was set up as an interest bearing account. These items account for the interest over time ($279,608 in the prior agreement and $127,321 in the current agreement).					

MCKNIGHT BRAIN INSTITUTE AT UAB
2013 ANNUAL REPORT
FINANCIAL SUPPLEMENT

Financial Schedule for the Evelyn F. McKnight Brain Institute at UAB

	MBRF CONTRIBUTION		*UAB MATCH*		
Date	**Endowment**	**Operations**	**Endowment**	**Operations**	**Endowment Distribution**
10/1/2009	$ 1,000,000	$ 500,000	$ 2,722,946	$ 2,170,000	$ 316,041
10/1/2010	$ 1,000,000	$ 500,000	$ -	$ 365,000	$ 341,804
10/1/2011	$ 1,000,000		$ 500,000	$ 100,000	$ 480,918
10/1/2012	$ 1,000,000		$ 2,005,519	$ 68,062	$ 581,128
10/1/2013	$ 1,000,000			$ 1,029,500	
Total	**$ 5,000,000**	**$ 1,000,000**	**$ 5,228,465**	**$ 3,732,562**	**$ 1,719,891**

Projected FY 13-14 Evelyn F. McKnight Brain Institute Budget					
Category	**McKnight Operations Amount**	**McKnight Endowment Spendable Earnings Amount**	**McKnight Endowed Chair Spendable Earnings Amount**	**UAB Encumbered Endowment Spendable Earnings Amount**	**Totals**
Salary and Benefits	$0	$203,121	$72,348		**$275,469**
Other McKnight Brain Institute Support					**$0**
F. Cleveland Kinney Endowed Chair in Geriatric Psychiatry				$66,963	**$66,963**
Geropsychiatry Research Chair				$92,742	**$92,742**
Warren Chair				$75,495	**$75,495**
Lowder Chair				$26,395	**$26,395**
Collat Chair				$19,400	**$19,400**
Spencer Chair				$24,664	**$24,664**
Total	**$0**	**$203,121**	**$72,348**	**$305,659**	**$581,128**

Department of Neurobiology
Active Extramural Funding
Fiscal year 2013-2014

		Type of Grant and Grant Number					Current Annual			All Years		
Faculty	Role	Percent Effort		Agency	Grant Period	Title	Direct Costs	F & A	Total	Direct Costs	F & A	Total
Brenner	PI	30%	P01 NS042803	NIH-Wisconsin	07/01/08-06/30/14- NCE	Alexander Disease: Cellular and Molecular Mechanisms	25,000	11,625	36,625	774,810	348,665	1,123,475
Brenner	Core Director	10%	P30 HD038985-07	NIH	07/01/08-06/30/14 -NCE	Intellectual Developmental Disabilities Research Center - Core B	12,000	5,580	17,580	847,472	382,134	1,229,606
Dobrunz	PI	50%	R01 MH098534-01	NIH	07/01/12 - 06/30/17	Interneuron Dysfunction Alters the Dynamics of the Inhibition Excitation Balance	240,000	111,600	351,600	1,250,000	581,250	1,831,250
Hablitz	PI	5%	P30 NS047466	NIH NINDS	02/1/11-01/31/16	UAB Neuroscience Core Center	484,149	149,434	633,583	2,420,745	1,125,795	3,546,540
King	PI	75%	R00 AG034989	NIH	07/01/11-06/30/14	Klotho Regulation and Aging	165,418	76,919	242,337	496,320	230,788	727,108
King	Pi	0%	UAB Spore Grant	Spore Pilot Project	10/01/12-09/30/14	Control of Glia Growth and Migration by Klotho	40,000	-	40,000	80,000	-	80,000
Lubin	PI	50%	R01 MH097909-01	NIH	07/01/12-06/30/17	Chromatin Remodeling Mechanisms of Gene Transcription in Memory	262,224	121,934	384,158	1,402,908	676,762	2,079,670
Lubin	PI	0%	Internal Grant	UABHSF	03/01/12-02/28/14	High Resolution Melt Instrument for the Creation of an Epigenetics Research Instrument	26,265	-	26,265	26,265	-	26,265
Parpura, Vladimir	PI	20%	R21 HD078678-01	NIH	12/01/13-11/30/15	The Role of Astroglia in the Enteric Nervous System and Gut Function	150,000	70,500	220,500	275,000	129,250	404,250
Parpura, Vladimir	PI	8%	CBET-0943343	NSF	09/01/09-08/31/14 - NCE	Cyberplasm - An autonomous Micro-robot constructed using Synthetic Biology	90,000	41,850	131,850	522,567	242,921	765,488
Pozzo-Miller	PI	20%	R01 NS065027	NIH	02/01/10-01/31/15	MECP2 Mutations and BDNF Signaling: Shared Mechanisms of Rett and Autism	218,750	101,719	320,469	1,093,750	508,595	1,602,345
Pozzo-Miller, Lucas	PI	0%	R01 NS065027 Adminstrative Supplement	NIH	06/01/13-01/31/15	MECP2 Mutations and BDNF Signaling: Shared Mechanisms of Rett and Autism	68,105	31,895	100,000	68,105	31,895	100,000
Pozzo-Miller, Lucas	PI	20%	New R21 Grant	NIH	12/01/12-11/30/14	Reversing BDNF Impairments in Rett Mice with TRPC Channel Activators	175,000	81,375	256,375	275,000	127,875	402,875
Pozzo-Miller	Core Director	20%	P30 HD038985-07	NIH-NICHD	07/01/08-06/30/14 - NCE	Intellectual Developmental Disabilities Research Center - Core C	-	0	-	859,631	387,618	1,247,249
Pozzo-Miller - LI	PI		Postdoctoral Fellowship	IRSF	01/01/12-12/31/13	A New Approach for Treating Rett Sydrome: Restoration of Interneuron Function by BDNF	45,455	4,545	50,000	90,910	9,090	100,000
Sontheimer	PI		R01 NS036692 CR	NIH NINDS	04/01/08-03/31/14 - NCE	The Role of Ion Transport in Glioma Cell Migration, Proliferation, and Apoptosis	100,000	46,500	146,500	1,093,750	492,190	1,585,940
Sontheimer	PI		R01 NS031234 CR	NIH NINDS	03/1/07-11/30/13 - NCE	Properties and Function of Glia Ion Channels	60,000	27,900	87,900	1,093,750	492,190	1,585,940

Sontheimer	PI		R01 NS082851	NIH-NINDS	09/30/13-08/31/17	Glioma-Astrocyte Vascular Interactions	218,750	102,813	321,563	875,000	411,252	1,286,252
Sontheimer	PI		R01 NS052634	NIH-NINDS	09/30/11-07/31/16	Amino-acid Transport and the Biology of Human Gliomas	218,750	101,719	320,469	1,093,750	508,595	1,602,345
Sontheimer/ Robel	PI/Mentor		Postdoctoral Fellowship	Epilepsy Foundation	01/01/13-12/31/13	The Role of Astrogliosis in Tumor-Associated Epilepsy	45,000	0	45,000	45,000	-	45,000
Sontheimer/ Robel	PI/Mentor		ABTA Grant	ABTA	07/01/13-06/30/15	Glutamate Release Promotes Tumor Growtha nd Tumor-Associated Epilepsy	50,000	-	50,000	100,000	-	100,000
Sweatt	PI	15%	R01 MH057014 CR	NIH-NIMH	08/01/10-07/31/15	Biochemical Mechanisms of Long-Term Potentiation	303,071	140,928	443,999	1,649,600	767,065	2,416,665
Sweatt	PI	15%	R01 MH091122	NIH-NIMH	06/03/11-03/31/16	DNA Methylation in Memory Formation	240,000	111,600	351,600	1,250,000	561,250	1,831,250
Sweatt	PI	8%	1R01 NR012686-01	NIH-University of Maryland-Baltimore	9/28/10 - 07/31/15	Epigenetic Modifications of BDNF and trkB Genes Underlie Pain Plasticity	92,150	42,850	135,000	593,695	276,070	869,765
Sweatt	PI	10%	HR0011-14-1-0001	DARPA	10/01/13-11/14/14	In Vivo Nanoplatforms for Epigenetic Enhancement of Memory - Phase II	564,975	179,688	744,633	564,975	179,688	744,633
Sweatt	PI	25%	FA8650-13-C-7339	DARPA	06/17/13-06/16/14	A Whole Epigenome Approach to Identify Novel Targets for Nano-Pharmacologic Memory Enhancement	984,399	426,752	1,411,151	984,399	426,752	1,411,151
Sweatt	PI	5%		DARPA	06/04/13-07/28/14	Epigenetic Based Neurotherapeutics	127,412	59,247	186,659	127,412	59,247	186,659
Sweatt	PI	8%	Ellison Foundation	Ellison Foundation	10/01/10-09/30/14	An Epigenetic Hypothesis of Cognitive Aging	150,000	69,750	219,750	600,000	279,000	879,000
Sweatt	PI		T32NS061788 CR	NIH	07/01/13-06/30/18	Training Program in the Neurobiology of Cognition and Cognitive Disorders	213,792	13,071	226,863	1,095,450	65,355	1,160,805
Day/Sweatt	PI/Mentor	75%	New K99/R00 Grant	NIDA	07/15/13-06/30/14	Epigenetic Regulation of cocaine-Induced Neuroadaptations	101,441	8,115	109,556	609,605	246,951	856,556
Visscher, Kristina	PI	15%	Foundation Grant	Dana Foundation	01/01/11-12/31/13	Age-Related Macular Degeneration: The Effect of Training on Visusal Performance and Neural Activity	85,361	-	85,361	199,542	-	199,542
Wadiche, Jaqcues	PI	35%	R01 NS065920	NIH-NINDS	06/01/09-05/31/14	Timing of Neurotransmitter Release	218,750	101,354	320,104	1,093,750	506,770	1,600,520
Wadiche, Linda	PI	40%	R01 NS064025	NIH	02/01/09-01/31/14	Newborn Neurons in the Adult Hippocampal Network	218,750	98,438	317,098	1,093,750	492,188	1,585,938
Wadiche, Linda/ Chancey	PI/Mentor		New F31 Grant	NIH-NINDS	01/01/12-12/31/13	Experience-Dependent Synaptogenesis in Adult Generated Neurons	34,200	-	34,200	102,600	-	102,600

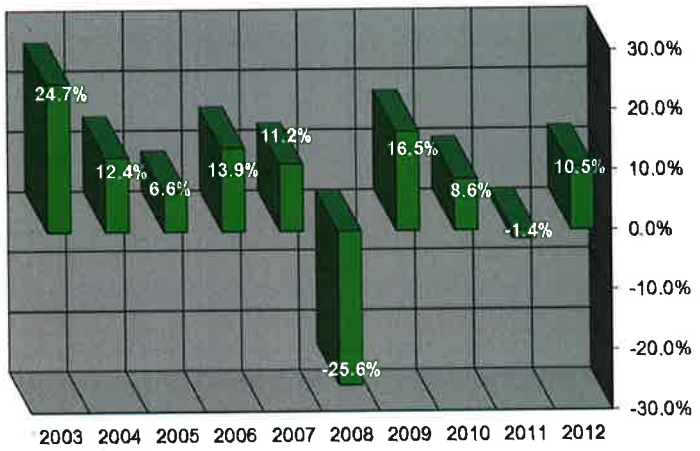
Wilson	PI	50%	R01 NS047533	NIH	02/1/10-12/31/14 -	The Role of Usp 14 in Regulating Neuronal Function	218,750	101,719	320,469	1,093,750	508,595	1,602,345
Wilson, Scott	PI		1R21 NS074456	NIH-NINDS	09/01/11 - 08/31/14- NCE	Enhancement of Proteasome to Facilitate Protein Accumulation in Chronic Neurological Diseases	125,000	47,430	172,430	275,000	127,875	402,875
					Total Active Grants		6,372,917	2,488,850	8,861,647	26,118,261	11,183,671	37,321,902

Investment Report

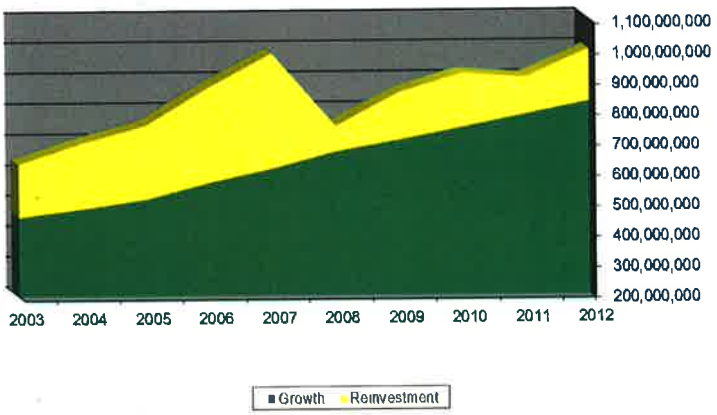
- Created in 1978, the University of Alabama Pooled Endowment Fund (UAPEF) is managed by the Chancellor's Office and is overseen by the Investment Committee of The Board of Trustees.
- As of December 31, 2012, the market value of the UAPEF was $1.003 billion. Of this amount, 34.2%, or $342.6 million, is attributable to UAB and the Hospital.
- The UAPEF had a ten-year annualized investment return of 6.8% for the period ending December 31, 2012, compared to a return of 10.6% for the custom index.*
- The Investment Committee oversees investment activities, monitors performance of professional money managers, and ensures the prudent control of the investment of funds.
- Participants include all three campuses of the University of Alabama System along with related foundations.
- The Board seeks superior investment returns through professional money management. Assets of the UAPEF are managed by 40 professional investment firms.
- The UAPEF also utilizes an investment consultant, Cambridge Associates, with expertise in investment policy development, spending policy analysis, manager evaluation and selection, and performance evaluation.

