Program Financials

UF | UNIVERSITY of FLORIDA

Prepared for the McKnight Brain Research Foundation by the University of Florida McKnight Brain Institute and Institute on Aging

McKnight Brain Research Grant
Age-related Memory Loss Program

Financial Summary
January, 1, 2012 to December, 31, 2012

Foundation Spendable Account		**Amount**
Endowment income transferred in:		
March 31, 2012	$	256,575
June 30,2012		256,575
Sept 30, 2012		256,575
Dec 31, 2012		256,575
Total endowment income transferred in		1,026,300
Transferred out:		
Dr. Bowers (VITAL Project), adjustment		465
Transferred to UF Peoplesoft spendable accounts		- [1]
Total transferred out		465
Net change in foundation spendable account		1,025,835
Beginning balance, January 1, 2012		399,942
Ending balance, December 31, 2012	**$**	**1,425,777**

Allocation of ending balance:

Amount due to the Institute on Aging / CAM-CTRP[2]	$ 784,804		
Remaining funds for Age Related Memory Loss	640,973	**$**	**1,425,777**

UF PeopleSoft Accounts		**Amount**
Received from foundation spendable account	$	- [1]
Transfers / awards to seed grants:		
Dr. Bowers (VITAL Project)		100,000
Dr. Frazier seed grant		100,000
Total transfers to seed grants		200,000
Expenditures:		
Dr. Ormerod seed grant, ended May 31, 2012		21,530
Recruitment expenses		10,016
Travel, Publications, and Other		18,591
Total expenditures		50,137
Total transfers out and expenditures		250,137
Net change in UF Peoplesoft accounts		(250,137)
Beginning balance, January 1, 2012		750,969
Ending balance, December 31, 2012	**$**	**500,832**

[1] No transfers to UF Peoplesoft accounts in 2012

[2] Accumulation of the Institute on Aging's portion of the endowment interest income (50%), per the 2009 Gift Agreement Amendment. Scheduled to be transferred in Jan 2013.

McKnight Brain Research Grant
Age-related Memory Loss Program

Seed Grant Balances
January, 1, 2012 to December, 31, 2012

Dr. Bowers - VITAL Project (UF PeopleSoft Accounts)		Amount
Received from MBRF grant spendable UF account	$	100,000
Expenditures:		
Salary expenses		115,515
Operating expenses (lab supplies, services, and other)		11,547
Total expenditures		127,062
Net change in UF Peoplesoft accounts		(27,062)
Beginning balance, January 1, 2012		61,605
Ending balance, December 31, 2012	**$**	**34,543**

Dr. Frazier - Seed Grant (UF PeopleSoft Accounts)		Amount
Received from MBRF grant spendable UF account	$	100,000
Expenditures:		
Salary expenses		53,626
Operating expenses (lab supplies, services, and other)		4,687
Total expenditures		58,313
Net change in UF Peoplesoft accounts		41,687
Beginning balance, January 1, 2012		67,815
Ending balance, December 31, 2012	**$**	**109,502**

Dr. Ormerod - Seed Grant (UF PeopleSoft Accounts)		Amount
Received from MBRF grant spendable UF account	$	-
Expenditures:		
Operating expenses (lab supplies, services, and other)		21,530
Total expenditures		21,530
Net change in UF Peoplesoft accounts		(21,530)
Beginning balance, January 1, 2012		21,530
Ending balance, December 31, 2012	**$**	**-**

McKnight Endowed Chair
Tom Foster, PhD

Financial Summary
January, 1, 2013 to December, 31, 2013

Foundation Spendable Account		Amount	
Endowment income transferred in:			
March 31, 2013	$	39,121	
June 30,2013		39,439	
Sept 30, 2013		39,439	
Dec 31, 2013		39,725	
Total endowment income transferred in		157,724	
Transferred to UF Peoplesoft spendable accounts[1]		176,670	[1]
Net change in foundation spendable account		(18,946)	
Beginning balance, January 1, 2013		90,847	
Ending balance, December 31, 2013	**$**	**71,901**	

UF PeopleSoft Accounts		Amount	
Received from foundation spendable account	$	176,670	[1]
Expenditures:			
Faculty and research staff salaries		122,458	
Research equipment, supplies, and services		149,362	
Travel and other		742	
Total expenditures		272,562	
Net change in UF Peoplesoft accounts		(95,892)	
Beginning balance, January 1, 2013		213,017	
Ending balance, Dec 31, 2013	**$**	**117,125**	

[1]Transfers to UF Peoplesoft accounts in 2013

Cognitive Aging & Memory
Clinical Translational Research Program

Financial Summary
January, 1, 2013 to December, 31, 2013

Foundation Spendable Account		Amount	
Transferred to UF Peoplesoft spendable accounts[1]	$	500,000	[1]
Net change in foundation spendable account		(500,000)	
Beginning balance, January 1, 2013		2,760,710	
Ending balance, December 31, 2013	**$**	**2,260,710**	
Due from McKnight Brain Research Grant:			
Endowment interest income to be transferred		517,212	
Total funds available to CAM-CTRP, December 31, 2013		**2,777,922**	

UF PeopleSoft Accounts		Amount	
Received from foundation spendable account	$	500,000	[1]
Expenditures:			
Faculty and research staff salaries		351,599	
Research equipment, supplies, and services		170,155	
Travel and other		54,733	
Total expenditures		576,487	
Net change in UF Peoplesoft accounts		(76,487)	
Beginning balance, January 1, 2013		280,453	
Ending balance, Dec 31, 2013	**$**	**203,966**	

[1]Transfers to UF Peoplesoft accounts in 2013

McKnight Brain Research Grant Fund Report with related accounts

Balances through December, 31, 2013

Evelyn F. McKnight Chair for Brain Research in Memory Loss	Market Value Balance of Endowment	Fiscal Year Ending	Annual Endowment Transfers from Principal	Total Expenses	Total Revenues	Ending Spendable Fund Balance
	F007889			F007890		
F007889 / 90	$ 1,988,345	2000	$ 3,438	$ (9,625)	$ -	$ (6,188)
	$ 1,988,345	2001	$ 99,417	$ -	$ (62)	$ 93,167
	$ 2,017,380	2002	$ 100,869	$ (7,810)	$ (1,258)	$ 184,968
	$ 3,447,965	2003	$ 125,768	$ (52,502)	$ 237,079	$ 495,313
	$ 3,866,391	2004	$ 124,127	$ (7,810)	$ 14,191	$ 625,820
	$ 4,068,286	2005	$ 127,813	$ -	$ 4,602	$ 758,235
	$ 4,435,787	2006	$ 134,384	$ (150,000)	$ 19,578	$ 762,197
	$ 5,054,277	2007	$ 161,019	$ (150,000)	$ 19,448	$ 792,663
	$ 4,980,774	2008	$ 178,827	$ (200,000)	$ 14,387	$ 785,877
	$ 3,895,655	2009	$ 165,660	$ (450,000)	$ (38,922)	$ 462,615
	$ 4,100,525	2010	$ 143,584	$ (499,000)	$ 739	$ 107,938
	$ 4,602,508	2011	$ 148,182	$ -	$ -	$ 256,121
	$ 4,396,479	2012	$ 156,485	$ (200,000)	$ -	$ 212,606
	$ 4,550,752	2013	$ 156,803	$ (200,000)	$ 73,330	$ 242,739
Through Dec. 31, 2013	$ 4,633,776	2014	$ 79,164	$ (250,000)	$ -	$ 71,903
Life-to-date Totals			**$ 1,905,539**	**$ (2,176,748)**	**$ 343,111**	

Evelyn F. McKnight Brain Research Grant	Market Value Balance of Endowment	Fiscal Year Ending	Annual Endowment Transfers from Principal	Total Expenses	Total Revenues	Ending Spendable Fund Balance
	F008057			F008058		
F008057 / 58	$ 12,967,682	2000	$ -	$ -		$ -
	$ 12,967,682	2001	$ 648,384	$ -	$ 7,264	$ 655,648
	$ 13,157,047	2002	$ 657,852	$ (37,840)	$ 315,280	$ 1,590,940
	$ 20,249,996	2003	$ 651,801	$ (1,139,621)	$ 89,549	$ 1,192,669
	$ 25,363,355	2004	$ 729,335	$ (944,138)	$ 266,063	$ 1,243,930
	$ 26,681,575	2005	$ 843,131	$ (502,502)	$ 174,351	$ 1,758,910
	$ 29,091,810	2006	$ 881,347	$ (250,000)	$ 52,383	$ 2,442,639
	$ 33,148,130	2007	$ 1,056,031	$ (500,000)	$ 73,172	$ 3,071,843
	$ 32,666,165	2008	$ 1,172,824	$ (350,003)	$ 66,972	$ 3,961,636
	$ 25,549,465	2009	$ 1,086,475	$ (1,300,000)	$ (479,678)	$ 3,268,433
	$ 26,893,099	2010	$ 941,689	$ (1,864,217)	$ 67	$ 2,345,972
	$ 30,185,328	2011	$ 971,846	$ (2,413,940)	$ -	$ 903,877
	$ 28,834,098	2012	$ 1,026,301	$ (1,017,551)	$ -	$ 912,627
	$ 29,845,891	2013	$ 1,028,384	$ (1,425,777)	$ 10,533	$ 525,768
Through Dec. 31, 2013	$ 30,390,397	2014	$ 519,191	$ (268,150)	$ 83	$ 776,889 [1,2]
Life-to-date Totals			**$ 11,695,399**	**$ (12,013,739)**	**$ 576,039**	

CAM-CTRP		Fiscal Year Ending	Transferred from F008058 (1/2 of MBRF Grant Income)	Total Expenses	Total Revenues	Ending Spendable Fund Balance
				F016327		
F016327		2010	$ 1,634,217	$ (200,000)	$ -	$ 1,434,217
		2011	$ 941,689	$ -	$ -	$ 2,375,906
		2012	$ -	$ -	$ -	$ 2,375,906
		2013	$ 784,804	$ (400,000)	$ -	$ 2,760,710
Through Dec. 31, 2013		2014	$ -	$ (500,000)	$ -	$ 2,260,710
Life-to-date Totals			**$ 3,360,710**	**$ (1,100,000)**	**$ -**	

AMENDED GIFT AGREEMENT - reconciliation		Fiscal Year Ending	Endowment Transfers from Principal	1/2 allocated to CAM-CTRP	Actual transfers to CAM-CTRP	Still due to CAM-CTRP
Initial Transfer	9/17/2009	2010		$ (1,634,217)	$ 1,634,217	$ -
		2010	$ 941,689	$ (470,845)	$ -	$ 470,845
		2011	$ 971,846	$ (485,923)	$ 941,689	$ 15,078
		2012	$ 1,026,301	$ (513,151)	$ -	$ 528,229
		2013	$ 1,028,384	$ (514,192)	$ 784,804	$ 257,617
	Through Dec. 31, 2013	2014	$ 519,191	$ (259,596)		$ 517,212
	Life-to-date Totals		**$ 4,487,411**	**$ (3,877,922)**	**$ 3,360,710**	

[1]The McKnight Brain Research Grant had a spendable account balance of $776,889 as of Dec. 31, 2013. However, $517,212 was due to the CAM-CTRP that had not been transferred at that date. The resulting available funds for each program are shown to the right...

[2]Adjusted for rounding.

Available for ARML: $ 259,678

Available for CAM-CTRP: $ 2,777,922

UF Foundation Endowment Reports

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Prepared for the McKnight Brain Research Foundation by the University of Florida McKnight Brain Institute and Institute on Aging

Evelyn F. McKnight Brain Research Grant

BOOK VALUE as of 09/30/13	**$25,967,781**
MARKET VALUE as of 09/30/13	**$30,650,930**
PROJECTED SPENDABLE INCOME for 2013/14	**$1,042,132**

ENDOWMENT MANAGEMENT

Endowment assets are invested through the University of Florida Investment Corporation (UFICO), created in 2004 to manage UF's investment portfolios. UFICO is headed by a Chief Investments Officer who reports to a volunteer Board of Directors and to the President of the University of Florida.

(Fund # 008057)

1938 W. University Ave., Gainesville, FL 32603 • 352-392-1691 (main) • 352-846-3444 (Donor Relations) • www.uff.ufl.edu

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Evelyn F. McKnight Chair for Brain Research in Memory Loss

BOOK VALUE as of 09/30/13	**$3,995,677**
MARKET VALUE as of 09/30/13	**$4,673,501**
PROJECTED SPENDABLE INCOME for 2013/14	**$158,899**

ENDOWMENT MANAGEMENT

Endowment assets are invested through the University of Florida Investment Corporation (UFICO), created in 2004 to manage UF's investment portfolios. UFICO is headed by a Chief Investments Officer who reports to a volunteer Board of Directors and to the President of the University of Florida.

(Fund # 007889)

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McKnight Brain Research Foundation

Evelyn F. McKnight Brain Research Grant (008057)

Spendable Fund Transfers since endowment inception

FY 2013/2014	**$258,658 (09/30/13 YTD)**
FY 2012/2013	**$1,028,384**
FY 2011/2012	**$1,026,301**
FY 2010/2011	**$971,846**
FY 2009/2010	**$941,689**
FY 2008/2009	**$1,086,475**
FY 2007/2008	**$1,172,824**
FY 2006/2007	**$1,056,031**
FY 2005/2006	**$881,347**
FY 2004/2005	**$843,131**
FY 2003/2004	**$729,335**
FY 2002/2003	**$651,801**
FY 2001/2002	**$657,852**
FY 2000/2001	**$648,384**
TOTAL	**$11,954,058**

Evelyn F. McKnight Chair for Brain Research in Memory Loss (007889)

Spendable Fund Transfers since endowment inception

FY 2013/2014	**$39,439 (09/30/13 YTD)**
FY 2012/2013	**$156,803**
FY 2011/2012	**$156,485**
FY 2010/2011	**$148,182**
FY 2009/2010	**$143,584**
FY 2008/2009	**$165,660**
FY 2007/2008	**$178,827**
FY 2006/2007	**$161,019**
FY 2005/2006	**$134,384**
FY 2004/2005	**$127,813**
FY 2003/2004	**$124,127**
FY 2002/2003	**$125,768**
FY 2001/2002	**$100,869**
FY 2000/2001	**$99,417**
FY 1999/2000	**$3,438**
TOTAL	**$1,865,815**

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THE UNIVERSITY OF FLORIDA FOUNDATION

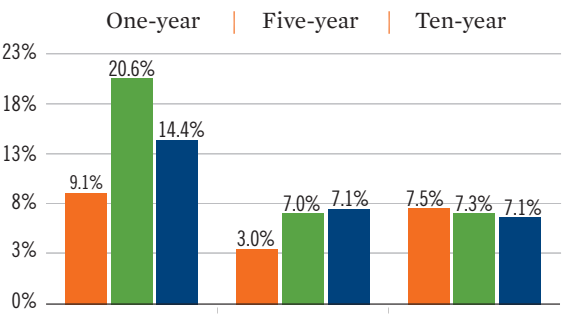
ENDOWMENT MANAGEMENT AND INVESTMENT PERFORMANCE REPORT

Endowments are an irreplaceable source of quality, stability, productivity and creativity for the University of Florida. The thoughtful individuals and organizations who create endowments provide security and confidence for our students and faculty, now and in the future. As such, the University of Florida Foundation invests your gift assets to protect the ability of the endowment to provide, in perpetuity, an income stream sufficient to support the university activity you designated, and to ensure the proceeds thereof are used in accordance with your designation.

The endowment investment pool is managed by the University of Florida Investment Corporation, a direct support organization.

The long-term goal for the endowment investment pool is to earn a total return of 8.2%, sufficient to provide a 4.0% income stream to support the university activity you designated, fund the Office of Development and Alumni Affairs through a 1.2% administrative fee and provide 3% to protect against inflation. The endowment investment pool's growth and investment returns are summarized in the charts below.

Endowment Investment Pool Annualized Return*

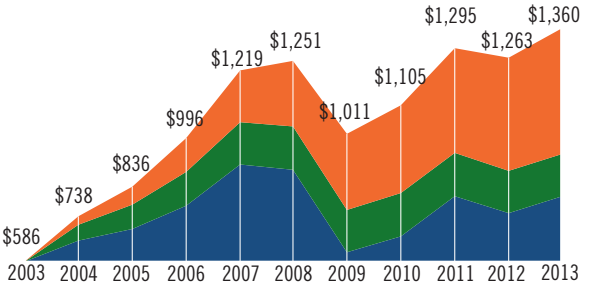


- Endowment Investment Pool
- S&P 500 Index
- 70% Russell 3000 / 30% Barcap Aggregate

Returns are net of investment manager fees, before endowment spending.

Endowment Growth

(in $ millions)



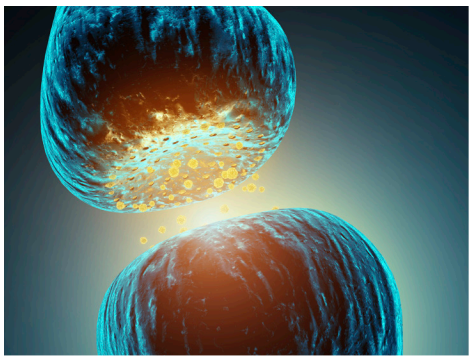
- Investment Growth*
- State Match
- Gifts

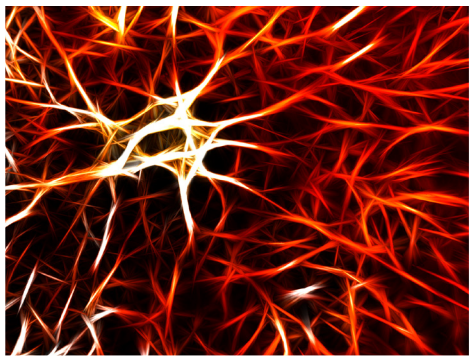
Net of fees and distributions

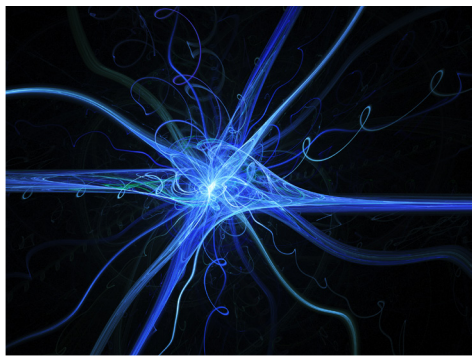
FOR MORE INFORMATION, CONTACT:
Office of Donor Relations
(352) 392-3881 | DonorRelations@uff.ufl.edu

Age-related Memory Loss (ARML) Program and Cognitive Aging and Memory (CAM) Program

2013 Annual Report







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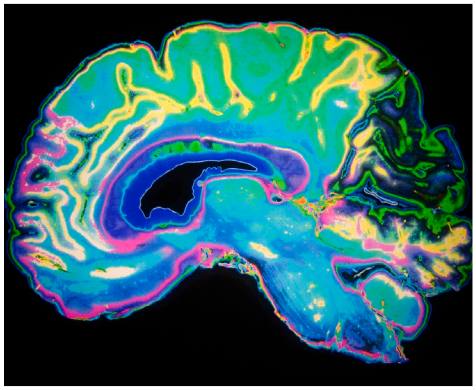
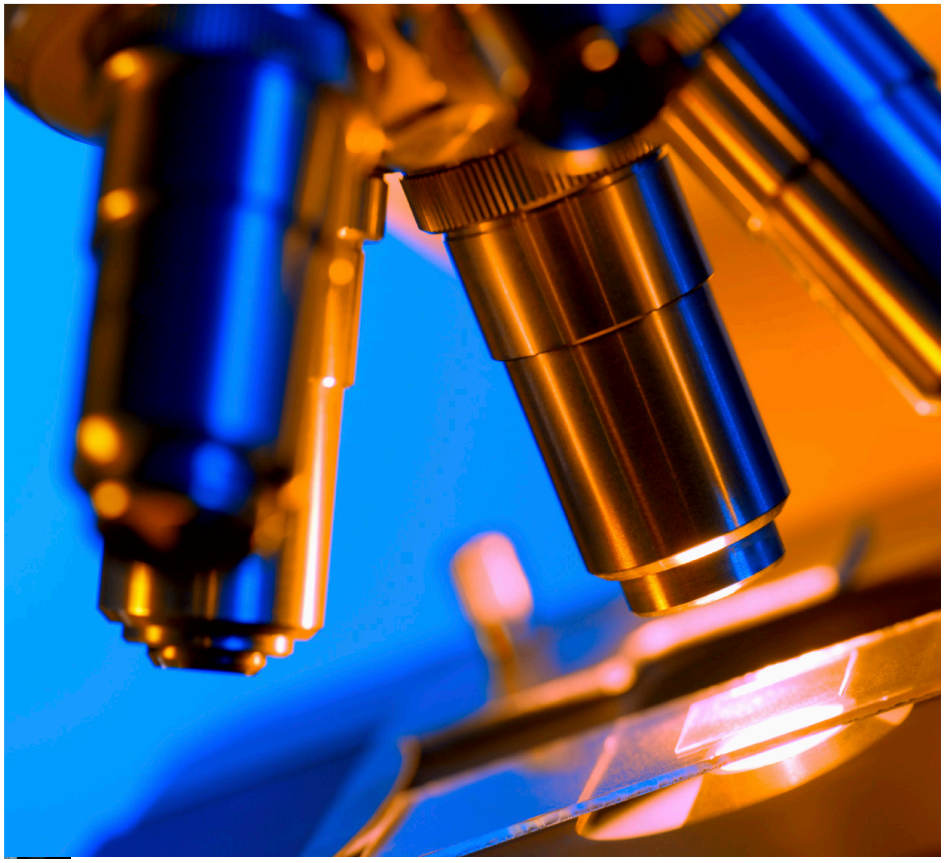
Prepared for the McKnight Brain Research Foundation by the University of Florida McKnight Brain Institute and Institute on Aging

Table of Contents





UFHealth
UNIVERSITY OF FLORIDA HEALTH

Office of the UF Senior Vice President for Health Affairs

1515 SW Archer Road, Suite 23C1
Gainesville, FL 32608
P.O. Box 100014
Gainesville, FL 32610-0014
Phone: 352.733.1700
Fax: 352.733.1701
UFHealth.org

January 9, 2014

The McKnight Brain Research Foundation
SunTrust Bank
Mail Code FL-ORL-2160
300 South Orange Avenue, Suite 1600
Orlando, FL 32801

Dear Trustees:

I would like to assert my tremendous gratitude to the McKnight Brain Research Foundation (MBRF) for its continued support toward UF's Age-related Memory Loss (ARML) and Cognitive Aging and Memory (CAM) Programs.