* The custom index is a blend of indices that closely represents the actual UAPEF portfolio and is used as a benchmark for comparison, both in terms of return and risk.

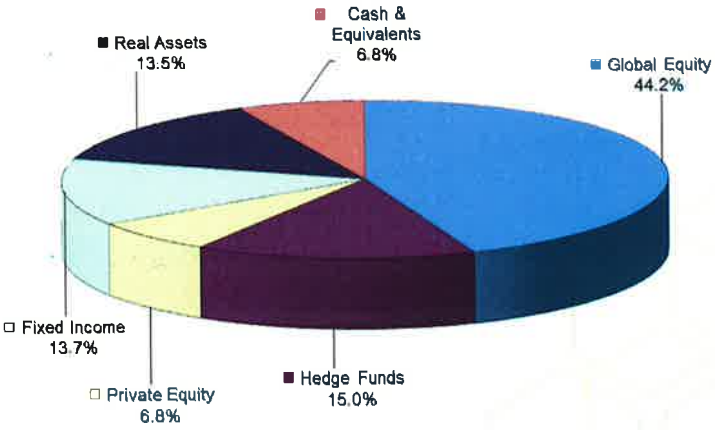
UAPEF Rates of Return
December 31, 2003 - December 31, 2012



UAPEF Growth in Endowment Funds
December 31, 2003 - December 31, 2012



Asset Allocation
as of December 31, 2012



LISTING OF INVESTIGATORS
AND
INDIVIDUAL FACULTY REPORTS

Investigators of the UAB McKnight Brain Institute:

Professors

J. David Sweatt, Ph.D.
Evelyn F. McKnight Chair, Department of Neurobiology
Director, UAB-MBI
Area of Interest: Signal transduction and transcriptional control in memory and aging

Karlene Ball, Ph.D.
Professor and Chair, Department of Psychology
Area of Interest: Aging-related cognitive function

James H. Meador-Woodruff, M.D.
Professor and Chair, Department of Psychiatry and Behavioral Neurobiology
Area of Interest: Cellular and subcellular alterations of neural circuitry and molecular expression in psychiatry

David Standaert, M.D., Ph.D.
Professor and Chair, Department of Neurology
Director, UAB Movement Disorders Center
Area of Interest: Striatal molecular and cellular biology, Parkinson's Disease

Michael Brenner, Ph.D.
Professor, Department of Neurobiology
Area of Interest: Glial cell biology, Alexander Disease

David Geldmacher, M.D. (Recruited to UAB from UVA, arrived March 2011)
Professor, Collat Scholar, Department of Neurology
Area of Interest: Aging-related memory disorders and visual cognition in AD.

John Hablitz, Ph.D.
Professor, Department of Neurobiology
Associate Director, UAB-MBRI
Area of Interest: Modulation of excitability in neocortial circuits

Robin Lester, Ph.D.
Professor, Department of Neurobiology
Area of Interest: Nicotinic receptors in CNS function

Lori McMahon, Ph.D.
Professor, Department of Physiology/Biophysics
Area of Interest: Hormonal control of synaptic plasticity in aging

Lucas Pozzo-Miller, Ph.D.
Professor, Department of Neurobiology
Area of Interest: Mechanisms controlling dendritic spine morphology

Harry Sontheimer, Ph.D.
Professor, Department of Neurobiology
Director, UAB Center for Glial Biology in Medicine
Area of Interest: Cell biology of glial function

Paul Gamlin, Ph.D.
Professor, Department of Ophthalmology
Area of Interest: Cell biology and systems neuroscience of vision and visual disorders

Erobo Ubogu, Ph.D.
Professor, Department of Neurology
Director of the Neuromuscular Division of Neurology
Area of Interest: Inflammatory neuropathies

Associate Professors

Lynn Dobrunz, Ph.D.
Associate Professor, Department of Neurobiology
Area of Interest: Regulation of short-term synaptic plasticity in the hippocampus

Alecia Gross, Ph.D.
Associate Professor, Department of Vision Sciences
Area of Interest: Signal transduction mechanisms in the CNS

Linda Overstreet-Wadiche, Ph.D.
Associate Professor, Department of Neurobiology
Area of Interest: Adult neurogenesis in the dentate gyrus

Vlad Parpura, M.D., Ph.D.
Associate Professor, Department of Neurobiology
Area of Interest: Imaging approaches to investigating synaptic and glial cell function

Erik Roberson, M.D., Ph.D.
Associate Professor, Department of Neurology
Area of Interest: Aging-related memory disorders

Anne Theibert, Ph.D.
Associate Professor, Department of Neurobiology
Area of Interest: PI-3-Kinase signal transduction in neuronal cell biology

Scott Wilson, Ph.D.
Associate Professor, Department of Neurobiology
Area of Interest: The ubiquitin/proteasome system in neuronal function

Kazu Nakazawa, Ph.D.
Associate Professor, Department of Psychiatry
Area of Interest: Epigenetics and cognition

Assistant Professors

Tara DeSilva, Ph.D. (Recruited to UAB from Harvard in 2009)
Assistant Professor, PM&R
Area of Interest: Neural-glial signaling mechanisms in the CNS

Michelle Gray, Ph.D. (Recruited to UAB from UCLA in 2008, newly appointed Asst Prof)
Assistant Professor, Dixon Scholar, Department of Neurology
Area of Interest: Neurogenetics, glial function, and Huntington's Disease

Gwen King, Ph.D. (Recruited to UAB from Boston University, arrived March 2011)
Assistant Professor, Department of Neurobiology
Area of Interest: Memory and aging, Klotho proteins in aging and cognition

David Knight, Ph.D.
Assistant Professor, Department of Psychology
Area of Interest: Human imaging approached to investigating memory

Farah Lubin, Ph.D.
Assistant Professor, Department of Neurobiology
Area of Interest: Signal transduction mechanisms in memory and memory disorders

Michelle Olsen, Ph.D.
Assistant Professor, Department of Physiology and Biophysics
Area of Interest: Signal transduction mechanisms in the CNS, epigenetics

Scott Phillips, Ph.D.
Assistant Professor, Department of Neurobiology
Scientist, UAB IDDRC Recombinant Technologies Core
Area of Interest: Neurogenetics, neurobiochemistry.

Christina Visscher, Ph.D. (Recruited from Harvard)
Assistant Professor, Neurobiology
Area of Interest: Human imaging approaches to investigating memory.

Jacques Wadiche, Ph.D.
Assistant Professor, Department of Neurobiology
Area of Interest: Synaptic plasticity and function in the cerebellum

UAB McKnight Institute New Faculty Recruits:

2006 Recruits:
Linda Overstreet Wadiche, Ph.D. (Recruited from the Vollum Institute)
Assistant Professor, Neurobiology
Area of Interest: Adult neurogenesis in the dentate gyrus.

Jacques Wadiche, Ph.D. (Recruited from the Vollum Institute)
Assistant Professor, Neurobiology
Area of Interest: Synaptic plasticity and function in the cerebellum.

2007 Recruits:
David Knight, Ph.D. (Recruited from the NIH)
Assistant Professor, Psychology
Area of Interest: Human imaging approaches to investigating memory.
Vlad Parpura, M.D., Ph.D. (Recruited from the University of California, Riverside)
Associate Professor, Neurobiology
Area of Interest: Imaging approaches to investigating synaptic and glial cell function.
Tong Ye, Ph.D. (Recruited from Duke University)
Assistant Professor, Neurobiology
Area of Interest: In vivo imaging, 2-photon imaging.
David Standaert, M.D., Ph.D. (Recruited from Harvard in 2006)
Professor, Neurology
Director, UAB Movement Disorders Center
Area of Interest: Striatal molecular and cellular biology, Parkinson's Disease

2008 Recruits:
Christina Visscher, Ph.D. (Recruited from Harvard)
Assistant Professor, Neurobiology
Area of Interest: Human imaging approaches to investigating memory.
Erik Roberson, M.D., Ph.D. (Recruited from the University of California, San Francisco)
Assistant Professor, Neurology and Neurobiology
Area of Interest: Using genetically engineered mice to investigate aging-related memory dysfunction. Dr. Roberson also sees patients at the aging-related memory disorders clinic here at UAB.
Farah Lubin, Ph.D. (Recruited from Baylor College of Medicine and UAB)
Assistant Professor, Neurobiology
Area of Interest: Epigenetic mechanisms in memory formation and memory dysfunction.

2009 Recruits:
Alecia Gross, Ph.D. (Recruited from Baylor College of Medicine in 2006)
Assistant Professor, Vision Sciences
Area of Interest: Signal transduction mechanisms in the CNS
James H. Meador-Woodruff, M.D. (Recruited from Michigan in 2005)
Professor and Chair, Department of Psychiatry and Behavioral Neurobiology
Area of Interest: Cellular and subcellular alterations of neural circuitry and molecular expression in psychiatric illnesses

2010 Recruits:
Karlene Ball, Ph.D.
Professor and Chair, Department of Psychology
Area of Interest: Aging-related cognitive function
Tara DeSilva, Ph.D. (Recruited to UAB from Harvard in 2009)
Assistant Professor, PM&R
Area of Interest: Neural-glial signaling mechanisms in the CNS

Michelle Gray, Ph.D. (Recruited to UAB from UCLA in 2008, newly appointed Asst Prof)
Assistant Professor, Dixon Scholar, Dept of Neurology
Area of Interest: Neurogenetics, glial function, and Huntington's Disease
Michelle Olsen, Ph.D.
Assistant Professor, Physiology and Biophysics
Area of Interest: Signal transduction mechanisms in the CNS, epigenetics

2011 Recruits:
David Geldmacher, M.D. (Recruited to UAB from UVA, arriving March 2011)
Professor, Collat Scholar, Department of Neurology
Area of Interest: Aging-related memory disorders and visual cognition in AD.
Gwen King, Ph.D. (Recruited to UAB from Boston University, arriving March 2011)
Assistant Professor, Neurobiology
Area of Interest: Memory and aging, Klotho proteins in aging and cognition
Scott Phillips, Ph.D. (Dr. Phillips was already a member of the UAB MBI in a Core Director capacity, and was promoted to an Assistant Professor position in 2011.)
Assistant Professor, Neurobiology
Scientist, UAB IDDRC Recombinant Technologies Core
Area of Interest: Neurogenetics, neurobiochemistry.

2013 Recruits:
Paul Gamlin, Ph.D.
Professor, Department of Ophthalmology
Area of Interest: Cell biology and systems neuroscience of vision and visual disorders

Erobo Ubogu, Ph.D.
Professor, Department of Neurology
Director of the Neuromuscular Division of Neurology
Area of Interest: Inflammatory neuropathies

Kazu Nakazawa, Ph.D.
Associate Professor, Department of Psychiatry
Area of Interest: Epigenetics and cognition

UAB McKnight Research Scientists:

Felecia Hester, B.S., MBA
Scientific Director, UAB McKnight Synaptic Plasticity Core
Area of Interest: Epigenetic control of neuronal biophysical properties.
Jing Wang, Ph.D.
Scientist, UAB McKnight Synaptic Plasticity Core
Area of Interest: Place cells in the hippocampus.

SWEATT INDIVIDUAL REPORT

McKnight Brain Research Foundation
Annual Report 2013
J. David Sweatt, Evelyn F. McKnight Chair
University of Alabama at Birmingham

This is an individual report for Dr. Sweatt as Evelyn F. McKnight Endowed Chair for Learning and Memory in Aging at UAB.

1. Summary of Scientific Achievements for 2013

Aging-related memory decline is manifest prominently in declarative/episodic memory and working memory, memory modalities anatomically based largely in the hippocampus and prefrontal cortex, respectively. The neurobiological underpinnings of age-related memory deficits include aberrant changes in gene transcription that ultimately affect the ability of the aged brain to be "plastic." This has led us to hypothesize that dysregulation of epigenetic control mechanisms and accumulation of aberrant epigenetic marks are a driver for aging-related cognitive dysfunction. Specifically, given that the transcription of key memory-promoting genes are known to decline during aging, we propose that these changes are regulated by aberrant epigenetic marks and control mechanisms within brain regions particularly vulnerable to the aging process (i.e. hippocampus and prefrontal cortex), which together result in age-related cognitive deficits. In studies over the last year we have made important discoveries concerning the role of epigenetic mechanisms in memory-associated areas of the CNS, which I will describe below.

DNA methylation controls associative reward learning

In a series of studies published in *Nature Neuroscience*, we discovered that epigenetic mechanisms regulate positive reinforcement memories. The ability to form memories about positive biological and emotional events is critical for human adaptive behavior and decision making. In vertebrates, this ability is controlled by the mesolimbic dopamine system, centered upon dopamine neurons located in the ventral midbrain. These neurons not only exhibit the remarkable capacity to signal primary rewards irrespective of sensory modality (including food, water, drugs of abuse, and potential mates), but also track environmental stimuli that predict these rewards. Our understanding of this basic process has had a far-reaching impact across disciplines, shedding new light on scientific research into learning, memory, addiction, impulsivity, and decision making. The present manuscript details groundbreaking evidence characterizing a neuroepigenetic substrate for these reward-based associative memories, and is therefore relevant not only to a broad neuroscience audience, but also to researchers investigating basic processes in molecular biology, cellular information storage, epigenetics, medicine, psychiatry, and psychology, as well as a non-scientific audience interested in the how the brain forms new memories.

In our manuscript, we reported that reward-based memory formation is controlled by DNA methylation in a dopamine-neuron containing brain region known as the ventral tegmental area. We first demonstrated that reward experiences alter DNA methylation patterns to turn on specific memory-associated genes in the ventral tegemental area, and that active DNA methylation within gene bodies is an essential part of this mechanism. Next, we presented novel evidence that site-specific blockade of DNA methylation in the ventral tegmental area (but not other reward-related brain structures) *in vivo* prevents the formation of new reward memories but does not alter general motivation or the long-term storage of reward memories.

These results mark a substantial advance in our understanding of the neurobiological processes that control reward memories, and also reveal new information about how neuroepigenetic mechanisms regulate activity-dependent processes within the central nervous system. Critically, this was the first report to implicate any molecular process in the neuroplastic changes that dopamine neurons undergo during natural reward learning and, as such, enables new insight into the potentially dissociable processes that regulate normal learning and maladaptive learning that involves drugs of abuse.

TET1 Oxidase Controls CNS 5-methycytosine Hydroxylation, Active DNA Demethylation, Gene Transcription, and Memory Formation

In an additional series of studies published in *Neuron*, we reported the discovery of a key new epigenetic mechanism controlling active DNA demethylation in the hippocampus. The manuscript detailed groundbreaking evidence that TET1 oxidase can regulate memory capacity. The manuscript also provided foundational evidence using novel analytical chemistry approaches and *in vivo* gene engineering techniques to provide compelling evidence that TET1 oxidase is a critical component regulating active cytosine demethylation in the CNS. The studies are relevant not only to a broad neuroscience audience, but also to researchers investigating basic processes in molecular biology, cellular information storage, and epigenetics, as well as a non-scientific audience interested in the how the brain forms new memories.

Thus, in this manuscript, we reported that: **1**. TET1 is an activity-regulated gene in the CNS; **2**. TET1 over-expression *in vivo* drives active hydroxymethylcytosine production and active DNA demethylation in the hippocampus, quantitated using an analytical GC/Mass-Spec method we established; **3**. TET1 regulates memory-associated gene transcription; and **4**. TET1 activity regulates fear conditioning memory, as over-expression of TET1 attenuates contextual fear conditioning memory.

These results mark a substantial advance in our understanding of the neurobiological processes that control memory and also reveal new information about how neuroepigenetic mechanisms regulate activity-dependent processes within the central nervous system. Critically, this is the first report to *directly demonstrate* TET enzymes as being capable of catalyzing hydroxymethylcytosine production in the CNS, and as being capable of driving active DNA demethylation in the brain. As such, these studies are foundational in establishing the identity of the heretofore mysterious memory-associated DNA de-methylase activity in the nervous system.

Significance of these studies. The ability to form memories about positive and negative biological and emotional events is critical for human adaptive behavior and decision making. These recent studies from our group as well as a number of other laboratories has demonstrated a role for active DNA methylation and demethylation in memory formation in the mammalian CNS. Our understanding of this basic process has had a far-reaching impact across disciplines, shedding new light on scientific research into learning, memory, addiction, stress disorders, decision making, and aging-related cognitive decline.

2. Publications in Peer Reviewed Journals

1. Lithner CU, Lacor PN, Zhao WQ, Mustafiz T, Klein WL, Sweatt JD, Hernandez CM. Disruption of neocortical histone H3 homeostasis by soluble Aβ: implications for Alzheimer's disease. Neurobiol Aging. 34:2081-90.

2. Kaas GA, Zhong C, Eason DE, Ross DL, Vachhani RV, Ming GL, King JR, Song H, Sweatt JD. (2013) TET1 Controls CNS 5-Methylcytosine Hydroxylation, Active DNA Demethylation, Gene Transcription, and Memory Formation. Neuron. 79:1086-93.

3. Day JJ, Childs D, Guzman-Karlsson MC, Kibe M, Moulden J, Song E, Tahir A, Sweatt JD (2013) DNA methylation regulates associative reward learning. Nat Neurosci. 16:1445-52.

4. Yokoi F, Cheetham CC, Campbell SL, Sweatt JD, Li Y. (2013) Pre-Synaptic Release Deficits in a DYT1 Dystonia Mouse Model. PLoS One. 2013;8(8):e72491.

5. Zovkic IB, Guzman-Karlsson MC, Sweatt JD. (2013) Epigenetic regulation of memory formation and maintenance. Learn Mem. 20(2):61-74. PMID:23322554.

6. Kosik KS, Rapp PR, Raz N, Small SA, Sweatt JD, Tsai LH. (2012) Mechanisms of age-related cognitive change and targets for intervention: epigenetics. J Gerontol A Biol Sci Med Sci. 67:741-6.

7. Zovkic IB, Sweatt JD. (2013) Epigenetic mechanisms in learned fear: implications for PTSD. Neuropsychopharmacology 38(1):77-93.

8. Sweatt JD. (2013) Pitt-Hopkins Syndrome: intellectual disability due to loss of TCF4-regulated gene transcription. Exp Mol Med. 2013 May 3;45:e21.

9. Zovkic IB, Guzman-Karlsson MC, Sweatt JD. (2013) Epigenetic regulation of memory formation and maintenance. Learn Mem. 20:61-74.

10. Zovkic IB, Meadows JP, Kaas GA, Sweatt JD. (2013) Interindividual Variability in Stress Susceptibility: A Role for Epigenetic Mechanisms in PTSD. Front Psychiatry. 4:60.

11. Sweatt, JD (2013) The emerging field of neuroepigenetics. Neuron. 80(3):624-32.

12. Sultan FA, Sweatt JD. (2013) The role of the gadd45 family in the nervous system: a focus on neurodevelopment, neuronal injury, and cognitive neuroepigenetics. Adv Exp Med Biol. 793:8-119.

3. Publications (other)

Books

Also for the last year I was lead Editor on a book that I feel will be foundational for the emerging field of behavioral epigenetics: *Epigenetic Regulation in the Nervous System; Basic Mechanisms and Clinical Impact.* The book was published by Elsevier in Feb 2013.

Book Chapters

I authored or co-authored three chapters in the book I edited.

4. Recent Presentations at Scientific Meetings (also includes invited research seminars)

2012 - (last three months only)

American College of Neuropsychopharmacology annual meeting, plenary speaker

2013 - Invited Speaker, Learning and Memory Biannual meeting, UT Austin
Keynote Speaker, IdeaFest, University of South Dakota
Department of Neuroscience, University of South Dakota School of Medicine
Department of Neuroscience, Rosalind Franklin University, Chicago
Emory University, GIN Excellence in Neuroscience Lecture
SfN Annual Meeting Symposium speaker
Longevity International Meeting, Venice, Invited speaker
International Society of Business Fellows, speaker
UAB Undergraduate Research Expo, keynote speaker
Dalhousie University, Killam Lecturer
American Speech-Hearing Association invited lecture

2014 - AAAS Annual Meeting Symposium speaker
UCSF, Gladstone Institute
NIMH, research symposium
UK Genetics Society, Psychopharmacology meeting Keynote speaker

5. Presentations at Public (non-scientific) Meetings or Events

Interviewed for *NPR All Things Considered* concerning epigenetic mechanisms in memory disruption in aging.

6. Awards and Honors

Editorial Board, NeuroEpigenetics, 2013

Civitan International Research Center Distinguished Scientist Award, 2013

Dalhousie University, Killam Lecturer, 2013

Interviewed by the journal *Neuron* for their 25th Anniversary issue in 2013, highlighting our 2007 *Neuron* paper on DNA methylation in memory. Our paper was the most highly cited paper published in *Neuron* in 2007.

New or recently renewed Grant Awards:

T32 Training Grant NS061788 – Training Program in the Neurobiology of Cognition and Cognitive Disorders
D. Sweatt PI
7/01/2013 – 6/30/2018 4-5 graduate student slots per year

Defense Advanced Research Projects Agency Advanced Project: In Vivo Nanoplatforms for Epigenetic Enhancement of Memory
D. Sweatt PI
10/1/12 – 9/30/14 $925,000 approximate total direct costs

Defense Advanced Research Projects Agency Advanced Project: A Whole-Epigenome Approach to Identifying Novel Targets for Nano-Pharmacologic Memory Enhancement
D. Sweatt PI
06/17/13 – 06/16/14 $925,000 total direct costs

Pitt-Hopkins Syndrome Foundation - Mouse Models for Pitt-Hopkins Syndrome
D. Sweatt PI
07/01/12 - 9/30/14 $240,000 total direct costs

Please note that Sections 7 through 9, and 11 through 16, are covered in the overall UAB MBI annual report, so I will not repeat them here.

Concerning Section 5b, trainee recruitment for my own laboratory – I recruited one new Post-doctoral Fellow to my laboratory this year, Cristin Gavin. I also recruited one new M.D/Ph.D. student to the lab, Mika Guzman Karlsson.

I had a total of approximately 15 post-doc and grad student applications for my laboratory this year.

Cristin Gavin joined the laboratory in the spring and was a Ph.D. graduate student in Neuroscience at UAB. Cristin's project in the lab will be to investigate the role of the TCF4 transcription factor in controlling synaptic plasticity and memory formation.

Mika Karlsson is an outstanding M.D./Ph.D. student in the UAB Medical Scientist Training Program, working on control of amygdala DNA methylation and amygdala-dependent memory formation. Mika received his BS degree from UCLA.

10. External Collaborations

A. Collaborative Programs with other McKnight Institutes, Institutions and Research Programs

University of Arizona and UF – We are continuing a very fruitful collaboration with Carol Barnes and Tom Foster concerning the possible role of DNA methylation in controlling aging-related transcriptional alterations in the CNS.

UAB – We are collaborating with a number of McKnight investigators here at UAB, including Farah Lubin, David Standaert, Scott Wilson, Gwen King, and John Hablitz.

B. Collaborative Programs with non McKnight Institutes, Institutions and Research Programs

Temple University – collaborating with Dan Liebermann's laboratory to investigate the involvement of GADD45 in memory formation and LTP induction.

Johns Hopkins – collaborating with Honjun Song's laboratory to investigate the role of TET oxidases in active DNA demethylation in memory formation.

University of Maryland – collaborating with Susan Dorsey to investigate BDNF gene methylation in spinal cord plasticity.

University of Delaware – collaborating with Tania and Eric Roth to investigate the role of epigenetic mechanisms in stabilizing hippocampal place cell function.

Aurasense Pharmaceuticals/Northwestern University – this collaborative project is developing nanotechnology-based next-generation histone de-acetylase inhibitors as memory-enhancing agents. This project is funded by the Defense Advanced Research Projects Agency (DARPA).

Ibis Pharmaceuticals - this year we obtained funding for an innovative collaborative project developing antisense oligonucleotide-based next-generation histone de-acetylase inhibitors as memory-enhancing agents. This project is funded by DARPA.