These Programs, under the leadership of Drs. Tom Foster and Ron Cohen, respectively, showed significant advances in 2013. Accomplishments over the past year include 1) increasing intramural and extramural recruitments of faculty investigators in both programs, 2) establishment of preclinical translational research in basic and translational scientists of the ARML program and full-swing operations of clinical research projects with multiple clinical trials for the CAM Clinical Translational Research Program (CAM-CTRP), 3) close collaborations between ARML and CAM Programs, 4) increasing productivity with a growing number of trainees, publications, and NIH and other grant funding, and 5) advances in McKnight inter-institutional collaborations.

The ongoing generosity of the MBRF plays a vital role in the successes outlined in this report. I look forward to another year of continued advancements and discovery for these programs and thank you again for your support.

Sincerely,

David S. Guzick, M.D., Ph.D.
Senior Vice President, Health Affairs
President, UF Health

UF UNIVERSITY of FLORIDA

Dean, College of Medicine
Folke H. Peterson Dean's Distinguished Professor

PO Box 100215
Gainesville, FL 32610-0215
352-273-7500 Tel
352-273-8309 Fax

January 9, 2014

The McKnight Brain Research Foundation
The SunTrust Bank
Mail Code FL-ORL-2160
300 South Orange Avenue, Suite 1600
Orlando, FL 32801

Dear Trustees:

The UF College of Medicine is once again extremely appreciative of the ongoing support from and our partnership with the McKnight Brain Research Foundation. As we enter 2014, our Age-related Memory Loss (ARML) Program and the Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP) are forming a strong combination in their basic science and translational research efforts under the leadership of Drs. Thomas Foster and Ronald Cohen.

These programs have expanded to include over two dozen leading researchers who are making important institutional and national collaborations in the effort to better understand the mechanisms of cognitive aging and age-related memory loss, and to develop prevention and treatment strategies. I will continue to push the ongoing recruitment efforts for a cognitive aging physician scientist.

The support that the McKnight Brain Research Foundation has provided since 1998 has been critical in the growth of these programs and their recent accomplishments in translational research. As you review the 2013 progress reports, we look forward to beginning an even stronger year of advancement and discovery.

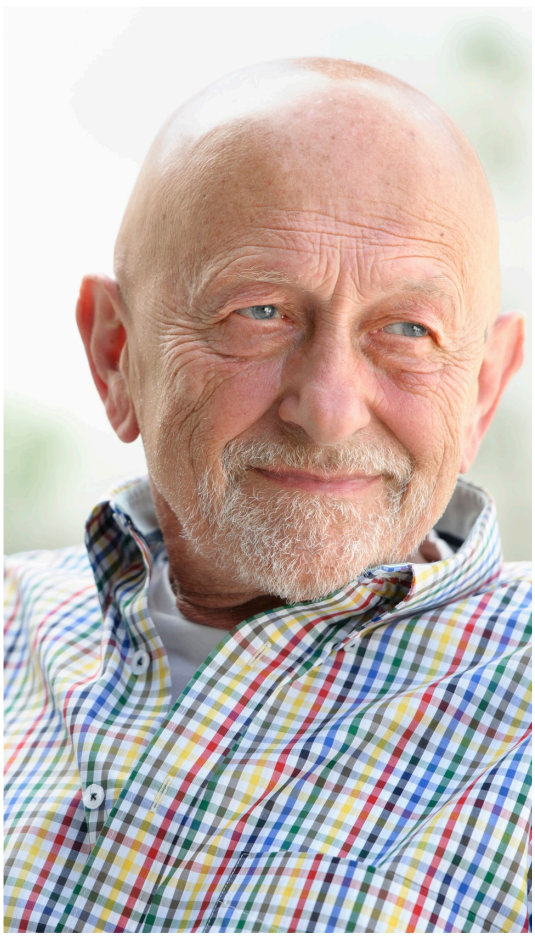
Sincerely,

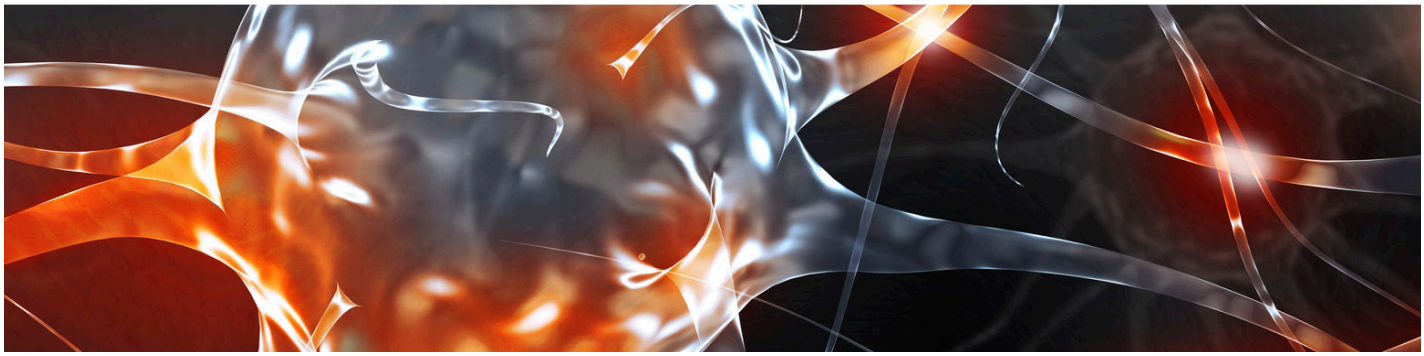
M L Good MD

Michael L. Good, M.D.
Dean, College of Medicine
Folke H. Peterson Dean's Distinguished Professor

Age-related Memory Loss (ARML) Program

2013 Progress Report





UF Evelyn F. & William L. McKnight Brain Institute
UNIVERSITY of FLORIDA

PO Box 100015
Gainesville, FL 32610-0015
352-273-8500 Office
352-846-0185 Fax
mbi.ufl.edu

January 7, 2014

Dear Trustees of the McKnight Brain Research Foundation:

This year's report of scientific achievements of the Age Related Memory Loss (ARML) Program and the Cognitive Aging and Memory – Clinical Translational Research Program (CAM-CTRP) distinguishes itself from reports of previous years. The distinction is the translational drive of the basic science research in the ARML Program and the full-fledged clinical research activities of the CAM-CTRP.

ARML Program

Investigators of the ARML Program are working together to generate a strong synergy in their investigation of the mechanism of the age-related memory loss and therapeutic discovery based on the mechanism. Dr. Tom Foster continues to play the central role in this synergy generation. He renewed the prestigious NIH MERIT award given by the National Advisory Council on Aging for his work on signaling cascades and memory deficits during aging. His studies on NMDA receptors and estrogen receptors in hippocampal function during aging receive international recognitions. Drs. Foster and Jennifer Bizon collaborate in studying key neurotransmitter receptors in memory loss of aging with molecular, cellular and behavioral approaches. Dr. Jason Frazier investigates quantitative optical imaging of intracellular calcium in individual dendritic spines, which involves collaborations with Drs. Foster and Bizon. Dr. Brandi Ormerod looks at age-related decline of olfactory discrimination and special memory by quantifying olfactory bulb neurogenesis in aged rats in collaboration with Drs. Foster and Bizon. The addition of Dr. Sara Burke to our ARML faculty has brought a systematic approach to how communication between different brain regions is affected by normal aging process. Dr. Burke uses a 96-channel digital neurophysiology acquisition system to simultaneously monitor signals from individual regions of the brain and their circuitry. Dr. Bizon, along with Drs. Barry Setlow, Kevin Felsenstein, Glen Finney, Ron Cohen, Tee Ashizawa and Foster, initiated a preclinical translational project toward clinical trials of $GABA_B$ receptor antagonist for treatment of ARML. Drs. Foster, Christiaan Leeuwenburgh, Bizon, Setlow, Frazier and Ormerod are also developing translatable therapeutic strategies to alter MNDA receptors in cognitive aging. Thus, translation of results from basic neuroscience studies has begun. We anticipate more of the development of such science-based therapeutics in coming years. For empirical clinical interventions, Drs. Dawn Bowers and Mike Marsiske continue to work on the VITAL project with encouraging progresses. Dr. Vonetta Dotson also investigates the effect of exercise in the elderly but in the context of geriatric depression using fMRI. Dr. Ormerod is investigating the mechanism of the exercise effect on cognitive aging.

UF | Evelyn F. & William L. McKnight Brain Institute
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CAM CTRP

The CAM-CTRP and the Institute on Aging (IoA) moved to new building adjacent to the CTRB. The new building opened in August 2013. The CAM-CTRP had already begun a wide variety of clinical studies of cognitive aging and memory using different disciplines under the direction of Dr. Cohen before the move. The CAM-CTRP's studies include: Obesity and type II diabetes: bariatric surgery effects on brain function and aging (the R01 application received a perfect score), the Active Brain Study (a multi-cohort study sharing a part of cohort with a LIFE Ancillary Study, to collect data of anatomical and functional neuroimaging, blood cytokines, inflammatory biomarkers and DNA, and a broad cognitive performance test battery including the NIH Toolbox Cognitive Measures). The CAM-CTRP is also conducting 13 pilot clinical studies. While 10 of these studies are important descriptive studies to characterize various aspects of cognitive aging, three others are interventional studies with transcranial magnetic stimulation (TMS), oxytocin intranasal administration, and oral methotrexate administration. The CAM-CTRP also started developing facilities and resources for their imaging, electrophysiological and neuropsychological studies under the direction of Drs. Cohen and Adam Woods.

Drs. Cohen and Marco Pahor have successfully hosted the first annual External Review Board Meeting of the CAM-CTRP. The External Advisory Committee of the CAM-CTRP recommended following actions: (1) increasing clinical expertise from M.D. researchers, such as neurologist with backgrounds in aging and neurodegenerative disease, (2) establishing a primary theme for research efforts and a branding, (3) increasing collaboration with investigators in other parts of the university, (4) placing emphasis on clinical translation of basic neuroscience findings coming from ARML Program, and (5) conducting a broad range of cognitive and behavioral functions that affect the elderly in the CAM-CTRP.

Progress Measures in 2013

One of the most straightforward documentation of our achievements is publications. Investigators in these two programs collectively published 126 papers and made 86 presentations. Another metric is grant funding. The total annual expenditure of grants awarded to our investigators by the NIH and other funding agencies exceeds $2.9 million, which matches and exceeds the amount of the annual MBRF funding. It is also important to note that the number of applications for program project grants and multi-PI grants has increased, indicating that our investigators are working together in collaborations rather than working in silos. Another important index of our progress is the number of faculty and trainees in these programs. The ARML Program recruited Sara Burke, Ph.D. from University of Arizona, and the CAM-CTRP acquired Adam Woods, Ph.D. from University of Pennsylvania. The recruitment of an M.D. clinician investigator is a high priority of the CAM-CTRP. Internally, the CAM-CTRP recruited Natalie Ebner, Ph.D. in the Department of Psychology and John Williamson, Ph.D. in the Department of Neurology.

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Additionally, 8 postdoctoral fellows and 28 graduate students were trained in the field of cognitive aging. Development of young investigators is the key for the future growth of the cognitive aging research, and we anticipate that some of these trainees will become next-generation leaders. Finally, it is important to recognize the increasing translational research in these two programs. This increase is a result of conscious efforts by the leadership and investigators.

Financial Contributions from UF

In addition to the MBRF fund, the UF and the MBI invested its own financial resources to support the ARML Program and CAM-CTRP. For the molecular core for epigenomics, the MBI paid one half of the cost to purchase the Ion Torrent Next-Gen Sequencer. The MBI funded Dr. Woods' proposal for brain ^{31}P-^{1}H phosphorus MRS whole brain coil for cerebral metabolic spectroscopy. In previous years the MBI purchased a 32-channel coil, which significantly enhanced the human 3T-MRI functionality to answer the needs of the CAM-CTRP investigators. The MBI and the Clinical and Translational Science Institute (CTSI) jointly recruited Song Lai, Ph.D. who enabled a turn-key 3T MRI operation for human subjects research. Dr. Lai has become an integral part of the CAM-CTRP. The MBI also removed the remaining funding of Dr. Matt Sarkisian's research from the MBRF/ARML source. He has received a new external grant which is supplemented by the MBI state fund. This arrangement enabled funding of Dr. Bizon's translational preclinical project.

McKnight Interinstitutional Collaborations

Meanwhile, the McKnight Inter-institutional Meeting in Tucson Arizona facilitated collaborations of the four institutions in three workgroups. For the molecular/epigenomics workgroup, the MBRF kindly committed a fund ($300K annually for two years) to support bioinformatics specialists, under the agreement that "all revenues received by the respective Institute from any commercialization of intellectual property created during the course of work on the Bioinformatics Core will be used for McKnight Inter-Institutional purposes as agreed upon by its members." Drs. Foster and Leonid Moroz are leaders of the UF group in this workgroup and have started working on single-cell epigenomics of key neurons. For a neuroimaging workgroup, the focus has been to standardize neuroimaging methods across the four institutes and to plan for the collection of multimodal MR I and MRS data. Under the plan of this workgroup, a single adult subject has travelled to all four institutes to provide a valuable standardization data. The neuroimaging workgroup will request for MBRF grant to complete the standardization by the collection of an initial samples of 200 (50 per site) healthy elderly adults. The clinical workgroup has been completing the standardization of the psychometric instruments for cognitive aging. The upcoming 2014 annual McKnight Inter-institutional meeting in Gainesville will further facilitate the efforts of the three workgroups.

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Challenges

There are challenges. Thanks to the MBRF, the money is not the issue for the current operation. Space is an issue. The IoA building and the CTRB are filling up very quickly. The MBI is anticipating recruitments of basic scientists, including those for the ARML Program and the Top10 initiative. We have initiated the preparation for moving Dr. Bowers' research operation from the MBI to the IoA building since she is using a wet lab space for dry lab research. Dr. Bowers' clinical research should benefit from closer interactions with the CAM-CTRP investigators. The current utilization of the 3T human magnet at the MBI is approaching the capacity, primarily due to the increasing CAM-CTRP research activities. We will soon need another 3T MRI. A business plan is being made to purchase the second 3T MRI. Recruitment of a physician-scientist who can translate the research of the ARML Program and CAM-CTRP into clinical applications is challenging. Although there are more than 80 NIH-funded M.D. investigators who included "cognitive aging" as a keyword in their "R" grant descriptions, many are not movable, some are only tangentially interested in cognitive aging, and the expected recruitment package of some are too expensive for our resources. We are working on over a dozen candidates at present.

Next Step

The next step is to proceed with strengthening of the translational programs at both the ARML Program and the CAM-CTRP. Closer interactions between these two programs are essential. Since pharmaceutical companies have significantly scaled down their drug development programs for neuroscience, the preclinical drug development has become an important role for academic programs. Such preclinical studies at ARML Program must be coordinated to the clinical trials machinery of the CAM-CTRP. The McKnight Interinstitutional workgroups should play key roles in the basic science, preclinical and clinical projects of cognitive aging to further facilitate the advances. We should also strongly promote collaborations with investigators of institutions outside our interinstitutional collaborations.

Best regards,

Tetsuo Ashizawa, M.D.
Executive Director, McKnight Brain Institute
Melvin Greer Professor of Neurology
Chair, Department of Neurology

SUMMARY OF SCIENTIFIC ACHIEVEMENTS SINCE LAST REPORT:

Jennifer Bizon, PhD

In the past year, my laboratory has made substantial progress in advancing our research program related to understanding the neural and cognitive mechanisms of memory and executive dysfunction in aging. In total, we have had 7 publications appear in peer-reviewed journals during the previous year, and have 4 other manuscripts related to our age-related memory program currently under review. In addition, my laboratory has presented 9 abstracts at international meetings and I have made several invited conference presentations. Among our publications are three large studies stemming from our work investigating GABAergic signaling as a causative factor in age-related executive dysfunction (Banuelos et al., 2013, Beas et al., 2013, Banuelos et al., Under Review). In Banuelos et al. (currently under review), we present findings showing that GABAergic signaling alterations in prefrontal cortex critically contribute to age-related deficits in working memory abilities. Further, we demonstrate that working memory can be improved in aged rats by targeting prefrontal cortical GABA(B) receptors. These findings served as the foundation for the competitive renewal of our R01 from NIA which was favorably reviewed in June (overall Impact Score of 23, 16th percentile). The focus of our renewal application is to elucidate the mechanisms whereby interneuron dysfunction and dysregulated GABAergic signaling negatively impact aspects of higher-order cognition such as working memory, cognitive control, and cost-benefit decision making. We have found that there are robust individual differences in the effects of normal aging on executive function, such that some aged subjects are impaired on an attentional set shifting test of cognitive flexibility whereas others are impaired on a delayed response test of working memory. Moreover, our preliminary data suggest that these distinct forms of executive dysfunction are linked to differences in patterns of GABAergic signaling

In addition to the research focus described above, I am co-I (20% effort) on Dr. Tom Foster's R37 NIH award which was recently renewed for three additional years. This success of this proposal highlights an exciting and growing collaboration between our laboratories in which we seek to determine common and unique mechanisms which underlie distinct forms of age-related memory loss (i.e., those supported by prefrontal cortical and hippocampal systems). I am also a co-I on a McKnight Brain Research Foundation grant awarded to Dr. Brandi Ormerod which is providing funding for foundational studies related to reversing altered neurogenic mechanisms in the aged brain. Dr. Ormerod and I submitted our first co-PI R01 proposal on this topic in June 2013, which will be reviewed in December. Finally, in this past year, we have established a productive collaboration with Dr. Jason Frazier, which is focused on understanding the role of altered GABAergic signaling in the decline of age-related prefrontal cortical dependent cognition. This collaboration has thus far yielded data for two publications (including Banuelos et al., currently under review and another in preparation).