Signature, date, and title of person submitting report

J. David Sweatt
Evelyn F. McKnight Endowed Chair
Director, Evelyn F. McKnight Brain Institute
Chairman, Department of Neurobiology
UAB School of Medicine

INDIVIDUAL INVESTIGATORS' SUMMARIES

1. Summary of Scientific Achievements for 2013

BRENNER

A method was developed to enrich for Rosenthal fibers, the protein aggregates that are the defining feature of Alexander disease. This method is superior to those previously published, particularly in removing nearly all GFAP that is present in intermediate filaments but not in the aggregates. The enrichment preparation is being used to analyze the protein composition of the protein aggregates.

^{15}N labeled and unlabeled wild type and mutant human recombinant GFAP standards have been prepared to be used for quantifying the relative amounts of mutant and wild type GFAP in mouse models and human patients by mass spectroscopy. Wild type recombinant GFAP has also been deiminated to serve as a standard in an ELISA Michael has developed as part of a project to determine if GFAP deimination has a role in Alexander disease.

With the assistance of a computer programmer, Michael has developed a proprietary algorithm for identification and quantification of proteins from mass spectrometry data. The algorithm has been patented by UAB (US provisional patent application #61/829,720), and is being evaluated by users at UAB, Vanderbilt University, and North Carolina State University.

DOBRUNZ

The Dobrunz lab has continued to investigate the effects of transcriptional dysregulation in inhibitory interneurons, which models aspects brain changes that are seen schizophrenia, on synaptic and circuit function in hippocampus. The lab discovered that the dynamic imbalance between inhibitory and excitatory synaptic transmission in this model is caused by enhanced strength of individual synapses along with altered recruitment of inhibitory neurons.

The lab has developed a new method for measuring the effects of endogenously released Neuropeptide Y (NPY), a potent anti-anxiety molecule. Using this method, a reduction was found in the effects of endogenously released NPY in hippocampus in an animal model of Post-traumatic Stress Disorder.

HABLITZ

Demonstrated the role of HCN channels in modulating interictal spike activity in animal models of epilepsy. Although HCN channels are known to be down-regulated in epilepsy, a role in regulating epileptiform discharges was not previously known.

HCN channels were also shown to modulate activity of GABAergic neurons in the neocortex, another role of these channels previously unknown.

KING

This year the lab produced its first 2 manuscripts on data solely developed at UAB. While not unique, I'm really proud that we've managed to develop 2 papers worth of data in our first two years of existence in addition to completing a project initiated at Boston University from when Dr. King was a postdoc. There are two additional manuscripts anticipated and waiting additional data.

The King lab has generated and characterized a new klotho antibody that is in the last steps of validation for specificity. If the initial findings are corroborated by mass spec data, they have developed the best antibody available in the world as it detects klotho across species and experimental modalities in a way no other antibody has done.

Data has been generated to support an RO1 application anticipated to be submitted in October on the role of klotho in adult neurogenesis. Largely spear headed by my graduate student, Ann Laszczyk, novel discoveries have been made of a role for klotho in adult neurogenesis making klotho one of the very rare postnatal only, modifiers of neurogenesis.

LESTER
Initiated collaborative discussions to study cholinergic transmission using optogenetic approaches with Jacques Wadiche.

LUBIN
Dr. Lubin has published manuscripts (18), book chapters (3) and 1 an Elsevier book entitled "*Epigenetics and Neuroplasticity: Evidence and Debate.*" She serves as Ad-hoc reviewer for several peer-reviewed journals (26) and grant application agencies (6), and served on a number of vitally important search committees (6).

In addition to the journal articles and services, 14 platform presentations were presented at Universities throughout the US or at national and international conferences in just the past year alone. In addition to obtaining research funding, service and teaching contributions are numerous.

OVERSTREET-WADICHE
The lab has evidence suggesting that a specific extracellular matrix molecule controls the sequence and timing of GABA synaptic innervation of adult generated neurons.

It was found that the first excitatory synapses on adult born neurons arise from hilar mossy cells. A manuscript will be submitted demonstrating pharmacology and optogenetic activation of the first excitatory synapses on adult born neurons from hilar mossy cells.

Using conditional genetic models to selectively block cell death of developing granule cells, we have identified evidence that adult-born neurons compete with existing mature neurons for synaptic partners. We are currently investigating the mechanisms underlying this competition.

PARPURA
The Parpura lab continues studying the applicability of dispersible nanomaterials in neurobiology. Studies indicate that carbon nanotube as aqueous solutes could have more beneficial effects at the injury site than previously thought; by affecting astrocytes, they could provide for a more comprehensive re-establishment of the brain computational power (JA#87).

The lab described that hyposmolality differentially and spatiotemporally modulates levels of glutamine synthetase (astrocytes) and serine racemase (neurons) in rat supraoptic nucleus in vivo (JA#93).

Canonical transient receptor potential 1 (TRPC1) plasmalemmal cation channels mediate Ca^{2+} and Na^{+} fluxes and control respective cytoplasmic ion signals in rat cortical astrocytes. The lab proposes that TRPC channels are amenable to changes in selective filtering differentially affect the flux of Ca^{2+} and Na^{+} (JA#99).

POZZO-MILLER

The first direct and physiological evidence of activity-dependent release of endogenous BDNF is impaired in slices from *Mecp2* knockout mice. Also, the first demonstration that TRPC3 and TRPC6 mRNA and protein levels are lower in *Mecp2* knockout mice, and confirmation that BDNF mRNA and protein levels are also reduced. Confirmation that MeCP2 is bound to the *Bdnf* promoter, as well as discovery that *Trpc3* is a direct MeCP2 target, using ChIP. Published in *PNAS*.

The first description that hippocampal slices from *Mecp2* knockout mice are hyperexcitable due to an hyperactive CA3 region arising from an excitatory/inhibitory imbalance with reduced GABAergic inhibition. In preparation.

The first description that BDNF trafficking is impaired in *Mecp2* knockout neurons, which can be rescued by a selective HDAC6 inhibitor. In preparation.

SONTHEIMER

The Sontheimer laboratory is executing a new clinical trial for the use of sulfasalazine in glioblastoma related epileptogenesis, funded by the UAB CCTA. This exciting new avenue of clinical research is based on Sontheimer's recent discovery of the utility of this approach in animal studies, which were published last year (2012) in *Nature Medicine*.

THEIBERT

The Theibert lab has used a novel pulse-chase assay, colocalization and live imaging studies in primary cultured neurons to identify, manipulate and characterize two regulators of neuronal secretory vesicle trafficking. They have demonstrated that two downstream targets of the PI 3-kinase pathway, ADAP1 and Arf6, are required for neuronal secretory granule maturation, and specifically of dendritic BDNF trafficking in hippocampal neurons. They have also identified an important candidate pathway whereby PI 3-kinase may control neuronal vesicular trafficking.

VISSCHER

Using fMRI, the Visscher lab has examined proactive and reactive control in central and peripheral primary visual cortex during visual and auditory attention. The data suggests that reactive control processes influence separate parts of visual cortex independently, while proactive, ongoing control processes influence the area as a unit. (Elkhetali, under review)

Processing speed training increases the efficiency of attentional resource allocation in young adults. Pupil diameters are used as an index of how much attentional resources are devoted to a task, and find that this changes after cognitive training. This work sets the stage for examining the neural mechanisms of cognitive training in younger and older adults. (Burge, under review)

Participants with Macular Degeneration show stronger attention-related activity in visual cortex than do controls. Work is being done with recruitment, training and testing pipeline incorporating 3 labs' and a clinic's infrastructure that allows measurement of neural activity in human low-vision participants in response to tasks involving visual stimulation. One finding is that participants with Macular Degeneration appear to compensate for their lack of visual input by augmenting attention-related neural activity.

WADICHE

The Wadiche lab demonstrated that physiological regulation of neuronal glutamate transporters is sufficient to alter signaling to neighbor glial cells. This work was published in the Journal of Neuroscience and is the major portion of my second graduate student's thesis, Ming-Chi Tsai, who earned his Ph.D. in April 2012.

The lab uncovered that neurotransmitter spills out to excite and inhibit interneurons not connected by canonical synapses. This form of neural communication that resembles volume transmission expands the computational range of interneuronal networks and affects Purkinje cells in a biphasic manner. This work was published in the journal Neuron. A new graduate student has continued this line of investigation to uncover that AMPARs activated synaptically or following volume transmission have distinct biophysical signatures (Ca2+ permeable or not, respectively).

The lab discovered that presynaptic protein kinase C regulation is masked by postsynaptic receptor occupancy, thus revealing additional targets for regulation of neurotransmitter release. This manuscript is nearly ready for peer review. We are also following up on our initial behavioral characterization of a mouse deficient in Purkinje cell glutamate transporters. Aside, from motor defects, this animal has an unexpected anxiety and/or social phenotype.

WILSON

Determined that acutely blocking USP14's deubiquitinase activity impairs pre-synaptic function.

Determined that blocking USP14's deubiquitinase activity alters postsynaptic MAPK signaling and results in enhanced long-term potentiation.

2. Publications in Peer Reviewed Journals

BRENNER

1. Yeo, S., Bandyopadhyay, S., Messing, A. and Brenner, M. (2013). Roles of multiple transcription factors in regulating *GFAP* expression strength, astrocyte specificity and brain region specificity. Glia (in press)

2.Nicholas, A., Heaven, M., and Brenner, M. Ongoing studies of deimination in neurodegenerative diseases using the F95 antibody. In: Bhattacharya, S. and Nicholas, A. eds., *Protein Deimination in Human Health and Disease*, Springer-Verlag, New York (publication expected Oct 2013)

3. Brenner, M. Alexander's Disease, In: Aminoff, MJ. and Daroff, RB., *Encyclopedia of the Neurological Sciences, 2nd Edition*, Elsevier, New York (publication expected 10 Feb 2014).

DOBRUNZ

1. Jin, Y.N., Chen, P.C., Watson, J.A., Walters, B.J., Phillips, S.E., Green, K., Schmidt, R., Wilson, J.A., Johnson, G.V., Roberson, E.D., Dobrunz, L.E. & Wilson, S.M. Usp14 deficiency increases tau phosphorylation without altering tau degradation or causing tau-dependent deficits. *PloS One* **7**, e47884 (2012).

3 other papers have been submitted.

HABLITZ

1. Parrish, R.R., Albertson, A., Buckingham, S.C., Hablitz, J.J., Mascia, K.L., Haselden, W.D. and Lubin, F.. Status epilepticus triggers early and late alterations in brain-derived neurotrophic factor and NMDA glutamate receptor grin2b DNA methylation levels in the hippocampus. Neuroscience (In Press).

Manuscripts and chapters accepted, in press or published (give full reference and official status)

1. Albertson, A., Williams. S.B. and Hablitz, J.J. Regulation of epileptiform discharges in rat neocortex by HCN channels. J. Neurophysiol. (Acceptable upon minor revision).
2. Olsen. M., Campbell, S.L. and Hablitz, J.J. Functional changes in glutamate transporters and astrocyte biophysical properties in focal cortical dysplasia. Neuroscience (Under Revision).
3. Dougherty, S.E., Hollimon, J.J., West, A.B.., Lesort, M., Hablitz, J.J., Cowell, R. M. Restricted expression of mutant huntingtin to parvalbumin-positive cells causes hyperactivity and altered synaptic function in the motor cortex. Neurobiology of Disease (Under Revision).

KING

1. Candolfi M, **King GD**, Yagiz K, Curtin JF, Mineharu Y, Muhammad AK, Foulad D, Kroeger KM, Barnet N, Josien R, Lowenstein PR, Castro MG. Plasmacytoid dendritic cells in the tumor microenvironment: immune targets for glioma therapeutics. Neoplasia (2012) 14(8):757-70. PMCID PMC3431182

Manuscripts and chapters accepted, in press or published (give full reference and official status)

1. Clinton SM, Glover ME, Maltare A, Mehi SJ, Simmons RK, **King GD**. Expression of Klotho mRNA and protein in rat brain parenchyma from early postnatal development into adulthood. Brain Research (2013) IN PRESS.
2. Mehi SJ, Maltare A, Abraham CR, **King GD**. MicroRNA-339 and microRNA-556 regulate Klotho expression in vitro. Age (2013) IN PRESS

LUBIN

1. S.J. Morse, R.L. Davis, and **F.D. Lubin**. Environmental enrichment reverses age-related hippocampal histone methylation changes. 2013, *Neurobiology of Aging* In Revision.
2. S. Gupta-Agarwal, Timothy Jarome, J. Fernandez, and **F.D. Lubin**. NMDA receptor- and ERK dependent changes in histone methylation in the lateral amygdala bidirectionally regulate fear memory formation. 2013, *J. Neuroscience* In Revision.
3. R.R. Parrish, A. Albertson, S. Buckingham, J. Hablitz, W. Haselden, and **F.D. Lubin**. Status epilepticus triggers early and late alterations in brain-derived neurotrophic factor and NMDA glutamate receptor GRIN2B DNA methylation levels in the hippocampus. 2013, June 27th *Neuroscience* In Press. http://dx.doi.org/10.1016/j.neuroscience.2013.06.029.
4. C.L. Ferland, W.R. Hawley, R.E. Puckett, K. Wineberg, **F.D. Lubin**, G.P. Dohanich, L.A. Schrader. Sirtuin activity in dentate gyrus contributes to chronic stress-induced behavior and ERK1/2 cascade changes in the hippocampus. 2013, *Biological Psychiatry* In Press.

5. T.J. Jarome and **F.D. Lubin**. Histone lysine methylation: critical regulator of memory and behavior. 2013. *Reviews in the neurosciences* May 27: 1-13.
6. R.R. Parrish and **F.D. Lubin.** Direct bisulfite sequencing for examination of DNA methylation with gene and nucleotide resolution from brain tissues. 2012. *Current Protocols in Neurosci.* Jul; Chapter 7:Unit7.24

OVERSTREET-WADICHE

1. Coddington LT, Rudolph S, Vande Lune P, **Overstreet-Wadiche L**, Wadiche JI (2013) Spillover mediated feedforward-inhibition functionally segregates interneuron activity. *Neuron* 78:1050-62.
2. Chancey JH, Adlaf EW, Sapp MC, Pugh PC, Wadiche JI, **Overstreet-Wadiche LS** (2013) GABA depolarization is required for experience-dependent synapse unsilencing in adult-born neurons. *Journal of Neuroscience*, 33:6614-22. PMCID: PMC3657840.
3. Dieni VC, Chancey JH, **Overstreet-Wadiche LS** (2012) Dynamic functions of GABA signaling during granule cell maturation. *Frontiers in Neural Circuits*, 6:113. PMCID: PMC3539683

PARPURA

1. Gottipati, M.K., Kalinina, I., Bekyarova, E., Haddon, R.C., Parpura, V. (2012) Chemically functionalized water-soluble single-walled carbon nanotubes modulate morpho-functional characteristics of astrocytes. Nano Lett 12: 4742–4747.
2. Parpura, V., Verkhratsky, A. (2012) Homeostatic function of astrocytes: Ca^{2+} and Na^{+} signaling. Translat Neurosci 3: 334-344.
3. De Pittà, M., Volman, V., Berry, H., Parpura, V., Volterra, A., Ben-Jacob, E. (2012) Computational quest for understanding the role of astrocyte signaling in synaptic transmission and plasticity. Front Comput Neurosci 6: 98.doi:10.3389/fncom.2012.00098 (25 pp).
4. Parpura, V., Verkhratsky, A. (2012) Astrocytes revisited: Concise historic outlook on glutamate homeostasis and signaling. Croat Med J. 53:518-528.
5. Parpura, V., Silva, G.A., Tass, P.A., Bennet. K.E., Meyyappan, M., Koehne, J., Lee, K.H., Andrews, R.J. (2012) Neuromodulation: Selected approaches and challenges. J Neurochem 124: 436-453.
6. Wang, Y-F., Sun, M-Y, Hou, Q., Parpura, V. (2013) Hyposmolality differentially and spatiotemporally modulates levels of glutamine synthetase and serine racemase in rat supraoptic nucleus. Glia 61:529-538.
7. Verkhratsky A., Rodríguez, J.J., Parpura, V. (2013) Astroglia in neurological diseases. Future Neurol. Future Neurol 8: 149-158.
8. Parpura, V., Verkhratsky, A. (2013) Astroglial amino acid-based transmitter receptors. Amino Acids 44:1151-1158.
9. Parnis, J., Montana, V., Delgado-Martinez, I., Matyash, V., Parpura, V., Kettenmann, H., Sekler, I., Nolte, C. (2013) Mitochondrial exchanger NCLX plays a major role in the intracellular Ca2+ signaling, gliotransmission and proliferation of astrocytes. J Neurosci. 33:7206-7219.
10. Parpura, V., Verkhratsky, A. (2013) Astrogliopathology: Could nanotechnology restore aberrant calcium signalling and pathological astroglial remodelling? Biochim Biophys Acta 1833: 1625-1631.
11. Lee, W., Reyes, R.C., Gottipati, K. Lewis, K., Lesort, M., Parpura, V., Gray, M. (2013) Enhanced Ca^{2+} dependent glutamate release from astrocytes of the BACHD Huntington's disease mouse model. Neurobiol Dis Neurobiol Dis. 58C:192-199.
12. Reyes, R.C., Verkhratsky, A., Parpura, V. (2013) TRPC1-mediated Ca^{2+} and Na^{+} signalling in astroglia: Differential filtering of extracellular cations. Cell Calcium 54: 120-125.
13. Kim, H-S., Montana, V., Jang, H-J., Parpura, V. Kim, J. (2013) Epigallocatechin-gallate (EGCG) stimulates autophagy in vascular endothelial cells: A potential role for reducing lipid accumulation. J Biol Chem jbc.M113.477505. First Published on June 10, 2013, doi:10.1074/jbc.M113.477505

14. Verkhratsky, A., Parpura, V. (2013) Store-operated calcium entry in neuroglia. Neurosci Bull, In Press -Verkhratsky, A., Reyes, R.C., Parpura, V. (2013) TRP channels coordinate ion signalling in astroglia. Rev Physiol Biochem Pharmacol, In Press

POZZO-MILLER

Full research papers:

1. Larimore J, PV Ryder, K-Y Kim, L.A. Ambrose, C Chapleau, G Calfa, C Gross, G Bassell, L Pozzo-Miller, Y Smith, K Talbot, I-H Park & V Faundez (2013). MeCP2 regulates the synaptic expression of a Dysbindin BLOC-1 network component in mouse brain and human induced pluripotent stem cell-derived neurons. *PLoS ONE* 8(6): e65069. doi:10.1371/journal.pone.0065069
2. Pitcher MR, CS Ward, EM Arvide, CA Chapleau, L Pozzo-Miller, A Hoeflich, S Saenger, F Metzger & JL Neul (2013). Insulinotropic treatments exacerbate metabolic syndrome in mice lacking MeCP2 function. *Human Molecular Genetics* 22: 2626-2633.
3. Leuner K, W Li, MD Amaral, S Rudolph, G Calfa, AM Schuwald, C Harteneck, T Inoue & L Pozzo-Miller (2013). Hyperforin modulates dendritic spine morphology in hippocampal pyramidal neurons by activating Ca^{2+}-permeable TRPC6 channels. *Hippocampus* 23: 40-52.
4. Arnold JJ, MS Hansen, Gorman GS, Rao V, Spellen S, Hunsinger R, Chapleau CA, L Pozzo-Miller & P Challa (2013). The effect of Rho-associated kinase (ROCK) inhibition on the ocular penetration of timolol maleate. *Investigative Ophthalmology & Visual Science* 54: 1118-1126.
5. Li W, G Calfa, J Larimore & L Pozzo-Miller (2012). Activity-dependent BDNF release and TRPC signaling is impaired in hippocampal neurons of *Mecp2* mutant mice. *Proceedings of the National Academy of Sciences of the USA* 109: 17087-17092.
6. Chapleau CA, EM Boggio, G Calfa, AK Percy, M Giustetto & L Pozzo-Miller (2012). Hippocampal CA1 pyramidal neurons of *Mecp2* mutant mice show a dendritic spine phenotype only in the presymptomatic stage. *Neural Plasticity* vol. 2012, Article ID 976164, 9 pages (doi:10.1155/2012/976164).
7. Amaral MD & L Pozzo-Miller (2012). Intracellular Ca^{2+} stores and Ca^{2+} influx are both required for BDNF to rapidly increase quantal vesicular transmitter release. *Neural Plasticity* vol. 2012, Article ID 203536, 10 pages (doi:10.1155/2012/203536).
8. Chapleau CA & L Pozzo-Miller (2012). Divergent roles of $p75^{NTR}$ and Trk receptors in BDNF's effects on dendritic spine density and morphology. *Neural Plasticity* vol. 2012, Article ID 578057, 9 pages (doi:10.1155/2012/578057).
9. Calfa G, CA Chapleau, S Campbell, T Inoue, SJ Morse, FD Lubin & L Pozzo-Miller (2012). HDAC activity is required for BDNF to increase quantal neurotransmitter release and dendritic spine density in CA1 pyramidal neurons. *Hippocampus* 22: 1493-1500.

Peer-reviewed Reviews

1. Li W & L Pozzo-Miller (2013). BDNF deregulation in Rett syndrome. *Neuropharmacology* In press.
2. Katz DM, JE Berger-Sweeney, JH Eubanks, MJ Justice, JL Neul, L Pozzo-Miller, ME Blue, D Christian, JN Crawley, M Giustetto, J Guy, J Howell, M Kron, SB Nelson, RC Samaco, LR Schaevitz, C St. Hillaire-Clarke, JL Young, HY Zoghbi & LA Mamounas (2012) Preclinical research in Rett syndrome: setting the foundation for translational success. *Disease Models & Mechanisms* 5: 733-745.
3. Li W & L Pozzo-Miller (2012) Beyond widespread *Mecp2* deletions to model Rett syndrome: Conditional spatio-temporal knockout, single-point mutations and transgenic rescue mice. *Autism* S1:005. doi:10.4172/2165-7890.S1-005
4. Chapleau CA, J Lane, J Larimore, W Li, L Pozzo-Miller & AK Percy (2012). Recent progress in Rett Syndrome and *MECP2* dysfunction: Assessment of potential treatment options. *Future Neurology* 8: 21-28.

5. Chapleau CA, J Lane, L Pozzo-Miller & AK Percy (2012). Evaluation of current pharmacological options in the management of Rett syndrome: from the present to future therapeutic alternatives. *Current Clinical Pharmacology* In press.
6. Hartmann D, J Drummond, E Handberg, S Ewell & L Pozzo-Miller (2012). Multiple approaches to investigate the transport and activity-dependent release of BDNF and their application in neurogenetic disorders. *Neural Plasticity* vol. 2012, Article ID 203734, 10 pages (doi:10.1155/2012/203734).

Peer-reviewed Book Chapters
1. Chapleau CA, J Lane, L Pozzo-Miller & AK Percy (2013). *Rett Syndrome: A Model of Genetic Neurodevelopmental Disorders*. In: "Genetic Disorders", M Puiu (Ed.). InTech (ISBN: 978-953-51-0886 3) Available from: http://www.intechopen.com/books/genetic-disorders/rett-syndrome-a-model-of-genetic neurodevelopmental-disorders (Open Access).
2. Chapleau CA, J Lane, L Pozzo-Miller & AK Percy (2012). *Defining and Diagnosing Rett Syndrome: Correlating Symptoms and Pathogenesis with Autism*. In: "The Comprehensive Guide to Autism", V Patel, V Preedy, C Martin (Eds.), pp. XX-XX. Berlin: Springer Reference, Springer-Verlag.
3. Calfa G, AK Percy & L Pozzo-Miller (2012). *Rett Syndrome: On Clinical and Genetic Features of Rett Syndrome and Experimental Models based on Mecp2 Dysfunction*. In: "The Autisms: Molecules to Model Systems", L Monteggia and C Powell (Eds.), pp. XX-XX. New York: Oxford University Press.
4. Calfa G, AK Percy & L Pozzo-Miller (2012). *Dysfunction of the methyl-CpG binding protein MeCP2 in Rett syndrome*. In: "Patho-Epigenetics of Disease", J Minarovits and HH Niller (Eds.), pp. 43-69. New York: Springer Science+Business Media.

Published Abstracts
1. Li W, G Calfa & L Pozzo-Miller (2012). Excitation/inhibition imbalance and hippocampal network hyperexcitability in *Mecp2* mutant mice: A role of impaired BDNF-TRPC channel signaling in CA3 interneurons. *Society for Neuroscience Abstracts* 246.24.
2. Xu X & L Pozzo-Miller (2012). Reduced BDNF vesicular trafficking in *Mecp2* mutant neurons. *Society for Neuroscience Abstracts* 246.18.
3. Chapleau C, W Li & L Pozzo-Miller (2012). Candidate BDNF mimetic prevents dendritic spine impairments in *Mecp2* mutant hippocampal pyramidal neurons: An *in* vitro study in mouse organotypic slice cultures. *Society for Neuroscience Abstracts* 246.01.
4. Ricart K, G Calfa, L Pozzo-Miller & A Landar (2012). Mitochondrial impairments in the hippocampus of *Mecp2* mutant mice. *Society for Neuroscience Abstracts* 246.16.
5. Hallengren J, BJ Walters, L Pozzo-Miller, SM Wilson & LE Dobrunz (2012). Modulation of short-term plasticity by proteasomal deubiquitinating enzyme Usp14. *Society for Neuroscience Abstracts* 144.16.
6. Pozzo-Miller L, W Li, JM Rutherford & G Calfa (2012). Excitation/Inhibition imbalance in area CA3 of symptomatic *Mecp2* mutant mice leading to hippocampal network hyperexcitability. *FENS Forum Abstract* 2012, 58.07.