During this past year we have begun to lay the foundation for establishing a translational drug discovery program for treatment of age-related cognitive decline. After a series of meetings between Drs.Tetsuo Ashizawa, Glenn Finney, Kevin Felsenstein, Barry Setlow and myself, we have developed what I hope is a tractable strategy for moving forward a translational program to assess the use of GABA(B) receptor antagonists as cognitive enhancers in aged individuals. This approach is based on a number of studies in which we have shown significant cognitive enhancement with such agents in aged rodents. We detailed this plan in a short proposal for the UF-McKnight board, and Dr. Tom Foster has generously provided some initial funding ($50,000.00) from The Evelyn F. McKnight Endowment Fund for Brain Research to enable us to begin these studies. Most recently, we have submitted a proposal to the McKnight Brain Institute Drug Discovery program ($75,000.00) to continue the necessary preclinical work. Our overall goal, should we be successful in competing for additional funding, is to perform targeted chemistry to optimize our lead compound(s) and complete the necessary preclinical studies that are required to support a strong drug development application (U01) to NIH/NIA.

I have presented our work on age-related memory loss in a number of forums, including at the International Behavioral Neuroscience meeting in Dublin, Ireland, the Southeastern Association for Behavioral Analysis Annual Conference in South Carolina, and the UF/FSU Joint Chemosensory Symposium in Gainesville. I was also invited to submit manuscripts related to our work on aging and decision making to both a special issue of Neurobiology of Learning and Memory as well as to new book entitled "Aging and Decision-Making: Empirical and Applied Perspectives" which will be published next year.

Dawn Bowers, PhD (& Michael Marsiske, PhD)

The activity supported was the VITAL pilot clinical trial with older community-dwelling adults, supported by the Age-Related Memory Loss program of the McKnight Brain Institute. Data collection was completed in 2013 (N=72), and grant preparation and manuscript preparation have occurred over the past year.

The innovative aspects of this project included: a) examining the effects of exercise pre-dosing on the cognitive training outcomes of older adults; b) enrollment of a much older cohort of elders (mean age = 82) that is typical of most studies, and c) developing a community based partnership with The Village and its owner, Santa Fe Healthcare corporation. The pre-dosing question is innovative because many studies have shown benefits of physical and cognitive training on mental outcomes for older adults in isolation, but few human studies have asked whether improved aerobic fitness might actually boost cognitive plasticity. The very old nature of our sample means that we have a higher proportion of adults in the "high decline" phase of lifespan, including a sample much more likely to experience negative cognitive changes within a very narrow time window.

The funding provided by the ARML for this project has been important in terms of providing essential data for establishment of effect sizes for these applications and has facilitated an extensive set of community-university partnerships that well serves future ARML studies. *We have also leveraged the McKnight support to establish an ongoing laboratory and clinical referral setting at the Village, using support provided by The Village and its owner, Santa Fe Healthcare corporation.*

In 2013, we (a) obtained pre- and post-intervention brain scans (functional MRI, resting state, DTI) on four participants in the final cohort. The scanning effort was supported by resources from the McKnight Foundation (via Dr. Ron Cohen) and by colleagues in Biomedical Engineering (Mingzhou Ding, Ph.D.). Based on the positive preliminary findings, we submitted two grant proposals to NIH in the summer of 2013: (Re-Vitalize: Improving Memory in MCI- Motion and emotion; NIH/NIA R21 AG103591; submitted 6/15/2013; MPI: Dawn Bowers & Michael Marsiske; VITAL 2: Engagement plus Training for Broad Cognitive Transfer in Elders. NIH/NIA R01AG047365; Submitted 6/1/2013. MPI: Michael Marsiske & Dawn Bowers)

Sara N. Burke, PhD

The central theme of my research is how communication between different brain regions necessary for learning memory is affected by normartive aging processes. This requires experimental approaches that allow one to examine distinct brain regions simultaneously as animals perform complex behaviors. Since starting as an Assistant Professor at the University of Florida, McKnight Brain Institute on October 1, 2013, I have made considerable progress in establishing my laboratory. A 96-channel digital neurophysiology acquisition system has been obtained from Neuralynx. When set-up, this system will allow for the sampling of neural activity on 96-channels in awake-behaving young and aged animals. This will allow for multiple brain regions to be monitored simultaneously, giving us increased power to detect the circuit disruptions that are associated with normal aging. Additionally, an acquisition system has been obtained from Intan Technologies. This system requires software development for synching video tracking and neural data, but once established will allow for 256-channels to be recorded simultaneously. As this is new technology to the University of Florida, high-density single-unit electrophysiology can serve to enrich collaborative efforts within the McKnight Brain Institute as well as across institutes by including a systems-level approach to examining the neurobiology of age-related memory loss. This work is also in line with the Presidential and NIH Brain Initiative. Specifically, among the high priority areas identified by the Brain Initiative Working Group were linking neuronal activity of behavior, and developing a suite of tools for circuit manipulation.

In addition to purchasing hardware, I have established collaborative projects with Dr. Brandi Ormerod in the Department of Biomedical Engineering and Dr. Jennifer Bizon. Dr. Ormerod and I submitted a Letter of Intent for the Opportunity Seed Fund to investigate the role of neurogenesis in hippocampal activity pattern dynamics. This project will provide insight into how the age-related decrease in neurogenesis affects information processing within the hippocampus. Regarding the second collaborative project, Dr. Bizon and I are obtaining cDNA of the HCN channel and are planning to look at expression of this gene in the prefrontal and peripheral cortices of young and old rats brains to see if changes in the expression of the HCN gene are linked to changes in the balance between excitation and inhibition that are observed with age.

To support these research endeavors I have hired a computer science student, Nick Topper, who is developing software programs, and a postdoctoral fellow, Dr. Andrew Maurer. Dr. Maurer is instrumental in setting up the acquisition systems and is also mentoring Mr. Topper. I also have a rotating graduate student, Sarah E. Burke, who is helping with the construction of electrode recording arrays and *in situ* hybridization of HCN mRNA.

Finally, I have also submitted an animal research protocol to the Institutional Animal Care and Use Committee that is currently under review.

Vonetta Dotson, PhD

Title: ***Effect of exercise on memory in geriatric depression: An fMRI pilot study***

The relationship between depression and age-related memory deficits is well established, and there is increasing evidence to suggest that the underlying neurobiological changes in depression may be the basis of this relationship. Consequently, interventions that reverse or minimize depression-related changes in the brain may have the potential to simultaneously treat memory deficits secondary to depression. The overall aims of this proposal are 1) to examine whether aerobic exercise (AE) improves memory functioning and alters memory-related brain functioning in depressed older adults, and 2) gather preliminary data for an R01 application examining potential mechanisms for the antidepressant and cognitive-enhancing effect of AE in older adults.

Funding for Dr. Dotson's award began in March 2011, and data collection was completed in May 2013. Despite initial difficulties in recruiting and retaining participants, the award has led to results related to the original aims as well as subprojects relevant to age-related memory loss. Baseline data were collected for 26 participants. Since this proposal used an fMRI protocol that was identical to studies that were conducted with funds from Dr. Dotson's start-up package, data were combined to from a larger dataset of cross-sectional data that is being analyzed for multiple studies. Longitudinal data are available for 10 participants. Highlights of current findings and productivity related to the results are as follows:

- **Effect of aerobic exercise on memory encoding in older adults with a history of depression:** Dr. Dotson had difficulty recruiting and retaining 15 subjects with a current diagnosis of depression for the exercise intervention, as originally proposed. However, 6 older adults with a history of depression completed the protocol, and were compared with 4 older adults without a history of depression. The rationale was that since research has shown that older adults with remitted depression often show persistent cognitive and brain changes even after mood has improved, the hypotheses formulated for current depression would be applicable to those with a history of depression as well. Results showed that compared to controls, the history of depression group showed increased activation after the exercise intervention in numerous frontal and temporal regions, including the prefrontal cortex and middle temporal gyrus. These are regions that typically show blood flow reductions in depression. Thus, preliminary findings suggest that exercise may reverse the persistent brain changes that are observed in remitted late-life depression. These results are particularly exciting in their potential real-world application. Adherence to an exercise regimen is often low in depressed patients due, at least in part, to their depressed mood and lack of motivation. Results suggest that exercise interventions can be implemented once mood has improved—and therefore adherence may be better—and can successfully reverse brain changes that lead to persistent deficits in memory and daily functioning in older adults with a history of depression. These data were presented at the Society for Neuroscience conference earlier this month. Currently a manuscript is in preparation that will include these preliminary results. This paper will first present results from baseline data on 11 participants with a history of depression compared to age- and sex-matched controls, and also include the preliminary results from the follow-up data. These results will also serve as pilot data for an R01 application to the NIH in 2014.
- **Sex differences in memory encoding and working memory in older adults:** As summarized in the last annual report, in the baseline data, sex differences in brain activity during working memory and episodic memory tasks were observed. A manuscript was submitted for publication based on the working memory findings in August, and Dr. Dotson is awaiting reviews from the journal. Additionally, she presented these findings at this year's Society for Neuroscience conference. She was selected to chair the Cognitive Aging nanosymposium in which the results were presented. This opportunity also resulted in Dr. Dotson being approached by a representative for Springer Publishing to edit a book on sex differences in cognitive and brain aging.
- **Impact of age and depressive symptoms on memory-related activity:** Also in preparation are manuscripts presenting the findings summarized in the last annual report that focused on adult age differences in memory-related brain activity, as well as the impact of depressive symptoms on memory-related brain activity. The adult age differences results were submitted to Neurobiology of Aging in August but the manuscript was not accepted. The lab is currently revising the manuscript, including running additional analyses, in response to the reviewers' comments. The manuscript will be resubmitted by the end of the year.
- **Cumulative effect of sub-threshold depression and anxiety on cognitive and brain functioning:** Dr. Dotson's lab recently submitted abstracts for the 2014 Cognitive Aging Conference focusing on the individual and combined effect of symptoms of depression and anxiety on brain functioning and neuropsychological test performance. In the fMRI analyses, greater depressive symptoms were associated with lower anterior cingulate activity during working memory in individuals with low trait anxiety, but with higher anterior cingulate activity in individuals with higher trait anxiety. Analysis of neuropsychological test performance revealed increasing depressive symptoms were associated with worse general cognition, but better visuospatial learning. Increasing anxiety was associated with worse verbal fluency, but better cognitive flexibility. The

cumulative effect of subthreshold depressive and anxiety symptoms was associated with better general cognition and worse visuospatial learning. Results suggest that comorbid symptoms of depression and anxiety may be related to unique patterns of cognitive and brain functioning compared to subclinical depression or anxiety alone. Dr. Dotson's lab is preparing a manuscript summarizing these results for publication in a special issue on depression and aging in the *Journal of Depression and Anxiety*.

- **Body Mass Index (BMI) and cognitive functioning:** Higher BMI was associated with poorer working memory, immediate memory, and general cognitive status. BMI may serve as a proxy for general or vascular health, thus highlighting the role of vascular factors in age-related memory and cognitive decline. These results were accepted for presentation at the 2014 International Neuropsychological Society conference.

Charles Jason Frazier, PhD

Title: ***The role of potassium activated calcium channels in geriatric memory dysfunction***

Our current ARML award is in direct support of a project designed to test the hypothesis that calcium activated potassium channels contribute to NMDA receptor hypofunction in aged CA1 pyramidal cells. At the time of our last report we had recently established techniques to allow for robust single cell electrophysiological recordings in slices from aged animals, and had further established the suitability of this preparation for quantitative optical imaging of intracellular calcium in individual dendritic spines. In the most recent year we have devoted our effort on this project to two primary areas: further refining technology and analysis, and obtaining extramural support.

In the first of these areas one major effort has been devoted to improving stability of the preparation to allow for increased use of within cell calcium measurements over time, and a second major effort has been devoted to refining off-line analytical tools to make the analysis more efficient, and to create final data that is more suitable for direct comparison between laboratories. Both are significant extensions compared to our position last year and in my opinion both increase overall viability and likelihood of success for the project.

We have also made several strong efforts in the last year to secure extramural funds for this project. First, we provided preliminary data for a competing renewal of an R01from Dr. Foster (submitted with Dr. Foster as PI and me as Co-I). This grant was scored at the 23rd percentile as an A1 but has not been funded. Second, we submitted an expanded version of this project to the American Federation of Aging Research (AFAR) as a Julie Martin Mid Career award, with me as PI. This grant mechanism offers $500K in direct costs over four years (with up to 10% additional indirect). I was informed by AFAR that this grant was one of the top few (of 30-40 total received) that went on to full review by the AFAR research committee. However, unfortunately, AFAR ultimately chose not to fund any awards last year despite soliciting applications with an RFA that indicated two would be fully funded. Third, we revised the AFAR application and re-submitted it as an R21 in response to an RFA from NIH for novel single cell approaches to study aging. This grant was scored and reviewed by the full panel as an A0, but is outside of the automatic funding range. We received summary statements just last week and will revise this application for an A1 submission next Spring.

Outside of the above progress on our ARML funded proposal, I would like to emphasize that ARML support for our SK project has facilitated an increasingly strong and broadening commitment to aging research in my lab. Specifically, in the last year we have continued to pursue a collaborative project with Dr. Jen Bizon focused on age related changes in GABAergic systems in medial prefrontal cortex. One collaborative manuscript is expected to be submitted by Dr. Bizon before the end of the year, while a second collaborative manuscript based heavily on work performed in my lab is also under development with expected submission in early 2014. Further, we have expanded our collaboration with Drs. Foster and Moroz by further developing techniques for successfully extracting the cytoplasm from single young and aged hippocampal neurons. Cytoplasms extracted in my lab are used by Dr. Moroz in an effort to create a complete transcriptome from a single cell. Ultimately, we hope to compare single cell transcriptomes across cell types, across age, across intrinsic electrophysiological properties, and across behavioral ability in hippocampal dependent tasks.

These additional age related projects have also supported additional efforts for extramural support. Specifically, Dr. Bizon and I developed much of an R01 on our collaborative work in PFC last summer. While not yet submitted, some of this effort is directly contributing to a project led by Dr. Bizon on an aging program project grant organized by Dr. Foster, while some of it may yet be submitted as an independent co-PI R01 by Dr. Bizon and I next Spring. Similarly, I have agreed to serve as PI on another project (Project 3) in the program project grant being organized by Dr. Foster that will contain a combination of our developing work in hippocampus and PFC. This program project grant is targeted for initial submission in 2014. Further, our effort to enable the single cell genomics projects in Dr. Moroz and Foster's labs has directly supported one submitted R21 application that was scored but not funded as an R21, and has similarly supported a grant that was funded intramurally via the Opportunity Incentive Seed Fund.

Brandi Ormerod, PhD

Title: ***Causes and relationships between olfactory and hippocampal neurogenesis and age-related cognitive decline***

We recently received funding from the MBRF ARML to extend upon our collaborative work with Dr. Tom Foster's laboratory and to embark on some exciting new collaborative work with Dr. Jennifer Bizon. We recently reported that aged rats exposed to an enriched environment exhibited rejuvenated hippocampus-dependent spatial and rejuvenated levels of hippocampal neurogenesis (Speisman et al., 2013, **Neurobiology of Aging**). We also found that weeks of daily exercise could rejuvenate spatial memory and hippocampal neurogenesis, potentially by modulating concentrations of cytokines in the blood and brain (Speisman et al., 2012, **Brain, Behavior and Immunity**). Interestingly, Dr. Bizon has shown previously that olfactory discrimination or spatial memory can be impaired in aged rats, but that aged rats rarely exhibit deficits in both cognitive domains. Our current MBRF ARML funding is currently being used to quantify olfactory bulb neurogenesis in aged rats that Dr. Foster has characterized in the water maze and that we have obtained measures of hippocampal neurogenesis and cytokines from. I have recently recruited James McGuiness, a Neuroscience graduate student to conduct this work. He has submitted an application for a prestigious NSF graduate fellowship already using preliminary data that he has already gathered and he is on track to submit an abstract for the Society for Neuroscience meeting next year and will potentially begin preparing a manuscript in the next few months. James McGuiness is continuing the work of Rachel Speisman, who graduated recently from the BME PhD program and is currently conducting her postdoctoral work at the National Institutes of Health. Dr. Bizon has already begun characterizing rats on an olfactory discrimination task so that we can directly relate measures of neurogenesis in those rats with their olfactory discrimination scores. We look forward to the data that our productive collaborations have generated regarding the mechanisms and potential interventions for age-related cognitive decline.

Matthew Sarkisian, Ph.D.

The potential of brain cells to renew themselves varies across the lifespan and can be significantly altered by disease and aging. My laboratory has made significant progress toward understanding how neuronal cilia influence neuronal development and plasticity in developing, aging, and diseased brain tissues, research that has been generously supported by the McKnight Brain Research Institute. Cilia are tiny hair-like organelles found on virtually every neuron in the brain. Changes in neural cilia function are known to disrupt learning and memory, food intake, generation of new neurons in the hippocampus, and neuronal plasticity. The breadth of the impact that cilia have on the brain and its function suggest that the diminishing neural plasticity and memory decline observed during aging could reflect age-related anatomical or physiological changes in cilia. In our quest to understand the contributions of cilia to brain function, and in particular, the aging brain, we have examined the consequences of altering ciliogenesis on neurons and the signaling properties of neuronal cilia across brain regions and over the lifespan. Earlier this year, we reported that when the growth or signaling capacity of neuronal cilia is impaired, neurons fail to extend and develop normal dendritic processes, an effect that is reversible. Remarkably, we now have preliminary data suggesting that the activity of an enzyme found within neuronal cilia is required for neurons to exhibit dendritic plasticity. These data suggest that cilia play an active role in supporting neuronal function, a role that may be increasingly critical in maintaining cortical plasticity and function in aging brain. Interestingly, the results of a recent collaborative study carried out with the Foster lab support this notion. This study, which is currently under review, shows that the normal molecular machinery present in the cilia of neurons in younger brains, including those that support learning and memory, is altered in aged rodent and human brain.

We believe that the findings described above will allow us to successfully procure competitive funding that will enable us to pursue these lines of investigation. Our results continue to provide a solid foundation for new investigations of markers of brain aging and potential mechanisms underlying the cognitive changes that can accompany aging. The data described above have been presented at local meetings and the Annual Society for Neuroscience.

PUBLICATIONS IN PEER REVIEWED JOURNALS:

Jennifer Bizon, PhD

1. Adolescent Risk Taking, Cocaine Self-Administration, and Striatal Dopamine Signaling. Mitchell MR, Weiss VG, Beas BS, Morgan D, **Bizon JL**, Setlow B. *Neuropsychopharmacology*. 2013 Oct 22. doi: 10.1038/npp.2013.295.

2. Centrally administered angiotensin-(1-7) increases the survival of stroke prone spontaneously hypertensive rats. Regenhardt RW, Mecca AP, Desland F, Ritucci-Chinni PF, Ludin JA, Greenstein D, Banuelos C, **Bizon JL**, Reinhard MK, Sumners C. *Exp Physiol*. 2013 Oct 18.

3. Characterization of age-related changes in synaptic transmission onto F344 rat basal forebrain cholinergic neurons using a reduced synaptic preparation. Griffith WH, Dubois DW, Fincher A, Peebles KA, **Bizon JL**, Murchison DA. *J Neurophysiol*. 2013 Oct 16.

4. Beas BS, Setlow B, **Bizon JL**. (2013) Distinct manifestations of executive decline in aged rats. *Neurobiology of Aging*. 34(9): 164-174.doi: 10.1016/j.neurobiolaging.2013.03.019.

5. Simon NW, Beas BS, Montgomery KS, Haberman RP, **Bizon JL**, Setlow B. (2013) Prefrontal cortical-striatal dopamine receptor mRNA expression predicts distinct forms of impulsivity. *European Journal of Neuroscience* 37(11): 1779-88. doi: 10.1111/ejn.12191.

6. Mendez IA, Damborsky JC, Winzer-Serhan UH, **Bizon JL**, Setlow B. (2013) A4β2 and α7 nicotinic acetylcholine receptor binding predicts choice preference in two cost benefit decision-making tasks. *Neuroscience*. 230:121-31. doi: 10.1016/j.neuroscience.2012.10.067.

7. Bañuelos, C, LaSarge, CL, McQuail, JA, Hartman, JA, Gilbert, RJ, Ormerod, BK, **Bizon JL**, Age-related changes in basal forebrain cholingergic and GABAergic neuron number: Relationship with spatial impairment. (2013) *Neurobiology of Aging*. 34(3):845-62. doi: 10.1016/j.neurobiolaging.2012.06.013.

(Under Review)

1. Yoder, W. M., Setlow, B., **Bizon, J. L.**, & Smith, D. W. Characterizing olfactory perceptual similarity using carbon chain discrimination in behaviorally-trained Fischer 344 rats. Under Revision at *Chemical Senses*.

2. Shimp, K. M.*, Mitchell, M. R.*, Beas, B. S.*, **Bizon, J. L.**, & Setlow, B. Affective and cognitive mechanisms of risky decision making. Under Revision at *Neurobiology of Learning and Memory*, Special Issue on Memory and Decision Making.

3. Beas, B. S.*, Setlow, B., Samanez-Larkin, G. R., & **Bizon, J. L.** Decision making in animal models of cognitive aging: a cross-species comparison of rodents and humans. Invited for Special Issue of Neurobiology of Learning and Memory on Memory and Decision Making. Currently Under Review.

4. Bañuelos, C.*, Beas, B. S.*, McQuail, J. A., Gilbert, R. J., Frazier, C. J., Setlow, B., & **Bizon, J. L.** Altered GABAergic signaling contributes to age-related impairments in working memory. Under Review.

Dawn Bowers, PhD (& Michael Marsiske, PhD)

1. Belchior, P., **Marsiske, M.**, Sisco, S. M., Yam, A., Bavelier, D., Ball, K., & Mann, W. C. (2013). Video game training to improve selective visual attention in older adults. *Computers in Human Behavior*, 29(4), 1318-1324. PMID: Pending, PMCID: Pending, NIHMSID: 492651, DOI http://dx.doi.org/10.1016/j.chb.2013.01.034, (PIF = 2.476).

2. Cook, S. E., Sisco, S. M., & **Marsiske, M.** (2013, in press). Dual-task effects of simulated lane navigation and story recall in older adults with and without memory impairment. *Aging, Neuropsychology, and Cognition*, PMID: 23043546 PMCID: Pending, NIHMSID: 492857, DOI http://dx.doi.org/10.1080/13825585.2012.725459, (PIF = 1.715).

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4. Dietz, J., Noecker, A., McIntyre, C.C., **Bowers, D.**, Foote, K., Okun, M.S. (2013). Stimulation region within the GPI does not affect verbal fluency: Results from field modeling. *Brain Stimulation*. 6, 248-53. [Epub 2012 June 16[]

5. Dotson, V. M., Sozda, C. N., **Marsiske, M.**, & Perlstein, W. M. (2013, in press). Within-session practice eliminates age differences in cognitive control. *Aging, Neuropsychology, and Cognition*, PMID: 23116428 PMCID: PMC3655128, DOI http://dx.doi.org/10.1080/13825585.2012.736469, (PIF = 1.715).

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7. Dzierzewski, J. M., **Marsiske, M.**, Aiken Morgan, A., Buman, M. P., Giacobbi Jr., P. R., Roberts, B., & McCrae, C. S. (2013, in press). Cognitive inconsistency and practice-related learning in older adults. *The Journal of Gerontopsychology and Geriatric Psychiatry*, PMID: pending PMCID: pending, NIHMSID: 501549, DOI: pending, (PIF = 0.28** approx).

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25. Roncoroni, J., Nghiem, K., Wall, W., **Marsiske, M.**, Tucker, C. M. (2013, in press). Validation of a patient-centered culturally sensitive clinic environment inventory using a national sample of adult patients, *Journal of Transcultural Nursing*. PMCID: Pending, NIHMSID: pending, DOI pending, (PIF = 0.933).

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27. Tucker, C. M., Butler, A., Kaye, L. B., Nolan, S. E. M., Flenar, D. J., **Marsiske, M.**, Bragg, M., Hoover, E., & Daly, K. (2013, in press) Impact of a culturally sensitive health self-empowerment workshop series on health behaviors/lifestyles, BMI, and blood pressure of culturally diverse overweight/obese adults. *American Journal of Lifestyle Medicine*. PMCID: Pending, NIHMSID: 494656, DOI pending, (PIF = not available).

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Sara N. Burke, PhD

1. **Burke SN**, Maurer AP, Nematollahi S, Uprety A, Wallace JL, Barnes CA (2013). Advanced age has dissociative effects on dual functions of the perirhinal cortex. Accepted pending revisions, *Journal of Neuroscience*.

2. **Burke SN**, Thome A, Plange K, Engle JR, Trouard TP, Gothard KM, Barnes CA (2013). Orbitofrontal cortex and basolateral amygdala volume show a dissociable relationship with reward devaluation in young and aged monkeys. Accepted pending revisions, *Journal of Neuroscience*.

3. Maurer AP, Lester AW, **Burke SN**, Ferng J, Barnes CA (2013). Back to the Future: Preserved hippocampal network activity during reverse ambulation. Under review, *Nature Neuroscience*.

Vonetta Dotson, PhD

1. **Dotson, V.M.**, Zonderman, A.B., Kraut, M.A., & Resnick, S.M. (2013). Temporal Relationships between Depressive Symptoms and White Matter Hyperintensities in Older Men and Women. *International Journal of Geriatric Psychiatry*, 28, 66–74. DOI: 10.1002/gps.3791.

2. **Dotson, V.M.**, Sozda, C.N., Marsiske, M., & Perlstein, W.M. (2013). Within-session Practice Eliminates Age Differences in Cognitive Control. *Aging, Neuropsychology and Cognition: A Journal on Normal and Dysfunctional Development*, 20 (5), 522-531. DOI:10.1080/13825585.2012.736469.

3. Kirton, J. W., Resnick, S. M., Davatzikos, C. Kraut, M. A. & **Dotson, V. M.** (2013). Depressive Symptoms, Symptom Dimensions and White Matter Lesion Volume in Older Adults: A Longitudinal Study. *American Journal of Geriatric Psychiatry*. DOI: 10.1016/j.jagp.2013.10.005.

(Under Review)

1. Kaufman, D.A.S., **Dotson, V.M.**, & Perlstein, W.M. Feeling ANTsy about the "golden years?" An event-related potential investigation of the effects of age on alerting, orienting, and executive function. *Neuropsychologia*
2. Kirton, J.W., Sozda, C.N., Perlstein, W.M., Manini, T.M., Anton, S.D., Szymkowicz , S.M., & **Dotson, V.M.** Older Men and Women Differ in Brain Activity during Working Memory. **Cerebral Cortex**
3. **Dotson, V.M.**, Green, M.L., Kirton, J.W., Szymkowicz , S.M., Sozda, C.N., Perlstein, W.M., Anton, S.D., & Manini, T.M. Adult age differences in fMRI activity during memory encoding. *Neurobiology of Aging*

(In Preparation)

1. Szymkowicz, S.M., Kirton, J.W., McLaren, M., Manini, T.M., Anton, S.D., & **Dotson, V.M.** *Functional Brain Activity in Remitted Depression and Preliminary Data on an Exercise Intervention*
2. Szymkowicz, S.M., Kirton, J.W., Sozda, C.N., Perlstein, W.M., Manini, T.M., Anton, S.D., & **Dotson, V.M.** *Impact of Time of Day on fMRI Activity*
3. **Dotson, V.M.**, Szymkowicz, S.M., McLaren, M., Kirton, J.W., Green, M., Anton, S.D., & Manini, T.M. *fMRI Activity during Working Memory Related to Subclinical Depression and Anxiety in Older Adults*

Charles Jason Frazier, PhD

1. De Kloet AD, Pati D, Wang L, Hiller H, Sumners C, **Frazier CJ**, Seeley RJ, Herman JP, Woods SC, Krause EG (2013) Angiotensin type 1a receptors in the paraventricular nucleus of the hypothalamus protect against diet-induced obesity. *Journal of Neuroscience*, 33(11):4825-4823.
2. **Frazier CJ**, Pati D, Hiler J, Nguyen D, Wang L, MacFadyen K, de Kloet AD, Krause EG (2013) Acute hypernatremia exerts an inhibitory oxytocinergic tone that is associated with anxiolytic mood in male rats. *Endocrinology*, PMID: 23653461.
3. **Frazier CJ** (2013) Preformed vs. on-demand: Molecular economics of endocannabinoid signaling. *Journal of Physiology*, 59:4683-4684.
4. Hofmann ME and **Frazier CJ** (2013) Marijuana, endocannabinoids, and epilepsy: potential and challenges for improved therapeutic intervention. *Experimental Neurology*, 244:43-50. PMID: 22178327.

(In Preparation)

1. Banuelos, C. Beas, BS, McQuail JA, Gilber RJ, **Frazier CJ**, Setlow, B, Bizon, JL *Prefrontal Cortical GABAergic Dysfunction Contributes to Age-Related Working Memory Impairment*. Expected submission Dec.-Jan.
2. Carpenter H, Kelly K, Bizon JL, **Frazier CJ**. *Age-related changes in GABAB receptor mediated inhibitory tone in the medial prefrontal cortex*. Expected Submission Jan. 2014.

Brandi Ormerod, PhD

1. Asokan A., Ball A.G., Laird C., Hermer L., and **Ormerod BK** (under review). Desvenlafaxine may accelerate neuronal maturation in the dentate gyri of adult male rats. *Neuroscience*.
2. Qia X, Shana Z, Jia Y, Guerra V, Alexander JC, **Ormerod BK**, Bruijnzeel AW (under review) Sustained AAV-mediated overexpression of CRF in the central amygdala diminishes the depressive-like state associated with nicotine withdrawal in rats. *Molecular Psychiatry*.
3. Hajihashemi MZ, Zhang T, **Ormerod BK**, Jiang H (under review). Non-invasive detection of seizure activity using time-series analysis of light scattering images in a rat model of generalized seizure. *Neural Engineering*.

4. Maden, M, Manwell, LA, **Ormerod BK** (2013). Proliferation zones in the axolotl brain and regeneration of the telencephalon. Neural Development, 8:1-15. JCR Impact Factor 3.70. ***BMC "Highly Accessed" publication.***

5. Speisman, RB, Kumar A, Rani A, Pastoriza JM, Severance JE, Foster TC and **Ormerod BK** (2013). Environmental enrichment restores neurogenesis and rapid acquisition in aged rats. *Neurobiology of Aging*, 34(1):263-274. JCR Impact Factor 6.634.

6. Bañuelos, C, LaSarge, CL, McQuail J, Hartman JJ, Gilbert RJ, **Ormerod BK**, Bizon JL (2013). Age-related changes in rostral basal forebrain cholinergic and GABAergic projection neurons: relationship with spatial impairment. *Neurobiology of Aging*, 34:845-862. JCR Impact Factor 6.634.

7. Ogle,WO, Speisman, RB, and **Ormerod BK**, (2013). Potential of treating age-related depression and cognitive decline with nutraceutical approaches: A mini-review. *Gerontology*, 59:23-31. JCR Impact Factor 2.203. ** ***Featured on MD Linx*** http://www.mdlinx.com/psychiatry/news-article.cfm/4190085

8. Speisman, RB, Kumar A, Rani A, Foster TC and **Ormerod BK** (2013). Daily exercise improves memory, stimulates hippocampal neurogenesis and modulates immune and neuroimmune cytokines in aging rats. *Brain, Behavior and Immunity*, 28:25-43. JCR Impact Factor 4.720. ** ***One of BBI's 25 most downloaded articles over the past 90 days*** (February–September 2013) http://www.journals.elsevier.com/brain-behavior-and-immunity/most-downloaded-articles/

9. Lee SW, Haditsch U, Cord BJ, Guzman R, Kim SJ, Boettcher C, Priller J, **Ormerod BK**, Palmer TD (2013). Absence of CCL2 is sufficient to restore hippocampal neurogenesis following cranial irradiation. *Brain Behav Immun*, 30:33-44. JCR Impact Factor 4.720.

10. **Ormerod BK**, Hanft SJ, Asokan A, Haditsch U, Lee SW, Palmer TD (2013). PPARγ activation prevents impairments in spatial memory and neurogenesis following transient illness. *Brain, Behavior and Immunity*, 29:28-38. JCR Impact Factor 4.720.

Matthew Sarkisian, PhD

1. Guadiana SM, Semple-Rowland S, Daroszewski D, Madorsky I, Breunig JJ, Mykytyn K, **Sarkisian MR**. Arborization of dendrites by developing neocortical neurons is dependent on primary cilia and type 3 adenylyl cyclase. *The Journal of Neuroscience* 2013; 33: 2626-2638.

2. Siebzehnrubl FA, Silver DJ, Tugertimur B, Deleyrolle LP, Siebzehnrubl D, **Sarkisian MR**, Devers K, Yachnis AT, Kupper MD, Neal D, Nabilsi NH, Kladde MP, Suslov O, Brabletz S, Brabletz T, Reynolds BA, Steindler DA. The ZEB1 pathway links glioblastoma initiation, invasion and chemoresistance. 2013 EMBO *Molecular Medicine* 5; 1196-1212.

PUBLICATIONS (OTHER):

Dawn Bowers, PhD (& Michael Marsiske, PhD)

1. Bauer, R.M., **Bowers, D.** (2013). Intellectual Antecedents to the Boston Process Approach to Neuropsychological Assessment. In D. Libon (Ed.), *Boston Process Approach to Neuropsychological Assessment*. New York: Oxford University Press.

2. **Bowers, D.**, Jones, J., Dietz, J. (2013, in press). Assessment of emotion, mood, and affect associated with neurologic disorders. In J. Synder, Nussbaum, Hamsher, K, and Parsons, M. (Eds). *Pocket Handbook of Neuropsychological Assessment*.

Sara N. Burke, PhD

1. **Burke SN**, Maurer AP, Cowen SL & Barnes CA (2013). Perirhinal cortical interneurons exhibit reduced firing rates with advanced age. *Society for Neuroscience Abstracts*, 43.

2. Plange K, Engle JR, **Burke SN**, Gray DT, Barnes CA (2013). Changes in sensory function are correlated with cognitive impairments in bonnet macaques. *Society for Neuroscience Abstracts*, 43.

3. Chance FS, Maurer AP, **Burke SN**, Barnes CA (2013). Dual input component models of CA1 activity in young and aged rats. *Society for Neuroscience Abstracts*, 43.

4. Lester AW, Maurer AP., **Burke SN**, Hoang LT, Barnes CA (2013). Preserved neural dynamics during reverse locomotion. *Society for Neuroscience Abstracts*, 43.

Matthew Sarkisian, PhD

1. **Sarkisian MR**, Arellano JI, Breunig JJ. Primary cilia in cerebral cortex: growth and functions on neuronal and non-neuronal cells. *In: Cilia and nervous system development and function*. Caspary T, Tucker KL (Eds). Springer, 2013: pp 105-129.

PRESENTATIONS AT SCIENTIFIC MEETINGS:

Jennifer Bizon, PhD

Invited

- "Alterations in Cholinergic and Noncholinergic Basal Forebrain Neurons in Aging: Consequences for Cognition". International Behavioral Neuroscience Society, Dublin, Ireland. July, 2013.
- "Aging Across Multiple Cognitive Domains", 30th Southeastern Association for Behavioral Analysis Annual Conference. Myrtle Beach, South Carolina, October"
- "Using Olfactory Function to Predict Age-related Memory Loss", UF/FSU Joint Chemosensory Symposium. Gainesville, Florida, June, 2013.
- "Using Animal Models of Memory and Cognition to investigate mechanisms of age-related cognitive decline", Center for Neuropsychological Studies Lecture Series, VA, Gainesville, Fl, September 2013.

Poster Presentations

- Bañuelos C, Beas BS, McQuail JA, Gilbert RJ, Setlow B, **Bizon JL** GABAergic signaling alterations contribute to impaired working memory in aged F344 rats. International Behavioral Neuroscience Society, Dublin, Ireland. July, 2013.***won first place for conference (out of 150 presentations)***
- Shimp, KM, Mitchell, MR, Beas, BS, **Bizon, JL**, & Setlow, B. Relationships between risky decision making and executive functions. International Behavioral Neuroscience Society, Dublin, Ireland. July, 2013.
- Bañuelos C, Beas BS, McQuail JA, Gilbert RJ, Setlow B, **Bizon JL** GABAergic signaling alterations contribute to impaired working memory in aged F344 rats. Nov 2013. Society for Neuroscience Annual Meeting. San Diego, CA.
- Beas, BS, Bañuelos, C. Gilbert, R, Setlow, B, **Bizon, JL** GABA(B) receptor signaling and behavioral flexibility in aging. Nov 2013. Society for Neuroscience Annual Meeting. San Diego, CA.
- Carpenter, H, Kelly, K, **Bizon, JL**, Frazier, CJ. Age-related changes in GABAB receptor mediated inhibitory tone in the medial prefrontal cortex. Nov 2013. Society for Neuroscience Annual Meeting. San Diego, CA
- Shimp, KM, Mitchell, MR, Beas, BS, **Bizon, JL**, & Setlow, B. Contributions of executive functioning to risky decision making. Nov 2013. Society for Neuroscience Annual Meeting. San Diego, CA
- Yoder, WM, Setlow, B, **Bizon, JL**, Smith, D. Methodological considerations for conducting odor-guided tasks in rodents. Nov 2013. Society for Neuroscience Annual Meeting. San Diego, CA
- McQuail, JA, Hibble, JP, **Bizon, JL**, Nicolle, MM., Selective deterioration of excitatory synapses in the aged dentate gyrus: Comparisons among glutamatergic, GABAergic and cholinergic synapses within the rat hippocampus. Nov 2013. Society for Neuroscience Annual Meeting. San Diego, CA
- **Bizon, JL**, Banuelos, C, Beas, BS, McQuail, J, Setlow, B., Altered prefrontal cortical GABAergic signaling contributes to impaired working memory in aged F344 rats. Dec 2013. American College of Neuropsychopharmacology Annual Meeting, Hollywood, Fl.