THEIBERT
Ewell, S.N., Larimore, J.L., Markwardt, S.J., Moore-Chapman, C., Gerdes, H-H., Faundez, V, and Theibert, A. (2013) The Arf GAP ADAP1 and Arf6 Function in Secretory Granule Trafficking in Neuronal Cells. (In Preparation)

VISSCHER

Vaden, R.J., Hutcheson, N.L., McCollum, L.A., Kentros, J.G., Visscher, K.M. (2012). Older adults, unlike younger adults, do not modulate alpha power to suppress irrelevant information. Neuroimage. PMID: 22885248

WADICHE

1. Coddington LT, Rudolph S, Vande Lune P, Overstreet-Wadiche L, Wadiche JI. (2013). Spillover mediated feedforward inhibition functionally segregates interneuron activity. Neuron 78:1050-62.
2. Chancey JH, Adlaf EW, Sapp MC, Pugh PC, Wadiche JI, Overstreet-Wadiche LS (2013). GABA depolarization is required for experience-dependent synapse unsilencing in adult-born neurons. Journal of Neuroscience 33:6614-22.
3. Tsai MC, Tanaka K, Overstreet-Wadiche L, Wadiche JI (2012) Neuronal glutamate transporters regulate glial excitatory transmission. Journal of Neuroscience 32:1528-35.

WILSON

1. Jin YN, Chen PC, Watson JA, Walters BJ, Phillips SE, Green K, Schmidt R, Wilson JA, Johnson GV, Roberson ED, Dobrunz LE, Wilson SM. 2012. Usp14 deficiency increases tau phosphorylation without altering tau degradation or causing tau-dependent deficits. PLoS One. 2012;7(10):e47884.
2. Hallengren J, Chen PC, Wilson SM. 2013. Neuronal Ubiquitin Homeostasis. Cell Biochem Biophys. 013 May 18.

3. Publications – Other

KING

1. Reish NJ, Maltare A, McKeown AS, Laszczyk AM, Kraft TW, Gross AK, King GD. The age-regulating protein klotho is vital to sustained retinal function. Under review at Investigative Opthalmology and Visual Science.
2. Tucker TB, King GD, Chen C, Abraham CR. Biochemical and functional characterization of the Klotho VS polymorphism. Under revision at Journal for Biological Chemistry.

LUBIN

1. F.D. Lubin, E.D. Roth, J.D. Sweatt, and T.L. Roth. 2008. A novel approach to understanding neural\ plasticity: epigenetic regulation of the *BDNF* gene. Neural Pathways Research; Editor: Florian L. Pichler. Nova Science Publishers, Inc., NY.
2. S. Gupta, R. Parrish, and F.D. Lubin. 2012. Epigenetics and Translational Medicine. Translational Neuroscience: Applications in Psychiatry, Neurology and Neurodevelopmental Disorders; James E. Barrett, Joseph T. Coyle and Michael Williams (Co-Editors), Cambridge University Press. Chapter 18: 321:333.
3. F.D. Lubin 2013. DNA-methylation and memory formation. Role of DNA-Demethylation in Cancer and Development; Samir K Patra (Editor), Moshe Szyf (Co-editor), and Cristina Alves dos Santos (Publishing editor, Springer). In *Press.*

Books

2014. Epigenetics and Neuroplasticity: Evidence and Debate. Farah D. Lubin and Schahram Akbarian (Co editors) (Publishing editor, Elsevier).

VISSCHER

1. Nenert, R., Ross, L.A., DeCarlo, D.K., Owsley, C., Graham, M., Visscher, K.M. (2012). Age-related macular degeneration affects local connectivity and activity associated with task-set initiation. Society for Neuroscience Abstracts.
2. Elkhetali, A.S., Vaden, R.J., Pool, S.M., Visscher, K.M. (2012). Mechanisms for preparing and maintaining task state compared in auditory and visual cortex Society for Neuroscience Abstracts.
3. Denning, C., Ross, L.A., Nenert, R., Burge, W., Visscher, K.M. (2012). Why is processing speed training effective?: Developing and testing tools to examine the neural mechanisms of training. Society for Neuroscience Abstracts.
4. Hadley, J.A., White, D.M., Nenert, R., Bolding, M.S., Visscher, K.M., Lahti, A.C. (2012). Antipsychotic drug treatment restores impaired limbic system connectivity in schizophrenia. Society for Neuroscience Abstracts.
5. Dubis, J.W., Siegel, J.S., Visscher, K.M., Petersen, S.E. (2012). Perceptual judgment tasks lack error effects where unaware of committed error. Society for Neuroscience Abstracts.
6. Hadley, J.A., Nenert, R., Bolding, M.S., White, D.M., Visscher, K.M., Lahti, A.C. (2013). Ventral tegmental area functional connectivity predicts antipsychotic drug response in schizophrenia. Organization for Human Brain Mapping Annual Meeting Abstracts.
7. Ross, L.A., Denning, C.R., Burge, W., Schmidt, E., Visscher, K.M. (2013). Neural Changes Associated with Processing Speed Training in Older Adults: Preliminary Results. Entertainment Software and Cognitive Neurotherapeutics Society Meeting Abstracts.
8. Burge, W.K., Ross, L.A., Visscher, K.M. (2013). Processing Speed Training increases the efficiency of attentional resource allocation in young adults. Entertainment Software and Cognitive Neurotherapeutics Society Meeting Abstracts.

WILSON

1. Jada J. Hallengren, Bula J. Bhattacharyya, Ping-Chung Chen, Jennifer A. Watson, Andrea G. Marshall, Scott E. Phillips, Christopher S. Theile, Julie A. Wilson, Hidde L. Ploegh, Gwendalyn E. King, Richard Miller, and Scott M. Wilson. Synaptic transmission is dependent upon dynamic ubiquitin signaling. Nature Neuroscience.
2. Andrea G. Marshall, Jennifer A. Watson, Jada J. Hallengren, Brandon J. Walters, Lynn E. Dobrunz, Ludwig Francillon, Julie A. Wilson, Scott E. Phillips and Scott M. Wilson. An ENU-induced model of USP14 deficiency shows a genetic background dependent effect on adult onset neuromuscular disease. PLoS One.
3. Brandon J. Walters, Jada Hallengren, Christopher S. Theile, Hidde L. Ploegh, Scott M. Wilson and Lynn E. Dobrunz. Synaptic plasticity and vesicle number are regulated by proteasome activity. Nature Neuroscience.

4. Presentations at Scientific Meetings

DOBRUNZ

1. University of Auckland, Auckland, New Zealand. April 26, 2013. Departmental seminar
2. Queensland Brain Institute, Brisbane, Australia. April 29, 2013. Departmental seminar
3. Gordon Research Conference "Inhibition in the CNS". Les Diablerets, Switzerland. June 18, 2013

HABLITZ

Gordon Research Conference

KING

1. McKnight Inter-institutional Meeting – April 2013 at UAB – seminar speaker
2. SPORE Brain Tumor Executive Committee Meeting – December 14th, 2012 at UAB – invited speaker
3. Neurodevelopment Working Group – October 2012 at UAB – invited seminar speaker
4. Department of Neurobiology Annual Retreat – September 2012 at UAB – invited seminar speaker

LESTER

UAB Medical School RIME week workshop on case-based small groups.

LUBIN

1. Novel Molecules and Mechanisms in Vulnerability and Resilience Throughout Life. 52nd American College of Neuropsychopharmacology (ACNP) Annual Meeting. Hollywood, Florida. Panel Participants: Drs. Tallie Baram, Marcelo Wood, Farah Lubin, Timothy Bredy and Tracy Bale.
2. Basic Mechanisms of Epilepsy: Mechanisms underlying cognitive and behavioral deficits associated with epilepsy. The American Epilepsy Society Annual Meeting, Washington D.C. Invited by Drs. Dane Chetkovich and Amy Brewster.
3. Epigenetics in Epilepsy: Epiphany or epiphenomenon?. Invited by Dr. Tallie Baram, Minisymposium. The Society for Neuroscience Annual Meeting, San Diego, CA.
4. Epigenetic Mechanisms in Memory. Health Administration Forum at UAB. Invited by Dr. Robert Kimberly.
5. Methylation and DeMethylation in Memory Formation and Aging. Evelyn F. McKnight Brain Institute Inter-Institutional annual meeting. Invited by Drs. J. Lee Dockery and the McKnight trustees.
6. Histone methylation mechanisms in memory. Seminar series at Mount Sinai School of Medicine. New York, NY. Invited by Drs. Eric Nestler, Schahram Akbarian, and Scott Russo.
7. Epigenomic mechanisms in Rett syndrome, epilepsy, and associated memory deficits. Rett Syndrome symposium at UAB. Invited by Dr. Alan Percy.
8. Chromatin remodeling mechanisms in memory. Grand Rounds at University of Alabama at Birmingham (UAB), Birmingham, AL. Invited by Dr. Rita Cowell.
9. Epigenetic mechanisms in learning and memory. "The Role of Epigenetic Mechanisms in the Development and Maintenance of Human Cognition." Invited by Drs. Suzana Petanceska and Paul Coleman, Minisymposium. The Society for Neuroscience Annual Meeting, New Orleans, LA.
10. Epigenetic mechanisms in epilepsy-related memory dysfunction. UAB Neurobiology Departmental Retreat. Invited by Drs. Michael Brenner and Anne Theirbert.
11. Histone methylation mechanisms in cognitive aging. Invited by Dr. Michele K. Evans, Deputy Scientific Director of the National Institute on Aging Intramural Research Program.
12. Epigenetic mechanisms in epileptogenesis and memory. Gordon Research Conference "Mechanisms of Epilepsy and Neuronal Synchronization". Invited by Drs. Amy Brooks-Kayal and Carolyn Houser.
13. Chromatin remodeling mechanisms in memory. Seminar series at The Nestle Institute of Health Sciences. Lausanne, Switzerland. Invited by Dr. Martin Kussmann.
14. Epigenetic histone methylation in memory. Neuroscience seminar series at Meharry Medical College/Vanderbilt University. Invited by Dr. Darryl Hood.

OVERSTREET-WADICHE

1. Invited speaker at the Queensland Brain Institute Symposium on Neural Plasticity. Brisbane, Australia. September 2012

2. A postdoctoral fellow in the lab (Dr. Cristina Dieni) was an invited speaker at the Keystone Symposium on Adult Neurogenesis (her abstract was chosen for 1 of 3 slots for all submitted abstracts). Santa Fe, New Mexico. February 2013
3. Invited speaker Ramsey Symposium on Neurodevelopment. UAB. April 2013
4. Speaker and Vice-Chair, Gordon Research Conference on Inhibition in the CNS.
Les Diablerets, Switzerland. June 2013
5. Department of Pharmacology, University of North Texas Health Sciences April 2013
6. Department of Pharmacology and Toxicology, University of Zurich June 2013

PARPURA

Presentations

1. Satellite Federation of European Neurosciences (FENS) Forum 2012 event, Barcelona, Spain 7/14/12
2. International Workshop: "Methods on the interface of Neurochemistry and Electrophysiology", Belgrade, Serbia8/30/12
3. Regional Biophysical Conference 2012, Kladovo, Serbia9/4/12
4. Bevill Conference on Glial Biology in Medicine, Birmingham, AL 11/6/12
5. 1st Meeting of the Federation of Neuroscience Societies in Latin America, the Caribbean and the Iberian Peninsula (FALAN), Cancún, Quintana Roo, Mexico. 11/8/12
6. International Astrocyte School IAS 2013 Gliotransmission in the brain network, Bertinoro, Italy 3/20/13
7. International Astrocyte School IAS 2013 Gliotransmission in the brain network, Bertinoro, Italy 3/22/13
8. 6th Scientific Colloquium, University of Rijeka, Rijeka, Croatia (given in Croatian language) 3/26/13
9. Workshop - 24th Biannual Joint Meeting of the International Society for Neurochemistry and the American Society for Neurochemistry, Cancun, Mexico 4/23/13
10. Project Glowbrain Workshop "Stem Cell Techniques", Zagreb, Croatia. 5/24/13
11. 5th Conference on Advances in molecular mechanisms underlying neurological disorders, Joint conference of the European Society for Neurochemistry and the Biochemical Society, Bath, UK. 6/24/13

Poster presentations

1. 10/26/12 Grubišić, V. [1], Gottipati, M.K. [1], Stout, R.F. Jr. [1], Grammer, .J.R. [2], Parpura, V. Generation of Muscle Using Synthetic Biology. Biomedical engineering Society 2012 Annual Meeting, Poster P-Fri-B 88.
2. 10/26/12 Gottipati, M.K. [1], Bekyarova, E., Haddon, R., Parpura, V. Functionalized Water Soluble Single-Walled Carbon Nanotubes Induce. Biomedical engineering Society 2012 Annual Meeting, Poster P Fri-B-135
3. 11/4/12 Stout, R.F., Jr. [1], Grubišić, V. [1], Parpura, V. Transgenic repeats of a glial gene promoter produce a severe and specific change in locomotion of *Caenorhabditis elegans.* ", Bevill Conference on Glial Biology in Medicine, Birmingham, AL
4. 11/5,6/12 Gottipati, M.K. [1], Kalinina, I., Bekyarova, E., Haddon, R., Parpura, V. Functionalized Water Soluble Single-Walled Carbon Nanotubes Induce. Bevill Conference on Glial Biology in Medicine, Birmingham, AL
5. 3/4, 5/13 Lee, W. [1], Reyes, R.C. [1], Gottipati, M.K. [1], Lewis, K., Lesort, M., Parpura, V., Gray, M. [3] Enhanced Ca^{2+}-dependent glutamate release from astrocytes of BACHD mice: implications for excitotoxicity. Gordon Research Conference on "Glial biology: functional interactions among glia and neurons", Ventura, CA.