Dawn Bowers, PhD (& Michael Marsiske, PhD)

Invited

- **Bowers, D.** (2013, October). Neuropsychology of Memory and Movement. Presented at 4th annual Case Management Symposium. Mission Inn, FL

Peer Reviewed

- Diemunsch, N., Kay, D. B., **Bowers, D.** (2013, June). Sleep-Related Impairment: Parkinson's Disease Symptoms and Insomnia. Presented at 27th annual meeting of the Associated Professional Sleep Societies, Baltimore, MD.
- Dietz, J., Bradley, M.M., Lang, P.J., Okun, M.S., **Bowers, D.** (2013, October). Psychophysiology of emotion in Parkinson's disease: from perception to action. Presented at the annual meeting of the Society for Psychophysiological Research, Florence, Italy.
- Dietz, J., Bradley, M.M., Perlstein W.E., Okun, M.S., **Bowers, D.** (2013, February). Parkinson's disease, apathy, and the ERP to emotional pictures. Presented at the 41st annual meeting of the International Neuropsychological Society, Kona, Hawaii.
- Hassan, A, Vallbhajosula, S., Zahodne, L.B., **Bowers, D.**, Okun, M.S., Fernandez, H.H., Hass, C. (2013, June). Apathy, depression and postural instability in Parkinson disease: Related to a common pathophysiology. Presented at the annual meeting of the International Parkinson Congress, Sydney Australia.
- Jones, J., Jacobson, C., Murphy, M., Okun, M.S., **Bowers, D.** (2013, February). Differential effects of hypertension and hypotension on executive and memory status in nondemented Parkinson disease patients. Presented at the 41st annual meeting of the International Neuropsychological Society, Kona, Hawaii.
- Lafo, J., Jones, J., Okun, M.S., Bauer, R.M., Price, C.E., **Bowers, D.** (2013, February). Memory dissociations in Essential Tremor and Parkinson disease: a Final common pathway? Presented at the 41st annual meeting of the International Neuropsychological Society, Kona, Hawaii.
- Mangal., P. Jones, J., Lafo, J., Okun, M.S., Bauer, R.M., Price, C.E., **Bowers, D.** (2013, February). Many faces of mild cognitive impairment in Parkinson's disease: Classification approaches matter. Presented at the 41st annual meeting of the International Neuropsychological Society, Kona, Hawaii.
- **Marsiske, M**, & Willis, S. L. (2013, November). The ACTIVE Study: Methodological considerations and lessons learned. Presented at the Annual Scientific Meeting of the Gerontological Society of America, New Orleans, LA.

Sara N. Burke, PhD

- Jan 5th, 2014: Invited speaker at the Neurobiology of Learning and Memory Winter Brain conference, "Beyond the hippocampus: medial temporal cortices' mnemonic functions and vulnerability to age-related decline"

Vonetta Dotson, PhD

- Kirton, J.W., Szymkowicz, S.M., Sozda, C.N., & **Dotson, V.M.** Cognitive sequelae of increased body mass index. Poster to be presented at the 2014 International Neuropsychological Society conference in Seattle, Washington.
- **Dotson, V.M.**, Kirton, J.W., Sozda, C.N., Perlstein, W.M., Anton, S. & Manini, T. (2013). An fMRI study of sex differences in memory encoding and working memory in older adults. Paper presented at the 2013 Society for Neuroscience conference in San Diego, CA.
- Szymkowicz, S. M., Kirton, J. W., Sozda, C. N., Perlstein, W. M., & **Dotson, V. M.** (2013). Effect of aerobic exercise on memory encoding in older adults with a history of depression: An fMRI pilot study. Poster presented at the 6th annual McKnight Brain Research Foundation Poster Reception at Society for Neuroscience (SfN), San Diego, CA.
- Szymkowicz, S.M., Kirton, J.W., Sozda, C.N., Perlstein, W.M. & **Dotson, V.M.** (2013). Effect of aerobic exercise on memory encoding in older adults with a history of depression: An fMRI pilot study. Poster presented at the 2013 Society for Neuroscience conference in San Diego, CA.

Charles Jason Frazier, PhD

(Abstracts from SFN meeting 2013)

- H. E. CARPENTER, K. B. KELLY, J. L. BIZON1, **C. J. FRAZIER**; Age-related changes in GABA-B receptor mediated inhibitory tone in the medial prefrontal cortex. 91.02
- D. PATI, K. B. KELLY, C. I. MCKELVEY, **C. J. FRAZIER**; The effect of cannabinoids on GABA-A receptor dependent tonic inhibition in the dentate granule cells of hippocampus. 129.13
- L. L. MOROZ, S. HARDEN, A. B. KOHN, A. FODOR, M. CITARELLA, A. KUMAR, **C. J. FRAZIER**, T. FOSTER; The genomic portrait of hippocampal CA1 neurons: Identification and quantification of virtually all RNAs in single mammalian neurons using semiconductor sequencing. 192.25
- **C. J. FRAZIER**, D. PATI, J. A. SMITH, A. D. DE KLOET, E. G. KRAUSE; The effect of peripheral salt loading on central circuits that regulate stress. 382.25
- S. W. HARDEN, E. G. KRAUSE, **C. J. FRAZIER**; Identification and selective stimulation of hypothalamic corticotropin releasing hormone containing neurons expressing light sensitive channelrhodopsin-2. 568.11.

Brandi Ormerod, PhD

- Speisman, R.B, Kumar, A., Rani, A., Asokan, A., Foster T.C., **Ormerod. B.K.** (2013). Unique age-related changes in circulating, hippocampal and cortical hormones, cytokines and chemokines relate to spatial ability. Annual Meeting of the Society for Neuroscience, San Deigo, CA. Soc Neurosci Abstr Vol 38. 334.10.
- Munikoti, V.V., **Ormerod B.K.** (2013). Lipopolysaccharide may compromise adult hippocampal neurogenesis by modulating the expression of vascular factors. Annual Meeting of the Society for Neuroscience, San Deigo, CA. Soc Neurosci Abstr Vol 38. 317.10.
- Asokan, A. and **Ormerod B.K.** (2013). Lipopolysaccharide reduces neuronal differentiation through its effects on serum and hippocampal cytokines and chemokines. Annual Meeting of the Society for Neuroscience, San Deigo, CA. Soc Neurosci Abstr Vol 38. 607.14.

Matthew Sarkisian, PhD

- **Sarkisian MR**, Siebzehnrubl D, Deleyrolle L, Silver DJ, Siebzehnrubl FA, Guadiana SG, Srivinasan G, Hoang-Minh L, Semple-Rowland S, Steindler DA, Reynolds BA. Detection of primary cilia in human glioblastoma. Soc Neurosci Abstr 2013

PRESENTATIONS AT PUBLIC (NON-SCIENTIFIC) MEETINGS OR EVENTS:

Dawn Bowers, PhD (& Michael Marsiske, PhD)

- **Bowers, D.** (2013, April) Improving memory in Parkinson Disease: Top 10 tips. Presented at Parkinson Day Symposium for Patients and Caregivers, UF, Gainesville Florida.
- **Bowers, D.**, & Marsiske, M. (May 2013). Combined Cognitive-Exercise Interventions in the Very Old: Update on the Vital Study, presented at McKnight CAM Site visit, Gainesville FL

Sara N. Burke, PhD

- Nov 4th, 2013 Animal Cognition, "Behavioral Insights Into the Neurobiology of Cognitive Aging"

Vonetta Dotson, PhD

- **Dotson, V.M.** One Diagnosis, Many Pathways: Implications of Clinical and Neurobiological Heterogeneity for the Diagnosis and Treatment of Psychological Disorders. Presented at the UF Department of Clinical and Health Psychology Case Conference, April 12, 2013.
- **Dotson, V.M.** Cognitive and Brain Aging: Patterns and Modifiers. Presented at the UF Department of Psychology Developmental Psychology Brown Bag Seminar, April 10, 2013

Brandi Ormerod, PhD

- **Ormerod, BK** (2013) – Neuroinflammation, neurogenesis and aging: Protecting cognition across lifespan. Oncology Department (University of Florida).

AWARDS (OTHER):

Dawn Bowers, PhD (& Michael Marsiske, PhD)

<u>Grants</u>
Source: **NIH/NINDS – R21NS079767** (2012-2014)
Emotion Regulation, Executive Function, and Parkinson Disease
Role **(Bowers)**: PI

NIH/NINDS R01-NS-082386 (2013-2018)
White Matter Connectivity and PD Cognitive Phenotypes.
Role **(Bowers)**: Co-I (Price – PI)

NIH/NINDS NRSA, F31 NS7033 (2010-2013) – to Jenna Dietz
Emotion Psychophysiology in Parkinson's disease
Role: Co-Mentor with M. Bradley, Ph.D.

NIH/NIA P30 AG028740 (2012-2017)
Claude Denson Pepper Older Americans Independence Center
Role **(Marsiske)**: Core Leader (Recruitment Core; Pahor – PI)

NIH/NIA U01 AG022376 (2009-2014)
The LIFE Study
Role **(Marsiske)**: Co-I (Pahor—PI)

Veteran's Administration Research and Development Service (2013-2016)
Virtual Environments for Therapeutic Solutions (VETS) mTBI/PTSD Phase II
Role **(Marsiske)**: Co-I (Levy—PI)

NIH/NIA T32 AG020499 (2013-2018)
Physical, Cognitive and Mental Health in Social Context
Role **(Marsiske)**: PI; Role (Bowers): Mentor

Brandi Ormerod

<u>Current</u>
Department of Defense PR121769 – Carney, King, **Ormerod** (Multi PI) 9/01/2013 – 8/31/2016
Advancement of Somatostatin Gene Delivery for Disease Modification and Cognitive Sparing in Epilepsy. The major goal of this award is to investigate whether somatostatin expression increased through delivery with a viral vector minimizes seizure behavior through its effects on neuroinflammation and/or neurogenesis.
Role: Multiple PI (30% effort) – $1,500,000

McKnight Brain Institute Age-related Memory Loss Panel 6/30/2013-6/31/2015
Causes of and relationships between olfactory/hippocampal neurogenesis and age-related cognitive decline. The major goal of this award is to quantify neurogenesis in samples already collected from young and aged male rats trained and tested in version of the water maze distinct from the one in the proposal.
Role: PI – $100,000

National Institute on Aging – NIH R37 AG036800 Foster (PI) 9/30/2010 – 8/31/2014
Signaling cascades and memory deficits during aging
The major goal of this MERIT award is to identify inflammatory and neuroinflammatory biomarkers that predict age-related changes in NMDAr signaling and hippocampus-dependent behavior in male rats. Dr. Ormerod's role on this award is to quantify circulating and central cytokines and chemokines across lifespan in male rats and relate them to measures of behavior in a rapid water maze task.
Role: Co-I (24% effort) – $1,174,000

National Science Foundation predoctoral fellowship to R.B. Speisman 09/10 – 09/13
DGE-0802270 Using Biomarkers to predict successful versus unsuccessful aging in rats.
Amount – $90,000
Role: Mentor

<u>Pending</u>
National Institute on Aging – 5R37AG036800-03 – Foster (PI) 09/1/2014 – 8/31/2019
Signaling cascades and memory deficits during aging
The goal of this project is to understand the influence of Ca2+ signaling on spatial and working memory deficits that emerge in normal aging. Dr. Ormerod's role on this award is to quantify circulating and central cytokines and chemokines across lifespan in male rats and relate them to measures of behavior in a rapid water maze task.
Role: Co-I (1 month) – $1,200,000

National Science Foundation predoctoral fellowship to J. McGuiness 05/14 – 04/17
Elucidating the impact of cytokines and neurogenesis on cognition in aged rats
Amount – $90,000
Role: Mentor

Matthew Sarkisian, PhD

1) University of Florida 2011 Research Opportunity Seed Fund Award Title: "Mechanisms of Abnormal Brain Development in the VPA Model of Autism" Award: $84,000 Funding Period: 05/01/11-04/30/13 Role: Co-PI (with Dr. Mark Lewis, Psychiatry)
2) American Cancer Society (Research Scholar Grant) Title: "Identifying and Targeting Therapy Resistant Cells in Glioblastoma" Award: $720,000 Funding Period: 01/01/13-12/31/16 Role: PI
3) Epilepsy Foundation of America Pre-doctoral Training Fellowship Role: Mentor (for Sarah Guadiana (my graduate student)) Award: $20,000 Award period: 01/01/13-12/31/13

FACULTY BIOGRAPHICAL SKETCHES: See page 67

TRAINEES:

Jennifer Bizon, PhD

a. **Post-doctoral**
Joe McQuail, PhD

b. **Pre-doctoral**
Cristina Bañuelos
Sofia Beas

Dawn Bowers, PhD (& Michael Marsiske, PhD)

a. **Post-doctoral**
Caleb Peck, PsyD
Danielle Cummings, PsyD
Tiffany Cummings, PsyD

b. **Pre-doctoral**
Jenna Dietz, MS
Jacob Jones, MS
Paul Mangal, BS
Jacqueline Maye, BS
Jacob Lafo, BS
Kelsey Thomas, MS
Anna Yam, MS

c. **Other (undergrad)**
Emily Jaalook
Jessica Helphrey
Salil Phadnis
Yereniz Murillo

Sara N. Burke, PhD

a. **Post-doctoral**
Andrew P Maurer, PhD

b. **Other (undergrad)**
Nick Topper

Vonetta Dotson, PhD

b. **Pre-doctoral**
Joshua Kirton, MS
Sarah Szymkowicz, MS
Molly McLaren, BS

c. **Other**
Mackenzie Green (post-baccalaureate)
Jessica Rohani (undergraduate honors student)

Charles Jason Frazier, PhD

b. **Pre-doctoral**
Haley Carpenter
Kyle Kelly
Dipa Pati
Scott Harden

Brandi Ormerod, PhD

b. **Pre-doctoral**
Rachel B. Speisman – graduated with a PhD in 06/2013; Currently a Postdoctoral Fellow at the NIH
James McGuiness – Interdisciplinary Studies PhD student in Neuroscience; Began dissertation work in the Ormerod lab in 05/2013
Aditya Asokan – PhD student in BME

Matthew Sarkisian, PhD

a. **Post-doctoral**
Lan Hoang-Minh, PhD

b. **Pre-doctoral**
Sarah M. Guadiana (graduated PhD Aug 2013)
Alexander Parker

c. **Other**
Undergraduates: Kathleen Park
Megan Le
George Ugartemendia
Tyler Smith

CLINICAL/TRANSLATIONAL PROGRAMS:

Jennifer Bizon, PhD

a. **New programs**
During this past year we have begun to lay the foundation for establishing a translational drug discovery program for treatment for age-related cognitive decline. After a series of meetings between Drs.Tetsuo Ashizawa, Glenn Finney, Kevin Felsenstein, Barry Setlow and myself, we have developed what I hope is a tractable strategy for moving forward a translational program to assess the use of a GABA(B) receptor antagonists as a cognitive enhancer in aged individuals. This approach is based on a number of studies in which we have determined significant cognitive enhancement with such agents in aged rodents. We detailed this plan in a short proposal for the UF-McKnight board and Dr. Tom Foster has generously provided some initial funding ($50,000.00) from The Evelyn F. McKnight Endowment Fund for Brain Research to enable us to begin these studies. Most recently, we have submitted a proposal to the McKnight Brain Institute Drug Discovery program for $75,000 to continue the necessary preclinical work. Our overall goal, should we be successful in competing for additional funding, is to perform targeted chemistry to optimize our lead compound(s) and complete the necessary preclinical studies that are required to support a strong U01 application to NIH/NIA.

Dawn Bowers, PhD (& Michael Marsiske, PhD)

a. **New Programs**
We are now in process of negotiating a new clinical-research program through the Village that directly builds on the VITAL project supported by the McKnight Research foundation. This program is called the UF Vitality Mind Program: A focus on Brain Health. Two components will focus on interventions for those with memory problems (Re-Vitalize) or difficulties with organization/multi-tasking (CEDAR). A third component will offer rapid access to clinical services through UF HSC. The first two components will be directed through the VITAL lab at the Village.

b. **Update on existing clinical studies**
See intro

TECHNOLOGY TRANSFER: NA

BUDGET UPDATE: See page 56

EDUCATIONAL PROGRAMS FOCUSING ON AGE RELATED MEMORY LOSS:

Dawn Bowers, PhD (& Michael Marsiske, PhD)

Scientific

Marsiske and **Bowers** direct/contribute to an online certificate program, "Precertification Training in Psychometry", which provides psychological testing information for non-licensed neuropsychological aides. One of four courses is entirely devoted to adulthood, aging, and cognitive disorders of later life (e.g., dementia, Parkinson's Disease).

Public

Bowers, D., & **Marsiske, M.** (May 2013). Combined Cognitive-Exercise Interventions in the Very Old: Update on the Vital Study

COLLABORATIVE PROGRAMS WITH OTHER MCKNIGHT INSTITUTES, INSTITUTIONS AND RESEARCH PROGRAMS:

Dawn Bowers, PhD (& Michael Marsiske, PhD)

Dr. Bowers is part of cross-center McKnight workgroup that is focused on examining elements of core neuropsychological battery.

COLLABORATIVE PROGRAM WITH NON-MCKNIGHT INSTITUTES, INSTITUTIONS AND RESEARCH PROGRAMS: NA

BRIEFLY DESCRIBE PLANS FOR FUTURE RESEARCH AND/OR CLINICAL INITIATIVES:

Jennifer Bizon, Ph.D.

In addition to the continuation of our primary work investigating the role of GABAergic systems in age-related memory loss (A1 for competitive R01 renewal currently under review) and the translational program described above (See Item 9), we have also begun work on a basic science Program Project Grant proposal with other age-related memory loss researchers at UF (Foster, Frazier, Ormerod, Setlow). My first role in this PPG grant is to anchor one of the three projects that are focused on advancing our understanding of the cellular mechanisms underlying age-related prefrontal cortical dysfunction. In addition to this project, I will, together with long-time collaborator Dr. Barry Setlow, lead the animal resource and behavioral core. Our team of researchers has been meeting regularly since early summer and has already made considerable progress in developing coordinated projects and obtaining key preliminary data to build a strong programmatically-focused grant on age-relate memory loss. We have a target date of submission in early February.

In addition, I am co-I (20% effort) on Dr. Tom Foster's R37 NIH award which was recently renewed for three additional years. This success of this proposal highlights an exciting and growing collaboration between our laboratories in which we seek to determine common and unique mechanisms for distinct forms of age-related memory loss (i.e., those supported by prefrontal cortical and hippocampal dysfunction). I am also a co-I on a McKnight Brain Research Foundation awarded to Dr. Brandi Ormerod which is providing funding for foundational studies related to reversing altered neurogenic mechanisms in aged brain. Dr. Ormerod and I submitted our first co-PI R01 proposal on this topic in June 2013, which will be reviewed shortly. Finally, Dr. Frazier and I have also actively advanced our collaborations over the past years which are focused on understanding the role of altered GABAergic signaling in the decline of age-related prefrontal cortical dependent cognition. This collaboration has thus far yielded data for two publications (one currently under review at J. Neuroscience and another in preparation) as well as providing the basis for several of the proposed experiments in the PPG. Dr. Frazier and I also plan to submit a separate proposal to NIH during the upcoming year in order to continue to advance our work related to understanding GABAergic mechanisms of prefrontal cortical decline.

Dawn Bowers, PhD (& Michael Marsiske, PhD)

NIH grants under review: Drs. Bowers and Marsiske have two grants under review at NIH/NIA to continue work on interventions for age-related memory in older adults. Reviews were pushed back to early-mid December due to government shutdown

- *Re-Vitalize: Improving Memory in MCI – Motion and Emotion*; NIH/NIA R21 AG103591; submitted 6/15/2013
  MPI: Dawn Bowers & Michael Marsiske.
- *VITAL 2: Engagement plus Training for Broad Cognitive Transfer in Elders*. NIH/NIA R01AG047365; Submitted 6/1/2013.
  MPI: Michael Marsiske & Dawn Bowers

UF VITALITY Mind Program

We are in process of finalizing a contract with the Village called the **UF Vitality Mind program**. This program has 3 distinct components: **Revitalize**, **CEDAR**, and **Neuro-Advantage**. The contract provides staff support, physical space (a multi-room laboratory) on The Village campus, and operational support with materials/supplies.

Revitalize is intended for older adults experiencing memory problems, whereas *CEDAR* is for individuals having difficulties with multi-tasking and organization. Individuals in these programs will be assigned to one of several potential interventions, typically lasting 8-12 weeks. The third component Neuro-Advantage is for individuals with more serious cognitive or emotional concerns. Individuals in this program will be guaranteed rapid appointments through the UF Neuropsychology Clinic and potential referral to other professionals.

Matthew Sarkisian, Ph.D.

Continue to write/publish manuscripts, mentor students/postdocs and apply for local and federal funding opportunities that relate to the contribution of neural cilia in brain plasticity.

IF APPLICABLE, PLEASE PROVIDE ENDOWMENT INVESTMENT RESULTS FOR THE REPORT PERIOD: See page 62

WERE ANY FUNDS USED FOR A PROHIBITED PURPOSE DURING THE REPORT PERIOD? No

DO YOU RECOMMEND ANY MODIFICATION TO THE PURPOSE OR MANDATES IN THE GIFT AGREEMENT? No

DID ALL ACTIVITIES DURING THE REPORT PERIOD FURTHER THE PURPOSE? Yes

NEGATIVE EVENTS (LOSS OF PERSONNEL, SPACE, BUDGET ETC.):

Charles Jason Frazier, Ph.D.

The senior post-doc originally hired to support this project left the lab at the end of 2012 and has been replaced by a new graduate student from the COP. As a result two graduate students (one senior, one junior) are currenty focused 100% on projects consistent with the ARML mission.

ADDITIONAL COMMENTS: See letter on page 6

SIGNATURE, DATE AND TITLE OF PERSON SUBMITTING THE REPORT:

Tetsuo Ashizawa, MD
Executive Director, McKnight Brain Institute
Melvin Greer Professor
Chairman, Department of Neurology

McKnight Endowed Chair

2013 Progress Report

SUMMARY OF SCIENTIFIC ACHIEVEMENTS SINCE LAST REPORT:

This year we have 6 manuscripts either published or accepted for publication in peer reviewed scientific journals and 1 invited review to be submitted in December. In addition, with Drs Bizon and Ormerod we have received word that my MERIT award will be renewed. Three NIH Grants were submitted, one in collaboration with Dr Kathy Magnusson at the University of Washington (not funded), Dr Bizon (16th percentile, waiting on information concerning possible funding), a grant examining grant on mechanisms for age-related deficits in working memory versus reference memory received a score at the 23rd percentile and was not funded.

Decline in NMDAR function mediates impaired episodic spatial memory. NMDA receptors (NMDARs) play a critical role in learning and memory; however, there is a lack of evidence for a direct relationship between a well characterized decline in NMDAR function and impaired cognition during aging. Two studies provide strong support for the hypothesis that oxidative stress mediates a decrease in the NMDAR component of synaptic transmission during aging and the decrease in NMDAR function is related to a specific cognitive phenotype: impaired memory for rapidly acquired novel spatial information. In the first study (Kumar and Foster, 2013), young and middle-aged animals were behaviorally characterized for rapid acquisition and retention of spatial memory. Subsequent examination of senescent hippocampal synaptic physiology confirmed an age-related decrease in synaptic responses, including the NMDAR component of synaptic transmission. Examination of synaptic transmission according to behavioral classification revealed that animals classified as impaired exhibited a decrease in the total and the NMDAR component of the synaptic response relative to unimpaired animals. Furthermore, bath application of the reducing agent dithiothreitol increased the NMDAR component of the synaptic response to a greater extent in impaired animals relative to unimpaired and young rats. These results provide evidence for a link between the redox-mediated decline in NMDAR function and emergence of an age-related cognitive phenotype, impairment in the rapid acquisition and retention of novel spatial information. In the second study (Brim et al., 2013), viral vectors were employed to increase NMDAR receptors in specific brain regions. Expression of the NMDAR subunit (NR2B) increased NMDAR synaptic responses and improved learning and memory in aged mice.

Role of estrogen receptor alpha and beta in preserving hippocampal function during aging. The expression of the ERalpha and ERbeta estrogen receptors in the hippocampus may be important in the etiology of age-related cognitive decline. To examine the role of ERalpha and ERbeta in regulating transcription and learning, ovariectomized wild-type (WT) and ERalpha and ERbeta knockout (KO) mice were used (Han et al., 2013). Hippocampal gene transcription in young ERalphaKO mice was similar to WT mice 6 h after a single estradiol treatment. In middle-age ERalphaKO mice, hormone deprivation was associated with a decrease in the expression of select genes associated with the blood-brain barrier; cyclic estradiol treatment increased transcription of these select genes and improved learning in these mice. In contrast to ERalphaKO mice, ERbetaKO mice exhibited a basal hippocampal gene profile similar to WT mice treated with estradiol and, in the absence of estradiol treatment; young and middle-age ERbetaKO mice exhibited preserved learning on the water maze. The preserved memory performance of middle-age ERbetaKO mice could be reversed by lentiviral delivery of ERbeta to the hippocampus. These results suggest that one function of ERbeta is to regulate ERalpha-mediated transcription in the hippocampus. This model is supported by our observations that knockout of ERbeta under conditions of low estradiol allowed ERalpha-mediated transcription. As estradiol levels increased in the absence of ERalpha, we observed that other mechanisms, likely including ERbeta, regulated transcription and maintained hippocampal-dependent memory. Thus, our results indicate that ERalpha and ERbeta interact with hormone levels to regulate transcription involved in maintaining hippocampal function during aging.

Other biological markers of cognitive decline. Speisman et al., (2013a,b) examined the neurogenesis and neuroinflammation as mechanisms for rescue of memory following exercise and environmental enrichment. The results provide an interesting idea, that serum markers of inflammation are predictive of cognitive decline and markers of cellular stress/neuroinflammation within defined neural systems are diagnostic as to which cognitive processes are impaired with aging.

PUBLICATIONS IN PEER REVIEWED JOURNALS:

1. Brim BL, Haskell R, Awedikian R, Ellinwood NM, Jin L, Kumar A, **Foster TC**, Magnusson KR. Memory in aged mice is rescued by enhanced expression of the GluN2B subunit of the NMDA receptor. *Behav Brain Res* 2013; 238:211-226. **PM:23103326**

2. Speisman RB, Kumar A, Rani A, Pastoriza JM, Severance JE, **Foster TC**, Ormerod BK. Environmental enrichment restores neurogenesis and rapid acquisition in aged rats. *Neurobiol Aging* 2013; 34(1):263-274. **PM:22795793**

3. Speisman RB, Kumar A, Rani A, **Foster TC**, Ormerod BK. Daily exercise improves memory, stimulates hippocampal neurogenesis and modulates immune and neuroimmune cytokines in aging rats. *Brain Behav Immun* 2013; 28:25-43. **PM:23078985**

4. Han X, Aenlle KK, Bean LA, Rani A, Semple-Rowland SL, Kumar A, and **Foster TC**. Role of estrogen receptor alpha and beta in preserving hippocampal function during aging. *Journal of Neuroscience* 2013, 33: 2671-2683. **PMID: 23392694**.

5. Kumar A and **Foster TC**. Linking redox regulation of NMDAR synaptic function to cognitive decline during aging. *Journal of Neuroscience* 2013; 33: 15710-15715. **PMID: 24089479**

6. Boye SL, Peshenko IV, Huang WC, Min SH, McDoom I, Kay CN, Liu X, Dyka FM, **Foster TC**, Umino Y, Karan S, Jacobson SG, Baehr W, Dizhoor AM, Hauswirth W, Boye SE. AAV-mediated gene therapy in the guanylate cyclase (RetGC1/RetGC2) double knockout mouse model of Leber congenital amaurosis. *Hum Gene Ther* 2013. **PM:23210611**

PUBLICATIONS (OTHER): NA

PRESENTATIONS AT SCIENTIFIC MEETINGS:

- The senescent synapse: Linking brain aging to cognitive decline. Institute of Neurosciences F. Olóriz Center for Biomedical Research, University of Granada. Granada, Spain (5/28/2013).
- Challenges and opportunities in characterizing cognitive aging across species. Department of Psychobiology, University of Granada. Granada, Spain (5/29/2013).
- Altered synaptic plasticity during aging: Role of redox state in Ca2+ dysregulation. Symposium on "The Senescent Synapse", Ancona Portonovo, (9/18/2013).
- The Genomic Portrait of Hippocampal CA1 Neurons: Identification and Quantification of Virtually all RNAs in Single Mammalian Neurons Using Semiconductor Sequencing. (2013) Moroz, L.L., Harden, S., Kohn A.B., Fodor, A., Citarella, M., Kumar, A., Frazier, C.J., **Foster, T.C.** Soc for Neurosci.
- Unique age-related changes in circulating, hippocampal and cortical hormones, cytokines and chemokines relate to spatial ability (2013) Speisman, R.B., Kumar, A., Rani, A., **Foster, T.C.**, and Ormerod, B.K. Soc for Neurosci.
- Dissociating oxidative damage and memory: NMDAR-redox regulation of memory during normal aging (2013) Kumar, A., Lee, W-H., Rani, A., **Foster, T. C.** Soc for Neurosci.
- Enhanced expression of estrogen receptor alpha with gene therapy extends the therapeutic window (2013) Bean, L., Rani, A., Kumar, A., **Foster, T.C.** Soc for Neurosci.
- Mouse Muscleblind-Like Compound Knockout models of Myotonic Dystrophy (2013) Lee, K-Y., Li, M., Manchanda, M., Finn, D., Kumar, A., **Foster, T.C.**, and Swanson, M.S. Soc for Neurosci.

PRESENTATIONS AT PUBLIC (NON-SCIENTIFIC) MEETINGS OR EVENTS: NA

AWARDS (OTHER):

a) External Advisory Committee of the Center for Aging at the University of Alabama at Birmingham.
b) 2013-15 University of Florida Research Foundation Professorship Award

FACULTY BIOGRAPHICAL SKETCHES: See page 67

TRAINEES:

a. Post-doctoral: NA

b. Pre-doctoral

Michael Guidi, Graduate Student, Department of Neuroscience, University of Florida
Linda Bean, Graduate Student, Department of Neuroscience, University of Florida
Lara Ianov, Graduate Student, Department of Genetics, University of Florida

c. Other
Dr. Ashok Kumar, Research Scientist
Asha Rani

CLINICAL/TRANSLATIONAL PROGRAMS:

a. New programs

Program Project Proposal: Currently, a group of researchers (Foster, Leeuwenburgh, Bizon, Setlow, Fraizer, Ormerod) are meeting in order to plan for a Program Project Proposal to NIA. **Overall Objectives** – This program project represents a multi-departmental and multi-disciplinary research effort to understand the causes and consequences of senescent physiology in mediating the emergence and progression of cognitive decline during aging. Deficits are associated with increased expression of genes related to inflammation and oxidative stress. Memory impaired animals also exhibit a decrease in expression of neuroprotective and synaptic genes. Similarly, memory impaired animals exhibit decreased N-methyl-D-aspartate receptor (NMDAR) synaptic responses due to the increase in oxidative stress. In vitro studies show a link between a decline in synaptic NMDAR activity and reduced expression of antioxidant, neuroprotective, and synaptogenesis genes. Together, the results suggest that oxidative stress mediates a decrease in synaptic NMDAR activity, which in turn shifts transcription to render neurons more vulnerable to age-related stressors, promoting a progressive weakening of hippocampal function. Questions remain concerning the source(s) of oxidative stress, cell specificity of gene changes, and whether transcriptional changes in vivo are a function of NMDAR synaptic activity.

Hypothesis – Brain regions are differentially vulnerable to aging and disruption of specific neural circuits results in explicit memory impairment phenotypes. *Inflammation/oxidative stress modify the balance of excitatory and inhibitory neural activity, resulting in a decrease in activation of N-methyl-D-aspartate receptors (NMDARs) and the emergence of cognitive deficits. In turn, disruption of NMDARs alters signaling cascades and the downstream transcription of genes for cell health and survival, contributing to cellular vulnerability to age-related stressors and the progression of inflammation and cognitive decline.* Therefore, early, directed application of treatments that correct the decline in NMDAR function in specific neural circuits will mitigate cognitive impairments, which are major contributors to overall health-span and quality of life in older individuals.

GABAB receptor antagonists as a treatment for age-related cognitive decline. In conjunction with Drs. Bizon and Setlow we have contacted PharMore Inc to develop second generation GABABR antagonists that show both high affinity and good oral bioavailability. The next step is to conduct studies of pharmacokinetics and safety.

b. Update on existing clinical studies

In 2009 I took over as Chair for the committee overseeing the Age-Related Memory Loss (ARML) Program. Other members of the committee include Drs. Lucia Notterpek, Tetsuo Ashizawa, and Christiaan Leeuwenburg.

a. During the past year I have been a member of a search committee, Chaired by Dr. Bizon and directed at hiring another faculty member for the ARML Program. This resulted in the hire of Dr. Sarah Burke.

b. A 2012 proposal that was contingent on researcher progress was approved ($100K) (Ormarod/Bizon) to examine **causes of and relationships between olfactory/hippocampal neurogenesis and age-related cognitive decline**. In addition, we had 5 submitted proposals in 2013. One pilot study, related to plans for the Program Project, was approved for $6K (Bizon).

I am a member of the Institute on Aging and Pepper Center Executive Committee. I regularly attend meetings with this group where I promote research on age-related cognitive decline. At this meeting I also confer with Dr. Ron Cohen, the CAM-CTRP Director about possible interactions and future directions.

TECHNOLOGY TRANSFER: NA

BUDGET UPDATE: See page 56

EDUCATIONAL PROGRAMS FOCUSING ON AGE RELATED MEMORY LOSS: NA

COLLABORATIVE PROGRAMS WITH OTHER MCKNIGHT INSTITUTES, INSTITUTIONS AND RESEARCH PROGRAMS:

The McKnight Brian Research Epigenetics Core: The goal is to establish the shared Inter-Institute resource to provide a catalyst for discoveries in the area of epigenetics of cognitive aging. This is envisioned to be a "core without walls" to provide support for bioinformatic analysis of high-throughput DNA sequencing and epigenomics, bio-informatics, and cross-correlation of human and animal studies. This comprehensive program will test an epigenetic hypothesis of cognitive aging, working collaboratively with the Evelyn F. McKnight Brain Institutes.

COLLABORATIVE PROGRAM WITH NON-MCKNIGHT INSTITUTES, INSTITUTIONS AND RESEARCH PROGRAMS: I have been working with Dr. Kathy Magnusson at the University of Washington. This has resulted in one paper (Brim et al., 2013) and a grant submission (not funded).

BRIEFLY DESCRIBE PLANS FOR FUTURE RESEARCH AND/OR CLINICAL INITIATIVES:

a) **To publish work related to:** 1) improved behavioral tests for early detection of cognitive decline in animal models, 2) use of antioxidant genes in the investigation of brain aging, 3) age-related changes in synaptic and metabotropic receptor-dependent synaptic plasticity, 4) expression of estrogen receptors in controlling the therapeutic window for hormone replacement benefits on cognition, 5) the role of inflammatory in age-related cognitive decline and brain aging.

b) Collaborate on projects related to GABAB receptor function and cognitive aging (Bizon).

c) Collaborate on projects related to DNA regulation and aging of single cells (Moroz).

d) Collaborate on projects related to Ca2+ regulation and hippocampal aging (Frazier).

e) Continue to work towards submission of a program project grant.

IF APPLICABLE, PLEASE PROVIDE ENDOWMENT INVESTMENT RESULTS FOR THE REPORT PERIOD. See page 62

WERE ANY FUNDS USED FOR A PROHIBITED PURPOSE DURING THE REPORT PERIOD? No

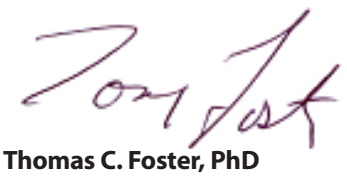
DO YOU RECOMMEND ANY MODIFICATION TO THE PURPOSE OR MANDATES IN THE GIFT AGREEMENT? No

DID ALL ACTIVITIES DURING THE REPORT PERIOD FURTHER THE PURPOSE? Yes

NEGATIVE EVENTS (LOSS OF PERSONNEL, SPACE, BUDGET, ETC.): NA

ADDITIONAL COMMENTS: NA

SIGNATURE, DATE AND TITLE OF PERSON SUBMITTING THE REPORT:



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Professor and Evelyn F. McKnight Chair for Research in Cognitive Aging and Memory

Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP)

2013 Progress Report

UF | UNIVERSITY of FLORIDA

Prepared for the McKnight Brain Research Foundation by the University of Florida McKnight Brain Institute and Institute on Aging

UF UNIVERSITY of FLORIDA

Institute on Aging
Dept. of Aging and Geriatric Research
Cognitive Aging and Memory-
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Dec. 3, 2012

Dear Trustees of the McKnight Brain Research Foundation:

We are pleased to provide you with a progress report of the Cognitive Aging and Memory-Clinical Translational Research Program (CAM-CTRP) for the year ending December 2013. This has been a very busy and productive year for the CAM-CTRP. A majority of projects that were initiated last year are in progress and a number of new initiatives have been undertaken. The CAM-CTRP has enjoyed many successes that will keep the program on track for a future of exciting and groundbreaking clinical-translational research. Our move to the Clinical Translational Research Building which occurred in June has proven to be extremely beneficial, as we are enjoying the benefits of close collaboration with the other IOA and CTSI faculty and departments as a direct result of our close proximity.

We hosted the first annual External Review Board Meeting at the new CTRB, which offered valuable insight and recommendations as noted in the summary report by Dr. Marc Fisher, M.D. attached to this report. These recommendations have been reviewed and we have taken steps to incorporate them into this year's program planning. We have also directly addressed several of these points including initiating clinical trial development of novel agents to enhance cognitive and behavioral function in the elderly. We have also initiated a national search for a physician researcher with a strong NIH track record. A number of other initiatives are underway as outlined in this report. Dr. Ron Cohen is currently co-mentoring 4 graduate students, and 2 Post-Doctoral Fellows. Dr. Adam J. Woods, Ph.D., has been successfully recruited to the program as an Assistant Professor, and has been an invaluable asset to development infrastructure and as the Core Leader for Electrophysiology and Neuromodulation.

The faculty of the CAM-CTRP has been extremely productive over the past year, publishing numerous manuscripts on topics related to cognitive and brain aging. We are particularly pleased to report that Dr. Cohen's RO1 proposal to the NIDDK on obesity and type II diabetes: bariatric surgery effects on brain function and aging, received a perfect score at the first percentile, and should be funded soon. This 5 year study

($492,000 per year) will be initiated in the Spring of 2014. The project has major implications in understanding the aging brain, particularly the influence of metabolic factors associated with obesity and diabetes on brain structure and function, and the brain effects resulting from reductions in these factors following bariatric surgery and significant weight loss. This clinical study provides an excellent experimental model for testing whether caloric reduction improves brain health, with major implications for healthy cognitive aging.

In addition, Dr. Cohen is the PI for 2 pending grants, and Co-I for 6, totaling approximately 3.1 million dollars in funding. These include collaborations with UCLA, UF-College of Public Health & Health Professions, Malcolm Randal VAMC, University of Pittsburgh and Brown University. The topics span a broad range of important areas for study of the aging brain, such as predicting brain changes, multi-modal brain training for broad cognitive transfer in elders, white matter integrity and ultra-high field neuroimaging of the aging brain.