[1] graduate students, [2] a senior research associate (SRA) in my laboratory; [3] KO1 Mentee

POZZO-MILLER

1. Instituto de Neurosciencias, CONICET, Universidad de Buenos Aires, Argentina (June 2012).
2. Department of Physiology, Northwestern University, Chicago IL (May 2012).
3. Department of Biochemistry and Molecular Cell Biology, Shanghai Jiao Tong University School of Medicine, China (April 2012).
4. Department of Biological Sciences, The University of Toronto (March 2012).
5. Rett Syndrome Symposium, Intellectual and Developmental Disabilities Research Center, UAB (February 2012).
6. Department of Cell, Developmental & Integrative Biology, UAB, Birmingham AL (January 2012).
7. Department of Cell Biology & Physiology, Washington University, St. Louis MO (May 2011).
8. Department of Neuroscience and Experimental Therapeutics, Texas A&M University Health Science Center, Bryan TX (March 2011).

THEIBERT

January, 2013 Undergraduate Neuroscience Colloquium-seminar

VISSCHER

1. American Speech-Language-Hearing Association Annual Meeting, invited speaker, November 16, 2012. Comparing auditory and visual processing systems using fMRI and behavior.
2. University of Michigan, invited speaker, Psychology Department, departmental seminar, December 7, 2012. The role of visual cortex in maintaining a task set.
3. Society for Philosophy of Science in Practice, Fourth Biennial Conference. Toronto, Canada. Speaker in Contributed Session, June 28, 2013. Taxonomic Practices in the Scientific Study of Cognition: Do Valid Constructs Matter? A view from the trenches.
4. UAB Neuroscience Retreat, September 14, 2012. How does the brain maintain a task set?: The role of intrinsic neural activity.
5. UAB Physics department colloquium, departmental seminar, October 5, 2012. Same input, different output: using neuroimaging to examine how your brain processes information.

WADICHE

1. 2012 May Departmental seminar: Inhibition through excitation beyond the synapse
Dept. of Neuroscience, Albert Einstein College of Medicine, Bronx, NY
2. 2012 Oct Poster presentation Society for Neuroscience Annual Meeting (2012)
GABAergic depolarization promotes excitatory synaptogenesis on adult-generated neurons
JH Chancey, E Adlaf, M Sapp, P Pugh, JI Wadiche, L Overstreet-Wadiche
3. Poster presentation Society for Neuroscience Annual Meeting (2012)
Distinct calcium cooperativity of synchronized and desynchronized multivesicular release
S Rudolph, L Overstreet-Wadiche, JI Wadiche
4. Poster presentation Society for Neuroscience Annual Meeting (2012)
Spillover activation of inhibition segregates subpopulations of interneurons in the cerebellar cortex
L Coddington, S Rudolph, L Overstreet-Wadiche, JI Wadiche
5. 2012 Nov Speaker: Neuronal glutamate transporters regulate glial excitatory transmission and motor coordination
Bevill Conference on Glial Biology in Medicine
Birmingham, AL

6. 2013 Apr Speaker: Cold Spring Harbor Laboratories Meeting on Synapses, Circuits and Behavior
Cold Spring Harbor, NY
7. 2013 Feb Departmental Seminar Series speaker, Department of Physiology and Neurobiology
Univ. of Connecticut, Storrs, CT
8. 2013 Aug Speaker: Gordon Research Conference on Cerebellum, New London, NH
9. 2013 Sep Departmental Seminar Series speaker, Department of Neuroscience
University of Minnesota, Minneapolis, MN

5. Presentations at public (non-scientific) meetings or events

LESTER
Lecture on Nicotine and Addiction to the New Horizon Birmingham Association (Sep 2012).

LUBIN
1. CHDI Foundation workshop on HDAC4 and Huntington's Disease (HD). Los Angeles, California.
2. Invited by CIRC to talk to guests at the annual Paisley's Bicycle Relay Across America event.
3. Spoke to students in SPIN (Summer program in Neuroscience) UAB.
4. Grant writing workshop sponsored by the Postdoctoral Association. University of Alabama at Birmingham, Birmingham, Alabama. Spoke to postdocs and faculty about the NIH-K99 funding mechanism.

VISSCHER
1. Presentation to Perimeter Civitan Club, (July, 2013), Birmingham Alabama. Presented lab's research to a lay audience.
2. Civitan Alabama Central District Convention (August 2012), Mobile Alabama. Presented information about the Civitan International Research Center to the convention.

WILSON
1. Invited talk at Proteostasis Incorporated (Cambridge, MA) May 2013.
2. Invited talk at UAB Department of Cell Biology, May 2013.

6. Awards

KING
Selected to participate in the 21st Annual NIA sponsored Summer Course in Experimental Aging Research. Hosted by the Barshop Institute in San Antonio, TX. The purpose was to educate young independent aging based researchers on the state of the science and assist in grant critique.

LUBIN
2010-Present- AES Official Fellows Host.

PARPURA
2012- Election to Academia Europaea, Physiology and Medicine Section, Member (MAE)

VISSCHER
UAB Interdisciplinary Institute for Imaging Grant. Modifications in brain connectivity after training examined with neuroimaging. (2012-2013)

WILSON
Appointed as a consultant for Progenra Incorporated (March 2013-present)

7. External collaborations with other McKnight Institutes, institutions and research programs

HABLITZ
Collaboration with Dr. Carol Barnes at Univ. of Arizona on dopamine modulation in aging PFC.

KING
1. Collaboration with Dr. Brian Simms to develop a neurosphere model for the study of klotho in neurogenesis
2. Collaboration with Dr. Bob Kesterson to develop conventional and conditional klotho knockout animals

LUBIN
Mike Brenner Lab
Lucus Pozzo-Miller Lab
McMahon Lab
Standaert Lab
Olsen Lab
Lester Lab

VISSCHER
Member of the McKnight MRI Standardization Workgroup.

WILSON
Lucas Pozzo-Miller

8. Collaborative programs with non-McKnight institutes, institutions and research programs

DOBRUNZ
Rita Cowell

KING
1. Dr. Brian Simms to develop a neurosphere model for the study of klotho in neurogenesis
2. Dr. Bob Kesterson to develop conventional and conditional klotho knockout animals
3. Dr. Sanjay Garg, University of Michigan
4. Dr. Darryl Quarles, University of Tennessee

LUBIN
1. Erich Jarvis-Duke University
2. Nigel Jones-University of Melbourne, Australia
3. Robert Lipsky, INOVA
4. Christophe Bernard, INSERM, Marseille, France
5. Molly Meffert, John Hopkins

6. Sookyong Koh, Children's Memorial Hospital, Northwestern University
7. Laura Schrader, Tulane University
8. Darryl Hood, Meharry Medical College

OVERSTREET-WADICHE
1. Candace Floyd, UAB
2. Dave Poulson, University of Montana Missoula
3. Karoly Mirnics, Vanderbilt

PARPURA
1. Cyberplasm (C. Voigt, Univ of California San Francisco, CA; J. Ayers, Northeastern University, MA; Daniel Frankel, Newcastle University, UK)
2. Pools of glutamate for exocytotic glutamate release (H.S. Waagepetersen and A. Schousboe; Univ of Copenhagen, Danmark)
3. The role of connexin 43 in astrocytic exocytosis (E. Scemes and D.C Spray, Albert Einstein College of Medicine, NY)
4. Optogenetic approaches for stimulation of astrocyte in vivo (S. Kasparov, Univeristy of Bristol, UK and P.G. Haydon, Tufts Univ, Boston, MA)
5. CNTs in modulation of neuronal growth, astrocytic maturation/stellation (R.C. Haddon, Univ of California Riverside, CA)
6. CNTs distribution in the brain (J.J. Rodriguez, Univ of the Basque Country, Bilbao, Spain and A. Verkhratsky, Univ of Manchester, UK)
7. CNTs in endocytosis (P. Lučin, University of Rijeka, Croatia)
8. CNTs in traumatic brain injury (G. Župan, University of Rijeka, Croatia)
9. CNTs and dental pulp stem cells (J. Milašin, University of Belgrade, Serbia)
10. CNTs and brain stem cells (S. Gajović, University of Zagreb, Croatia)
11. SNARE complex proteins (R. Zorec, Univ of Ljubljana, Slovenia)
12. VGLUTs trafficking in astrocytes (R. Zorec, Univ of Ljubljana, Slovenia)
13. The role of presenilins in vesicular trafficking in astrocytes (R. Zorec, Univ of Ljubljana, Slovenia)
14. Single molecule measurements of interactions between SNAREs and their associated proteins (U. Mohideen, Univ of California Riverside, CA)
15. Nanosieve-based detection of botulinum toxins (A. Gu, Univ Missouri, Columbia, MO)
16. Enteric glial cells and calcium dynamics (B. Gulbransen, Michigan State University, East Lansing, MI)
17. EGCG effects on calcium dynamics and cell growth (K. Pavelić, University of Rijeka, Croatia)
18. Purinergic status in astrocytes (S. Stojilkovic, NIH)
19. The role of astrocytes in modulation of synaptic transmission in Huntington's disease (A. Araque, Cajal Institute, Madrid, Spain)

POZZO-MILLER
1. Frank Longo, Stanford University, San Francisco, CA.
2. Jeff Neul, Baylor College of Medicine
3. Tien-Le Xu, Jiao-Tong University, Shanghai, China.
4. Arturo Romano, University of Buenos Aires, Argentina.
5. James Eubanks, Toronto Western Hospital, Canada.
6. Gabriela Paglini, Instituto Ferreyra, Córdoba, Argentina.
7. Yong Li, Jiao-Tong University, Shanghai, China.

8. Karl Braunewell, SRI, Birmingham AL.
9. Suzanne Oberholster, Samford University, Birmingham, AL.
10. Takafumi Inoue, Waseda University, Tokyo, Japan.

VISSCHER
1. Lesley Ross and Karlene Ball, Psychology Department
2. Cynthia Owsley and Dawn DeCarlo, Ophthalmology Department
3. Daniel Marson, Neurology Department
4. Adrienne Lahti, Psychiatry Department
5. Jerzy Szaflarsky, Neurology Department
6. Angela Gutchess, Brandeis University
7. Aaron Seitz, UC Riverside
8. Lyn Turkstra, University of Wisconsin, Madison

WADICHE
1. Dave Poulson PhD, University of Montana Missoula, MT
2. Anastassios Tzingounis PhD, University of Connecticut, Storrs, CT
3. Henrique von Gersdorff PhD, Vollum Institute, Portland, OR
4. Malin Stridh PhD and Helle S. Waagepetersen PhD University of Copenhagen, Copenhagen, Denmark
5. Rolf Sprengel PhD and Peter Seeburg PhD, Max Planck, Heidelberg, Germany
6. Shiwei Huang PhD and Erik De Schutter PhD, OIST, Okinawa, Japan

APPENDICES

List of Seminar Speakers sponsored by the Evelyn F. McKnight Brain Institute at UAB.