There are a number of pilot studies (12) that have been initiated or will be initiated over the next 12 months. These are detailed in the body of this report, which indicate substantial growth in the program as a whole, and successful collaborations among many disciplines. The CAM-CTRP has enjoyed a wonderful year of successes, and we are poised to continue that trend with enthusiasm.

Sincerely,

Ronald Cohen, Ph.D., ABPP, ABCN
Professor, Aging, Neurology, and Psychiatry
Director, CAM-CTRP

Marco Pahor, M.D.
Professor and Chair
Department of Aging and Geriatric Research
Director, Institute on Aging

SUMMARY OF SCIENTIFIC ACHIEVEMENTS SINCE LAST REPORT:

The Cognitive Aging and Memory – Clinical Translational Research Program has had many achievements since the last annual report, including major developments within its administrative structure, faculty and affiliate faculty collaboration, an External Advisory Board full program review, startup of a large scale "normal aging" research study, multiple other pilot studies to support cognitive aging research, participation in the McKnight Inter-Institutional Initiative, a perfect score on an NIH RO1 Grant on Type II Diabetes/Bariatric Surgery/Aging and Cognition, and many important infrastructure development successes that will enable successful continuation of this important program.

A. Since the last report, the Cognitive Aging and Memory – Clinical Translational Research Program (CAM-CTRP) has created and hosted the first annual External Review Board Meeting. The distinguished board of external reviewers for the program were:

Dr. Marc Fisher, MD – University of Massachusetts Medical School

Dr. Peter Monti, PhD – Brown University

Dr. Jeff Williamson, MD, MHS – Wake Forest University

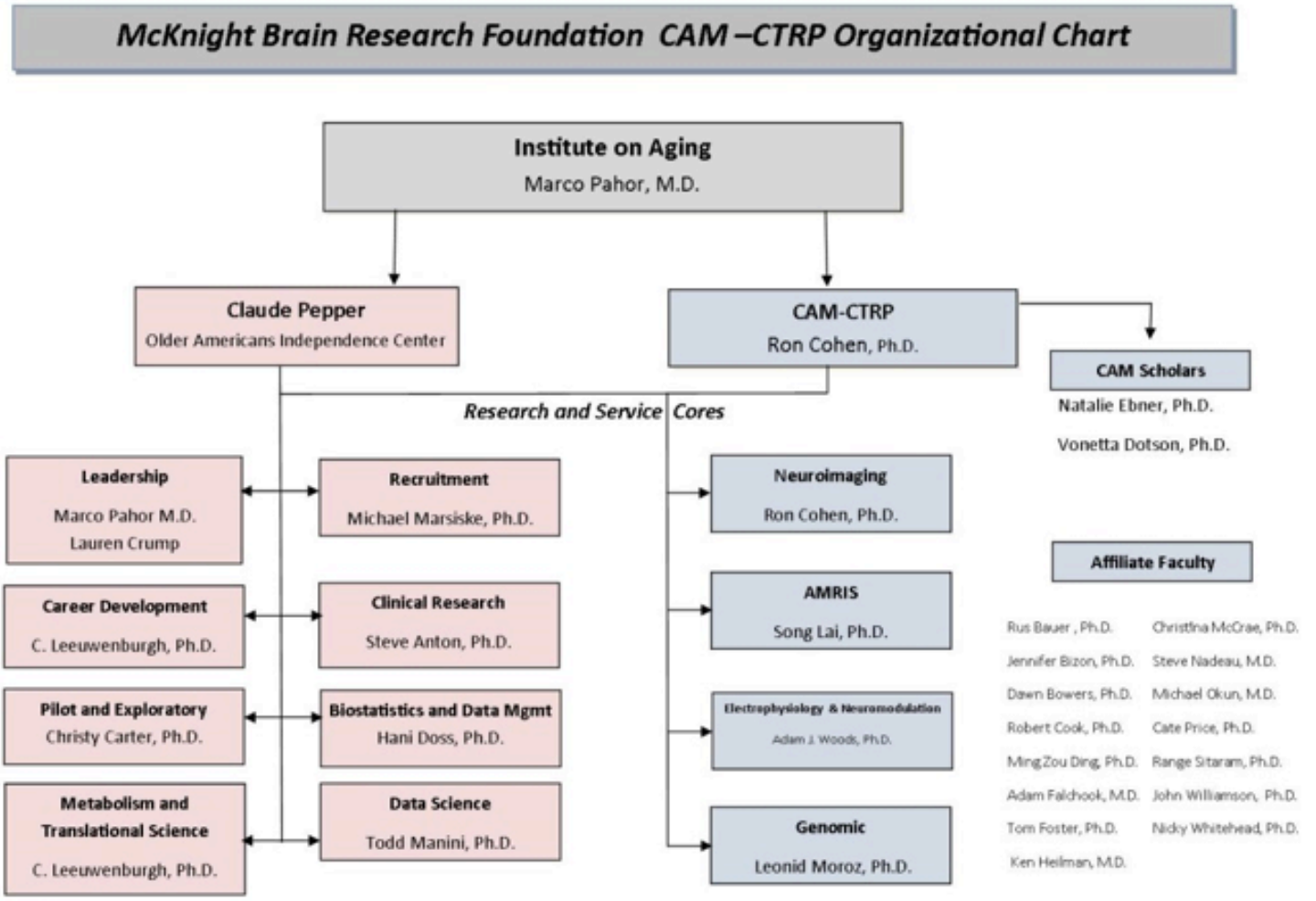
Dr. Mark Espeland, PhD – Wake Forest University

The reviewers were significantly impressed with the success and progress achieved in a relatively short time since the program's launch, and wrote the executive summary introducing this report. The advisory board was particularly impressed by the vision, scientific expertise and resources available in the CAM-CTRP. The leadership was perceived as being exceptionally strong and there is broad faculty involvement from across the University. Primary areas that the board felt should be focused on for future developments include; an emphasis on increasing clinical expertise from MD researchers, such as neurologists with backgrounds in aging and neurodegenerative disease. They also recommended establishing a primary theme for research efforts and a branding of the CAM-CTRP. Also, increasing collaboration with investigators in other parts of the university was recommended. With respect to research, it was recommended that emphasis be placed on clinical translation of basic neuroscience findings coming from Dr. Foster and others in the MBI-AMRL program. Furthermore, the group suggested that the CAM-CTRP conduct research on a broad range of cognitive and behavioral functions that affect the elderly. These recommendations have been reviewed and we have taken steps to incorporate them into this year's program planning. We have also directly addressed several of these points including initiating clinical trial development of novel agents to enhance cognitive and behavioral function in the elderly. We have also initiated a national search for a physician researcher with a strong NIH track record. A number of other initiatives are underway as outlined in this report.

The Administrative Chart on the next page gives a brief summary of specialized Core areas, and demonstrates the collaborations that have been established to assist with fulfilling the vision and mission of the CAM-CTRP, within the Institute on Aging. These include the highly productive Pepper Center Cores which are now partially funded by CAM-CTRP to support the CAM-CTRP mission, and the newly specialized CAM-CTRP Cores of Neuroimaging, AMRIS, Electrophysiology and Neuromodulation, and Genomic Science.

For more information on the mission, vision, administrative structure and collaborating programs, please visit the website portfolio link below, for the complete External Advisory Board meeting and its presentations: ***http://aging.ufl.edu/research/cognitive-aging-and-memory-clinical-translational-research-program/cam-ctrp-external-advisory-board-meeting***

The CAM-CTRP webpage is in a continued development phase, and there are new informational pieces being posted and made available to the community, regarding faculty development, Clinical and Translational Research Studies and future areas of research interests: ***http://aging.ufl.edu/research/cognitive-aging-and-memory-clinical-translational-research-program***



B. **Obesity and type II diabetes: bariatric surgery effects on brain function and aging.** This RO1 grant proposal to the NIDDK (RO1DK099334-01A1) received a perfect score and was at the first percentile in the past review cycle (5 years; direct cost approx. $492,000/yr). This project will likely be initiated in the spring of 2014 when funding becomes available. The focus of the project is the effects of chronic obesity on brain structure and function and subsequent improvements that occur following bariatric surgery. The study employs multimodal neuroimaging to address these aims. Participants include 120 individuals undergoing bariatric surgery, half of whom have type II diabetes. Sixty participants with severe obesity who are not undergoing bariatric surgery will serve as controls in this longitudinal study.

C. **The ACTIVE BRAIN Study – (Cerebral metabolic, vascular and functional neuroimaging, NIH Toolbox Cognitive Measures, and physical activity as predictors of age associated cognitive dysfunction.)** All infrastructure and administrative groundwork has been prepared, and data is being collected for the first IRB approved (IRB #2013000168) study for CAM-CTRP. This is a multi-cohort study with two separate research arms; including the Institute on Aging's LIFE Study participants from Gainesville and Jacksonville, and seniors from the greater North Florida community. The LIFE Study participants are part of a LIFE Ancillary Study, reviewed and approved by the LIFE Emerging Science Board. The study will collect three primary pieces of information from 200 total participants, including anatomical and functional neuroimaging, blood cytokines, inflammatory biomarkers and DNA analysis, and a broad cognitive performance test battery including piloting of the newly released NIH Toolbox Cognitive Measures. The study will cover a broad age range from 60-100 years, to establish a database of images and cognitive performance data for analysis, which will serve as the foundation for gathering independent peer review grant funding.

OTHER PILOT STUDIES FUNDED BY CAM-CTRP:

1. **Proteomics and genomics of cognitive aging:** (Cohen, Leeuwenburgh, Moroz) This pilot will study 50 elderly participants from the ACTIVE BRAIN Study, to analyze various circulating serum biomarkers, including inflammatory cytokines, metabolic

factors and other proteins. Using the new UF Genomics System and in collaboration with the MBRF Genomics workgroup, DNA and RNA epigenetic biomarkers will also be examined in exploratory research on factors influencing normal brain aging.

2. **Aging effects on semantic neural networks (Talking Brain Study):** (Cohen, Heilman, Nadeau, Reilly) Study of 50 elderly participants, designed to analyze the semantic networks in the healthy aging brain. It will consist of newly designed tasks for performance during fMRI scans, with a variety of concrete vs. abstract words, across several different experimental paradigms including semantic generation tasks.

3. **Aging effects on visual cortical systems (Seeing Brain Study):** (Cohen, Porges) Study of 50 elderly participants, aimed at characterizing age-associated changes in structural and functional brain systems involved in visual processing. This fMRI study will examine functional brain response across 7 visual paradigms that are sensitive to different processes underlying visual perception and higher order visual functions.

4. **Age-associated changes in attention and arousal (Attentive Brain Study):** (Woods) 40 participants will undergo a comprehensive attentional battery while undergoing fMRI. This study is intended to identify unique elements of attention that decline with age, and the brain systems that govern these elements.

5. **Transcranial direct stimulation effects on cognitive aging (Stimulated Brain):** (Woods) 40 subjects in a pilot randomized clinical trial, investigating the benefit of Transcranial Direct Current Stimulation on working memory training in older adults. The study will utilize a multi-disciplinary neuroscientific approach to determine optimal parameters for enhancement of working memory related cognitive abilities.

6. **Induced arousal; an intervention in cognitive aging (Alert Brain Study):** (Woods) IRB approved study of 50 participants to investigate the role of brain arousal mechanisms on cognitive decline and susceptibility to cognitive frailty. This study will use a combination of fMRI, ERP, and physiological recording to identify biomarkers of frailty.

7. **Effects of oxytocin on socio-emotional decisions in aging (FACES):** (Ebner) Examines the effects of oxytocin administration on various measures of socio-emotional functioning and social decision making in aging adults. Young and older adults self-administer oxytocin or a placebo intranasally before working on a trust-related decision making task, a facial trustworthiness rating task, and an emotion recognition task. The central hypothesis is that older compared to younger adults particularly benefit from enhanced levels of oxytocin, as they experience increased difficulties with socio-emotional tasks.

8. **Oxytocin Clinical Trial (OXY):** (Ebner) This clinical trial investigates the effects of 4 weeks of intranasal oxytocin administration on physical performance, cognitive functioning, and socioemotional functioning in older males. Older men will self-administer intranasal oxytocin or a placebo, twice daily over a period of 4 weeks. At baseline and post intervention, they will be examined on various measures of physical, cognitive, and socioemotional functioning, as well as various inflammatory markers will be analyzed. The central hypothesis is that older males in the oxytocin group will experience improvement in their physical health, their cognitive performance, and their social and emotional engagement over the trial period, mediated by oxytocins anti-inflammatory effects.

9. **Development of Clinical Methods to Evaluate Neural Function in Aging MIND:** (Buford, Woods) The Aim of the Mind study is to develop the ability of Clinical Research Core (RC1) to assess novel neural contributors to mobility and overall physical function in older adults. The development of these techniques will provide the RC1 with the tools to evaluate the potential involvement of the central and peripheral nervous systems in age-related cognitive decline. Co-funded by the NIH Pepper Center Grant and CAM-CTRP Pilot Research.

10. **The metabolic costs of daily activity in older adults; A pilot study to evaluate the role of brain integrity on post-hospital sarcopenia and cognition in aging adults (The Strong Brain Study):** (Manini, Woods)

11. We will examine the integrity of the cortical-spinal tract and sarcopenia outcomes using the infrastructure of Dr. Catherine Price's funded R01 entitled, *Neuroimaging biomarkers for post-operative cognitive decline in older adults* (R01 NR014181; IRB # 487-2012). This R01 is a prospective longitudinal study with two groups: older adults (age > 60 years) having total knee replacement (n=80) and non-surgery age and education matched peers with osteoarthritis (n=80). Both groups will acquire baseline MRI using sophisticated diffusion and functional measures to define specific neuronal regions of interest that relate to cognition, and complete cognitive testing at a pre-surgery/baseline time point followed by repeat testing at 2 days, 3 weeks and three-months, and one-year post-operative/post-baseline. Funds from this pilot study will be used to support additional MRI scan time baseline and 3 weeks and 3 months post-surgery. Co-funded by the NIH Pepper Center Grant and CAM-CTRP Pilot Research.

12. **Methotrexate study on systemic inflammation of older adults (ICE):** (Anton, Woods) – This study is investigating the effects of methotrexate on systemic inflammation, physical and cognitive function, and pain perception in moderately functioning

older adults with elevated levels of inflammation. The proposed study will be the first to test whether a selected anti-inflammatory agent, methotrexate, reduces systemic and cellular inflammation, improve cognitive and physical function, and reduce pain levels in older adults at risk for functional decline due to systemic inflammation. Co-funded by the NIH OAIC Pepper Center Grant, and CAM-CTRP Pilot Research.

13. **Think-2-Walk:** (Clark, Williamson) This study is investigating whether peripheral sensory impairment increases cortical demand of walking. The primary hypotheses are that peripheral sensory impairments in older adults disrupt sub-cortical control of walking, leading to increased cortical demand of walking and concomitant deficits in mobility function. Co-funded by the NIH Pepper Center Grant.

D. **McKnight Inter-Institute Neuroimaging Initiative:**
A neuroimaging workgroup was formed last year to foster collaboration among the four McKnight Brain Institutes. Dr. Cohen is the UF group leader for this initiative. Steps were taken towards development of a NIA-sponsored multicenter cognitive and brain aging study. The focus of this workgroup was to standardize neuroimaging methods across the four institutes, to plan for the collection of multimodal MR and MRS data that would provide a normative dataset of functional and structural neuroimaging data on healthy elderly adults at advanced age, and to collect preliminary data that would support future grant submissions. Considerable progress was made by the group, including the collection of MR data from a single adult who travelled to all MBI sites. We established initial reliability data for the scanners at the four sites. We are currently are developing a grant proposal to be submitted to the MBRF for a block grant to enable completion of standardization efforts and the collection of an initial sample of 200 elderly adults (50 per site). This sample will consist of individuals who are over the age of 80, and in good physical health, without significant medical disease or physical frailty, and who do not have evidence of AD, MCI, or other neurodegenerative disease. Contingent on receiving these funds, we will initiate a cross-sectional study, which we believe will set the stage for external funding aimed at achieving greater understanding of the structural and functional brain manifestations of normal cognitive aging.

E. **Infrastructure Development:** (Cohen, Woods)
   a. Developed and supplied technology for the CAM-CTRP Neuroimaging Processing and Data Analysis Lab on the second floor of the IoA-Clinical Translational Research Building.
   b. Established IoA/CAM-CTRP connection to University HiPerGator computing system.
   c. Established first connection between AMRIS 3T human magnet and HiPerGator for data transfer and analysis.
   d. Successful McKnight Brain Institute Instrumentation grant proposal to acquire a whole brain 31P-1H phosphorous MRS whole brain coil for cerebral metabolic spectroscopy.
   e. Established cognitive testing space in the Health Promotion Center for CAM/IOA use.
   f. Designed and established the Human Electrophysiology Laboratory in the Clinical Translational Research Unit, on the 1st floor of IoA-CTRB.
   g. Assigned Dr. Adam Woods, Ph.D., to direct the Human Electrophysiology and Neuromodulation Core for the CAM-CTRP.
   h. Established Transcranial Direct Current Stimulation Facilities and equipment in the IoA/CAM (Woods).
   i. Established University-wide Neuroimaging User Group comprised of over 60 UF investigators (Cohen, Woods).
   j. Established University-wide Human Neuroimaging Lecture Series (Woods).
   k. Initiation of Clinical Trial Development with MBI's Age Related Memory Loss Program.
   l. Initiation of the Brain Wellness Program.

F. **Past scientific achievements are best summarized in the list of publications for this year noted in section #2: some highlighted findings for the year would include the following collaborations:**
   a. Gongvatona, Cohen et al – Progressive cerebral injury in the setting of chronic HIV infection and antiretroviral therapy. *J Neurovirol*. Apr 24 2013. Demonstrates that there are progressive cardiovascular changes that occur in the context of HIV and aging, that include reductions in NAA and GLX indicating neuronal loss. This finding points to premature brain aging.
   b. Alosco, M. L., Spitznagel, M. B., Raz, N., Cohen, R., Sweet, L. H., Garcia, S., . . . Gunstad, J. (2013). The Interactive Effects of Cerebral Perfusion and Depression on Cognitive Function in Older Adults With Heart Failure. *Psychosom Med*. doi: PSY.0b013e31829f91da [pii] Relate mood and cognition and brain aging in older adults with heart failure and depression and cerebral blood flow, all interacting to affect cognitive function.
   c. Zahodne LB, Gongvatana A, Cohen RA, Ott BR, Tremont G. Are Apathy and Depression Independently Associated With Longitudinal Trajectories of Cortical Atrophy in Mild Cognitive Impairment in older people? *Am J Geriatr Psychiatry*. Apr 28 2013.
   d. Alosco ML, Benitez A, Gunstad J, et al. Reduced memory in fat mass and obesity-associated allele carriers among older adults with cardiovascular disease. *Psychogeriatrics*. Mar 2013;13(1):35-40.

e. Miller LA, Crosby RD, Galioto R, et al. Bariatric Surgery Patients Exhibit Improved Memory Function 12 Months Postoperatively. *Obes Surg*. Apr 30 2013.
f. Garcia S, Alosco ML, Spitznagel MB, et al. Cardiovascular fitness associated with cognitive performance in heart failure patients enrolled in cardiac rehabilitation. *BMC Cardiovasc Disord*. 2013;13(1):29.