Evelyn F. McKnight Brain Institute Seminars 2013		
1/17/2013	Robert Schwarcz, Ph.D. Professor University of Maryland	*"Glial Cells as Pharmacological Targets: Focus on the Kynurenine Pathway of Tryptophan Degradation"*
1/31/2013	Garret Stuber, Ph.D. Assistant Professor UNC School of Medicine	*"Dissecting the neural circuits that mediate reward and aversion"*
2/7/2013	James Mastrianni, M.D., Ph.D. Associate Professor University of Chicago Medicine	"Defining the Molecular and Cell Biological Mechanisms of Human Prion Disease"
2/14/2013	Marsha R. Mailick, Ph.D. Director University of Wisconsin-Madison Waisman Center	"Fragile X Syndrome and Associated Disorders: *Prevalence and Impacts"*
2/14/2013	Albee Messing, VMD, PhD Professor University of Wisconsin-Madison	*"Stress pathways as therapeutic targets in Alexander disease - the prototype astrogliopathy"*
2/21/2013	Andrew Bean, Ph.D. Professor University of Texas Medical School of Houston	*"Molecular Mechanisms of Endocytosis"*
2/22/2013	Ivan Milenkovic, Ph.D. University of Leipzig, Germany	*"Purinergic modulation of neuronal activity in developing central auditory circuit"*
2/28/2013	Tao Ma, MD, PhD Asst. Research Scientist New York University	"Reversal of AD-related Synaptic Plasticity and Memory Deficits by Suppressing PERK-eIF2α Signaling"
3/7/2013	Shane Hentges, Ph.D. Assistant Professor Colorado State University	*"The many transmitters of hypothalamic neurons: pre and postsynaptic actions"*
3/14/2013	Benjamin Hall, Ph.D. Assistant Professor Tulane University	*"NMDA Receptor Regulation of Excitatory Synaptic Strength and Behavioral Despair"*
3/21/2013	Han-Xiang Deng, M.D., Ph.D. Professor Northwestern University	*"Ubiquilin2-mediated defects of protein degradation in neurodegenerative diseases"*
4/3/2013	Paul J. Kenny Associate Professor The Scripps Research Institute	*"Discovery of a new pathway controlling nicotine intake"*
4/4/2013	Robert McCullumsmith, M.D., Ph.D. Assistant Professor UAB	*"Abnormalities of glutamate transporter expression in schizophrenia"*

5/09/2013	Todd Cohen, Ph.D. Post Doc University of Pennsylvania, Perelman School of Medicine	*"Novel mechanisms of neurodegeneration via post-translational modifications"*
08/29/2013	Jeremy H. Herskowitz, Ph.D. Instructor Emory University SOM	*"Targeting the Rho/ROCK Pathway to Combat Cognitive Decline"*
09/19/2013	Helen Scharfman, Ph.D. Professor NY University, Langone Medical Center Center for Dementia Research	*"Actions of estrogen and androgen in hippocampus and the role of BDNF"*
09/26/2013	John Hogenesch, Ph.D. Professor University of Penn, Perelman SOM	*"Neurogenomics of the Circadian Clock"*
10/10/2013	John T. Williams, Ph.D. Senior Scientist Vollum Institute	*"Dopamine mediated synaptic inhibition in the ventral midbrain"*
10/24/2013	Steve Kaminsky, Ph.D. Chief Science Officer International Rett Syndrome Foundation	"Rett Syndrome and preparing a grant toa private organization"
11/07/2013	Christian Giaume, Ph.D., DRI Cnts Collège De France Paris, France	*"Glial connexin/pannexin expression and function in the context of Alzheimer's disease"*
11/07/2013	Vincent Prévot, Ph.D. Inserm, Jean-Pierre Aubert Research Center University of Lille 2, France	"*Tanycytes as gatekeepers of the Metabolic Brain*"
11/07/2013	Brian Gulbransen, Ph.D. Michigan State University	*"Death stars of the gut: Interactions between enteric glia and neurons in health and disease"*
11/07/2013	Nanna MacAulay, Ph.D. University of Copenhagen	*"Cx43 hemichannel permeability – half the story?"*
11/07/2013	Alfonso Araque, Ph.D. Cajal Institute, CSIC Madrid, Spain	*"Astrocytes mediate cholinergic-induced synaptic plasticity in vivo"*
11/07/2013	Richard Robitaille, Ph.D. University of Montréal, Canada	*"Dynamic deciphering and modulation of synaptic competition by glial cells at the neuromuscular synapses"*
11/07/2013	Stéphane Oliet, M.D., Ph.D. Inserm U862 - Neurocentre Magendie University of Bordeaux, France	*"Surface dynamics of astroglial glutamate transporter GLT-1"*
11/07/2013	Pavle Andjus, Ph.D. University of Belgrade, Serbia	"*Humoral basis of neuroinflammation in amyotrophic lateral sclerosis-studies onastrocytes in culture*"
12/19/2013	Catrina Sims Robinson, Ph.D. Research Fellow Institute of Gerontology, Medical School	"Central insulin resistance may play a role in obesity-induced cognitive impairment"

ARTICLES AND OTHER NEWS ITEMS

Fearful Memories Haunt Mouse Descendants

by Ewen Callaway, Nature
December 1st, 2013

Certain fears can be inherited through the generations, a provocative study of mice reports1. The authors suggest that a similar phenomenon could influence anxiety and addiction in humans. But some researchers are sceptical of the findings because a biological mechanism that explains the phenomenon has not been identified.

According to convention, the genetic sequences contained in DNA are the only way to transmit biological information across generations. Random DNA mutations, when beneficial, enable organisms to adapt to changing conditions, but this process typically occurs slowly over many generations.

Yet some studies have hinted that environmental factors can influence biology more rapidly through 'epigenetic' modifications, which alter the expression of genes, but not their actual nucleotide sequence. For instance, children who were conceived during a harsh wartime famine in the Netherlands in the 1940s are at increased risk of diabetes, heart disease and other conditions — possibly because of epigenetic alterations to genes involved in these diseases2. Yet although epigenetic modifications are known to be important for processes such as development and the inactivation of one copy of the X-chromsome in females, their role in the inheritance of behaviour is still controversial.

Kerry Ressler, a neurobiologist and psychiatrist at Emory University in Atlanta, Georgia, and a co-author of the latest study, became interested in epigenetic inheritance after working with poor people living in inner cities, where cycles of drug addiction, neuropsychiatric illness and other problems often seem to recur in parents and their children. "There are a lot of anecdotes to suggest that there's intergenerational transfer of risk, and that it's hard to break that cycle," he says.
Heritable traits

Studying the biological basis for those effects in humans would be difficult. So Ressler and his colleague Brian Dias opted to study epigenetic inheritance in laboratory mice trained to fear the smell of acetophenone, a chemical the scent of which has been compared to those of cherries and almonds. He and Dias wafted the scent around a small chamber, while giving small electric shocks to male mice. The animals eventually learned to associate the scent with pain, shuddering in the presence of acetophenone even without a shock.

This reaction was passed on to their pups, Dias and Ressler report today in *Nature Neuroscience*1. Despite never having encountered acetophenone in their lives, the offspring exhibited increased sensitivity when introduced to its smell, shuddering more markedly in its presence compared with the descendants of mice that had been conditioned to be startled by a different smell or that had gone through no such conditioning. A third generation of mice — the 'grandchildren' — also inherited this reaction, as did mice conceived through in vitro fertilization with sperm from males sensitized to acetophenone. Similar experiments showed that the response can also be transmitted down from the mother.

These responses were paired with changes to the brain structures that process odours. The mice sensitized to acetophenone, as well as their descendants, had more neurons that produce a receptor protein known to detect the odour compared with control mice and their progeny. Structures that receive signals from the acetophenone-detecting neurons and send smell signals to other parts of the brain (such as those involved in processing fear) were also bigger.

The researchers propose that DNA methylation — a reversible chemical modification to DNA that typically blocks transcription of a gene without altering its sequence — explains the inherited effect. In the fearful mice, the acetophenone-sensing gene of sperm cells had fewer methylation marks, which could have led to greater expression of the odorant-receptor gene during development.

But how the association of smell with pain influences sperm remains a mystery. Ressler notes that sperm cells themselves express odorant receptor proteins, and that some odorants find their way into the bloodstream, offering a potential mechanism, as do small, blood-borne fragments of RNA known as microRNAs, that control gene expression.

Contentious findings

Predictably, the study has divided researchers. "The overwhelming response has been 'Wow! But how the hell is it happening?'" says Dias. David Sweatt, a neurobiologist at the University of Alabama at Birmingham who was not involved in the work, calls it "the most rigorous and convincing set of studies published to date demonstrating acquired transgenerational epigenetic effects in a laboratory model".

However, Timothy Bestor, a molecular biologist at Columbia University in New York who studies epigenetic modifications, is incredulous. DNA methylation is unlikely to influence the production of the protein that detects acetophenone, he says. Most genes known to be controlled by methylation have these modifications in a region called the promoter, which precedes the

gene in the DNA sequence. But the acetophenone-detecting gene does not contain nucleotides in this region that can be methylated, Bestor says. "The claims they make are so extreme they kind of violate the principle that extraordinary claims require extraordinary proof," he adds.

Tracy Bale, a neuroscientist at the University of Pennsylvania in Philadelphia, says that researchers need to "determine the piece that links Dad's experience with specific signals capable of producing changes in epigenetic marks in the germ cell, and how these are maintained".

"It's pretty unnerving to think that our germ cells could be so plastic and dynamic in response to changes in the environment," she says.

Humans inherit epigenetic alterations that influence behaviour, too, Ressler suspects. A parent's anxiety, he speculates, could influence later generations through epigenetic modifications to receptors for stress hormones. But Ressler and Dias are not sure how to prove the case, and they plan to focus on lab animals for the time being.

The researchers now want to determine for how many generations the sensitivity to acetophenone lasts, and whether that response can be eliminated. Scepticism that the inheritance mechanism is real will likely persist, Ressler says, "until someone can really explain it in a molecular way", says Ressler. "Unfortunately, it's probably going to be complicated and it's probably going to take a while."

Inherited Fears

Mice appear to pass certain fears onto their offspring, according to a new study.

By Jef Akst | December 2, 2013

WIKIMEDIA

Mice trained to fear the smell of a cherry-and-almond-scented chemical called acetophenone passed their anxieties onto their pups, according to a study published this week (December 1) in *Nature Neuroscience*. Compared to control mice, mice born to acetophenone-fearing fathers shuddered more in response to the scent the very first time they smelled it, and the same was true for a third generation of mice. The researchers provide evidence to suggest that the effect may be mediated by epigenetic changes, but the field is divided.

"The claims they make are so extreme they kind of violate the principle that extraordinary claims require extraordinary proof," Columbia University molecular biologist Timothy Bestor told *Nature*.

Others are more convinced. Neurobiologist David Sweatt of the University of Alabama at Birmingham told *Nature* that the manuscript is "the most rigorous and convincing set of studies published to date demonstrating acquired transgenerational epigenetic effects in a laboratory model."

For example, the researchers, Kerry Ressler and Brian Dias of Emory University in Atlanta, Georgia, noted differences in the numbers of neurons that produce an acetophenone-detecting receptor protein in mice trained to fear the scent, as well as their descendants, as compared to control mice. And the brain structures that receive projections from these neurons and help process smells were also bigger in acetophenone-fearing mice. Furthermore, the sperm of these mice displayed fewer methylation tags on the Olfr151 gene, which encodes an acetophenone-sensitive receptor, suggesting epigenetics as a possible mechanism for the inheritance of fear. Those methylation marks presumably fell within the body of the gene, however, not the promoter, leading Bestor to question their role in regulating the expression of *Olfr151*.

"I don't see any way by which that gene could be directly regulated by methylation," Bestor told *National Geographic*'s Only Human.

But evidence that epigenetics can influence behavior across generations seems to be accumulating. In people, children conceived in the midst of famine in a war-torn Netherlands in the 1940s have been noted for an increased risk of diabetes, heart disease, and other conditions, for example, and some researchers suspect that a parent's anxiety can influence their children or children's children via epigenetic changes to receptors for stress hormones.

More work is needed to nail down the epigenetic pathways that might orchestrate such changes, however. "Until someone can really explain it in a molecular way," skepticism will persist, Ressler told *Nature*. "Unfortunately, it's probably going to be complicated and it's probably going to take a while."

Tags

transgenerational epigenetic inheritance, inheritance, fear, epigenetics, behavior and animal behavior

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Comments

December 3, 2013