PUBLICATIONS IN PEER REVIEWED JOURNALS:

Ron Cohen, PhD, CAM-CTRP Director

1. Gongvatana A, Harezlak J, Buchthal S, et al. Progressive cerebral injury in the setting of chronic HIV infection and antiretroviral therapy. *J Neurovirol*. Apr 24 2013.
2. Stanek KM, Strain G, Devlin M, et al. Body mass index and neurocognitive functioning across the adult lifespan. *Neuropsychology*. Mar 2013;27(2):141-151.
3. Zahodne LB, Gongvatana A, **Cohen RA**, Ott BR, Tremont G. Are Apathy and Depression Independently Associated With Longitudinal Trajectories of Cortical Atrophy in Mild Cognitive Impairment? *Am J Geriatr Psychiatry*. Apr 28 2013.
4. Alosco ML, Benitez A, Gunstad J, et al. Reduced memory in fat mass and obesity-associated allele carriers among older adults with cardiovascular disease. *Psychogeriatrics*. Mar 2013;13(1):35-40.
5. Alosco ML, Brickman AM, Spitznagel MB, et al. Cerebral Perfusion is Associated With White Matter Hyperintensities in Older Adults With Heart Failure. *Congest Heart Fail*. Mar 20 2013.
6. Alosco ML, Brickman AM, Spitznagel MB, et al. Poorer physical fitness is associated with reduced structural brain integrity in heart failure. *J Neurol Sci*. May 15 2013;328(1-2):51-57.
7. Alosco ML, Brickman AM, Spitznagel MB, et al. The adverse impact of type 2 diabetes on brain volume in heart failure. *J Clin Exp Neuropsychol*. Mar 2013;35(3):309-318.
8. Alosco ML, Gunstad J, Jerskey BA, et al. Left atrial size is independently associated with cognitive function. *Int J Neurosci*. Mar 14 2013.
9. Alosco ML, Spitznagel MB, Raz N, et al. Dietary habits moderate the association between heart failure and cognitive impairment. *J Nutr Gerontol Geriatr*. 2013;32(2):106-121.
10. Alosco ML, Spitznagel MB, Raz N, et al. Executive dysfunction is independently associated with reduced functional independence in heart failure. *J Clin Nurs*. May 8 2013.
11. Alosco ML, Spitznagel MB, Strain G, et al. Improved memory function two years after bariatric surgery. *Obesity* (Silver Spring). Apr 27 2013.
12. Alosco ML, Spitznagel MB, van Dulmen M, et al. Depressive symptomatology, exercise adherence, and fitness are associated with reduced cognitive performance in heart failure. *J Aging Health*. Apr 2013;25(3):459-477.
13. Garcia S, Alosco ML, Spitznagel MB, et al. Cardiovascular fitness associated with cognitive performance in heart failure patients enrolled in cardiac rehabilitation. *BMC Cardiovasc Disord*. 2013;13(1):29.
14. Miller LA, Crosby RD, Galioto R, et al. Bariatric Surgery Patients Exhibit Improved Memory Function 12 Months Postoperatively. *Obes Surg*. Apr 30 2013.
15. Zhu T, Zhong J, Hu R, et al. Patterns of white matter injury in HIV infection after partial immune reconstitution: a DTI tract-based spatial statistics study. *J Neurovirol*. Feb 2013;19(1):10-23.
16. Gongvatana A, Harezlak J, Buchthal S, et al. Progressive cerebral injury in the setting of chronic HIV infection and antiretroviral therapy. *J Neurovirol*. Jun 2013;19(3):209-218.
17. Hua X, Boyle CP, Harezlak J, et al. Disrupted cerebral metabolite levels and lower nadir CD4 + counts are linked to brain volume deficits in 210 HIV-infected patients on stable treatment. *Neuroimage Clin*. Aug 2013;3:132-142.
18. Correia S, Cohen R, Gongvatana A, et al. Relationship of plasma cytokines and clinical biomarkers to memory performance in HIV. *J Neuroimmunol*. Sep 27 2013.

Natalie Ebner, PhD, Assistant Professor, CAM Scholar

1. **Ebner, N. C.**, Maura, G., MacDonald, K., Westberg, L., & Fischer, H. (2013). Oxytocin and socio-emotional aging – Current knowledge and future trends. [Research topic] *Frontiers in Human Neuroscience*, 7(487), 1-14. DOI: 10.3389/fnhum.2013.00487
2. Lovén, J., Svärd, J., **Ebner, N. C.**, Herlitz, A., & Fischer, H., (2013). Face gender modulates women's brain activity during face encoding. *Social Cognitive and Affective Neuroscience*. [Epub ahead of print]
3. Voelkle, M. C., **Ebner, N. C.**, Lindenberger, U., & Riediger, M. (2013). Here we go again: Anticipatory and reactive mood responses to recurring unpleasant situations throughout adulthood. *Emotion*, 13(3), 424-433. DOI: 10.1037/a0031351
4. **Ebner, N. C.**, Johnson, M. K., & Fischer, H. (2012). Neural mechanisms of reading facial emotions in young and older adults. [Special section] *Frontiers in Integrative Neuroscience / Emotion Science*, 3, 1-19. DOI: 10.3389/fpsyg.2012.00223

Adam J. Woods, PhD, Assistant Professor, CAM Scholar

1. **Woods, A.J.**, Cohen, R.A., Pahor, M. (2013). Cognitive frailty: frontiers and challenges. *Journal of Nutrition, Health, and Aging*, 17, 741-743.
2. Kessler, S., Minhas, P., **Woods, A.J.**, Rosen, A., Bikson, M. (2013). Dose considerations for transcranial direct current stimulation in children: a computational modeling study. *PLoS ONE*
3. **Woods, A.J.**, Philbeck, J.W., & Wirtz, P. (2013). Hyper-arousal decreases human visual thresholds. *PLoS ONE*, 8(4): e61415. doi: 10.1371/journal.pone.0061415
4. **Woods, A.J.**, Goksun, T., Chatterjee, A., Zelonis, S., Mehet, A., Smith, S. (2013). The development of organized visual search. *Acta Psychologica*. 143(2): 191-199. doi: 10.1016/j.actpsy.2013.03.008
5. Göksun, T., **Woods, A.J.**, Chatterjee, A., Zelonis, S., Glass, L., Smith, S.E. (2013). Elementary school children's attentional biases in physical and numerical space. *European Journal of Developmental Psychology*, 10(4): 433-448. doi: 10.1080/17405629.2012.692965

John Williamson, PhD, Assistant Professor, CAM Scholar

1. Acosta LM, **Williamson JB**, Heilman KM. Agency and the Annunciation. *Journal of Religion and Health 2013* [epub, ahead of print]. DOI 10.117/s10943-013-9724-y.
2. Behforuzi H., Burtis DB, **Williamson JB**, Stamps JJ, Heilman KM. Impaired initial vowel versus consonant letter-word fluency in dementia of the Alzheimer type. *Cognitive Neuroscience 2013* (epub, ahead of print) 10.1080/17588929..2013.854200
3. Burtis DB, **Williamson JB**, Mishra M, Heilman KM. The blindside: Impact of monocular occlusion on spatial attention. *Journal of Clinical and Experimental Neuropsychology 2013*, in press.
4. Kabasakalian A, **Williamson JB**, Heilman KM. Hypometric allocentric and egocentric distance estimates in people with Parkinson's disease. *Cognitive and Behavioral Neurology 2013*.
5. **Williamson JB**, Lewis GF, Nyenhuis DL, Stebbins GT, Murphy C, Handelman M, Harden E, Heilman KM, Gorelick PB, Porges SW. The effects of cerebral white matter changes on cardiovascular responses to cognitive and physical activity in a stroke population. *Psychophysiology 2012*, in press.
6. Acosta, LMY, **Williamson JB**, Heilman KM. Which cheek did Jesus turn? *Religion, Brain Behavior 2012*, in press.
7. Claunch J, Falchook A, **Williamson JB**, Fischler I, Jones E, Baum J, Heilman KM. Famous faces but not remembered spaces influence vertical line bisections. *Journal of Clinical and Experimental Neuropsychology 2012*, in press.
8. Falchook AD, Mosquera D, Finney GR, **Williamson JB**, Heilman KM. The relationship between semantic knowledge and conceptual apraxia in Alzheimer's disease. *Cognitive and Behavioral Neurology 2012*, in press.
9. Susveri K, Falchook A, **Williamson JB**, Heilman KM. Right up there: Hemispatial and hand asymmetries of altitudinal pseudoneglect. *Brain and Cognition 2012*, in press.
10. Harciarek M, **Williamson JB**, Haque S, Burtis D, Heilman KM. Ipsilateral neglect from a subcortical lesion: The effects of spatial position, distractors, and repeated trials. *Cognitive and Behavioral Neurology 2012*, 25, 42-49.
11. Harciarek M, **Williamson John B**, et al. Risk factors for selective cognitive decline in dialyzed patients with end stage renal disease: evidence from verbal fluency analysis. *Journal of the International Neuropsychological Society 2012*, 18, 162-167.

Josh Kirton, MS, Graduate Student

1. **Kirton, J.W.**, Resnick, S.M., Davatzikos, C., Kraut, M.A., & Dotson, V.M. (in press) Depressive symptoms, symptom dimensions and white matter lesion volume in older adults: A longitudinal study. *American Journal of Geriatric Psychiatry*.

Vaughn E. Bryant, MS, Graduate Student

1. **Bryant, V. E.**, Kahler, C. W., Devlin, K. N., Monti, P. M., & Cohen, R. A. (2013). The effects of cigarette smoking on learning and memory performance among people living with HIV/AIDS. *AIDS Care*, doi: 10.1080/09540121.2013.764965
2. Devieux, J. G., Rosenberg, R., Saint-Jean, G., **Bryant, V. E.**, & Malow, R. M. (2013). The Continuing Challenge of Reducing HIV Risk among Haitian Youth: The Need for Intervention. *J Int Assoc Provid AIDS Care*. doi: 10.1177/2325957411418119
3. **Bryant, V.E.** National Institutes of Health. (2012). *Encyclopedia of Behavioral Medicine*. McMahon, R.C.
4. **Bryant, V.E.**, Jean-Gilles, M., Devieux, J., Malow, R., Rosenberg, R. (2012) Haitian Adolescent Personality Clusters and Their Problem Area Correlates. *Journal of Immigrant and Minority Health*.

5. Malow RM, McMahon RM, Devieux J, Rosenberg R, Frankel A, **Bryant VE**. (2012). Cognitive Behavioral HIV Risk Reduction in Those Receiving Psychiatric Treatment: A Clinical Trial. *AIDS and Behavior*.

Thomas Buford, PhD, Assistant Professor

1. **TW Buford***, SD Anton. Resveratrol as a supplement to exercise training: Friend or Foe? *J Physiol*. (in press)
2. **TW Buford***, SD Anton, DJ Clark, TJ Higgins, MB Cooke. Optimizing the Benefits of Exercise on Physical Function in Older Adults. *PM&R*. (in press)
3. MM McDermott, WB Applegate, DE Bonds, **TW Buford**, T Church, MA Espeland, TM Gill, JM Guralnik, W Haskell, LC Lovato, M Pahor, CJ Pepine, KF Reid, A Newman. Ankle Brachial Index Values, Leg Symptoms, and Functional Performance among Community-Dwelling Older Men and Women in the Lifestyle Interventions and Independence for Elders (LIFE) Study. *J Am Heart Assoc*. (in press)
4. WJ Rejeski, R Axtell, R Fielding, J Katula, AC King, TM Manini, AP Marsh, M Pahor, A Rego, C Tudor-Locke, M Newman, MP Walkup, ME Miller, LIFE Study Investigator Group. Promoting physical activity for elders with compromised function: the Lifestyle Interventions and Independence for Elders (LIFE) Study physical activity intervention. *Clin Interv Aging*. 8: 1119-31. 2013.
5. CW McDonough, NK Gillis, A Alsultan, SW Chang, M Kawaguchi-Suzuki, JE Lang, MHA Shahin, **TW Buford**, NM El Rouby, ACC Sa, TY Langaee, JG Gums, AB Chapman, RM Cooper-DeHoff, ST Turner, Y Gong, JA Johnson. Atenolol Induced HDL-C Change in the Pharmacogenomic Evaluation of Antihypertensive Responses (PEAR) Study. *PLOS ONE*. (in press)
6. E Marzetti, R Calvani, M Cesari, **TW Buford**, M Lorenzi, BJ Behnke, C Leeuwenburgh. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. *Int J Biochem Cell Biol*. (in press)
7. SA Anton, C Karabetian, K Naugle, **TW Buford***. Obesity and Diabetes as Accelerators of Functional Decline: Can Lifestyle Interventions Maintain Functional Status in High Risk Older Adults? *Exp. Gerontol*. (in press)
8. AP Marsh, K Kennedy, LC Lovato, C Castro, K Domanchuk, NW Glynn, E McDavitt, R Rodate, M Marsiske, J McGloin, EJ Groessel, M Pahor, JM Guralnik, LIFE Research Group. Lifestyle Interventions and Independence for Elders Study: Recruitment and Baseline Characteristics. *J Gerontol A Biol Sci Med Sci*. (in press)
9. **TW Buford***, RG MacNeil, LG Clough, M Dirain, B Sandesara, M Pahor, TM Manini, C Leeuwenburgh. Active muscle regeneration following eccentric contraction-induced injury is similar between healthy young and older adults. *J Appl Physiol*. (in press)
10. TM Manini, **TW Buford**, D Lott, K Vandenborne, MJ Daniels, J Knaggs, H Patel, M Pahor, MG Perri, SD Anton. Effect of dietary restriction and exercise on lower extremity tissue compartments in obese older women: A pilot study. *J Gerontol A Biol Sci Med Sci*. (in press).
11. **TW Buford***, MD Roberts, TS Church. Toward exercise as personalized medicine. *Sports Med*. 43(3): 157-165. 2013.

Todd Manini, PhD, Assistant Professor

1. Buford TW, Macneil RG, Clough LG, Dirain M, Sandesara B, Pahor M, **Manini TM**, Leeuwenburgh C. Active muscle regeneration following eccentric contraction-induced injury is similar between healthy young and older adults. *J Appl Physiol*. 2013 Mar 14. [Epub ahead of print] PubMed PMID: 23493365.
2. Jeff Parr, Paul Borsa, Roger Fillingim, Mark Tillman, **Todd Manini**, Chris Gregory, Steven George. Psychological Influences Predict Recovery Following Exercise Induced Shoulder Pain. *International Journal of Sports Medicine*. In press.
3. Jamie A Cooper, **Todd M Manini**, Chad M Paton, Yosuke Yamada, James E Everhart, Steve Cummings, Dawn C Mackey, Anne B Newman, Nancy W Glynn, Fran Tylavsky, Tamara Harris and Dale A Schoeller. Longitudinal change in energy expenditure and effects on energy requirements of the elderly. *Nutr J*. 2013 Jun 6;12(1):73. PMID: 23742706 PMCID: PMC3679966.
4. Jennifer S Yokoyama, PhD; Shana M Katzman, PhD; Michael A Nalls, PhD; Anne B Newman, MD; Tamara B Harris, MD; Matteo Cesari, MD, PhD; **Todd M Manini, PhD**; Nicholas J Schork, PhD; Steven R Cummings, MD; Yongmei Liu, PhD; Kristine Yaffe, MD. MtDNA sequence associations with dementia and amyloid-ß in elderly African-Americans. *Neurobiology of Aging*. In Press.
5. Christina L. Bell MD, Andrea LaCroix PhD, Kamal Masaki MD, Erinn M. Hade PhD, **Todd Manini PhD**, W. Jerry Mysiw, MD, J. David Curb MD, Sylvia Wassertheil-Smoller. Pre-Stroke Factors Associated with Post-Stroke Mortality and Recovery in Older Women in the WHI. *Journal of the American Geriatrics Society*. In Press.
6. Vellas B, Pahor M, **Manini T**, Rooks D, Guralnik JM, Morley J, Studenski S, Evans W, Asbrand C, Fariello R, Pereira S, Rolland Y, Abellan Van Kan G, Cesari M, Chumlea WMC, Fielding R. Designing pharmaceutical trials for sarcopenia in frail older adults: EU/US Task Force Recommendations. *The Journal of Nutrition, Health & Aging*. In press.
7. Higgins TJ^, Janelle CM, **Manini TM***. Origins and measurement of pre-clinical disability. Submitted to *Journals of Gerontology: Psychological and Social Sciences*. In press 9/13.

8. **Manini TM***, Rodriguez B, Manson J, Garcia L, Stefanick M, Hingle M, Sims S, Song Y, Seguin R, Lamonte M, Limacher M. Sitting time and incidence diabetes in the Women's Health Initiative. *Obesity*. In press 9/13.
9. Endeshaw Y; Rice TB; Schwartz AV; Stone KL; **Manini TM**; Satterfield S; Cummings S; Harris T; Pahor M; for the Health ABC Study. Snoring, daytime sleepiness, and incident cardiovascular disease in the health, aging, and body composition study. *SLEEP 2013*;36(11):1737-1745.
10. Rillamas-Sun E, LaCroix AZ, Waring ME, Kroenke CH, LaMonte MJ, Vitolins MZ, Seguin R, Bell CL, Gass M, **Manini TM**, Masaki KH, and Wallace RB. Obesity and Survival to Age 85 Years without Major Disease or Disability in Older Women. *JAMA Internal Medicine*. In press 9/13.
11. McGregor KM, Nocera J, Sudhyadhom A, Patten C, **Manini TM**, Kleim JA, Crosson B, Butler AJ. Effects of Aerobic Fitness on Aging-related Changes of Interhemispheric Inhibition and Motor Performance. *Frontiers in Aging Neuroscience*. In press 9/13.
12. Seguin R, Buchner DM, Liu J, Allison, M; **Manini T**, Wang C, Manson JE, Messina CR, Patel MJ, Moreland L, Stefanick ML, LaCroix AZ. Sedentary behavior and mortality in older women: Findings from the Women's Health Initiative. *American Journal of Preventive Medicine*. In press 10/13.
13. Tranah GJ, Yokoyama JS, Katzman SM, Nalls MA, Newman AB, Harris TB, Cesari M, **Manini TM**, Schork NJ, Cummings SR, Liu Y, Yaffe K; for the Health, Aging and Body Composition Study. Mitochondrial DNA sequence associations with dementia and amyloid-β in elderly African Americans. *Neurobiol Aging*. 2013 Oct 17. doi:pii: S0197-4580(13)00236-4. 10.1016/j. neurobiolaging.2013.05.023. [Epub ahead of print] PMID: 24140124 [PubMed – as supplied by publisher].
14. Goodman D, Park H, Stefanick M, LeBlanc E, Bea J, Qi L, Kapphahn K, LaMonte M, **Manini T**, Desai M, Anton-Culver H. Relation Between Self-Recalled Childhood Physical Activity And Adult Physical Activity: The Women's Health Initiative. *Open Journal of Epidemiology (OJEpi)*. In press 11/13.

UNDER REVIEW:

Talia Seider, BA, Graduate Student

1. **Seider, TR**, Luo, X, Gongvatana, A, Devlin, KN, de la Monte, SM, Chasman, JD, Tashima, KT, Navia, B, & Cohen, RA. Verbal memory declines more rapidly with age in HIV infected vs. uninfected adults. *Journal of Clinical and Experimental Neuropsychology*.

Note: This list only includes core faculty and CAM-CTRP Scholars. For a complete listing of the publications of all CAM-CTRP affiliated faculty, please see our website.

Other Publications

1. Cohen, RA (1993, 2013) *Neuropsychology of Attention*, Plenum Publishing: New York.
2. West, R.L., Ebner, N.C., & Hastings, E. C. (2012). Linking goals and aging: Experimental and life-span approaches. In E. A. Locke & G. P. Latham (Eds.), *New developments in goal setting and task performance* (pp. 439-459). London, UK: Routledge Academic

PRESENTATIONS AT SCIENTIFIC MEETINGS

Ron Cohen, PhD, Professor

Grand Rounds, Dept. of Psychiatry, 3/2013 – *Obesity and Bariatric Surgery Effects on Brain Function*
McKnight Inter-Institutional Mtg., 4/2013 – *Neuroimaging; Cognitive Aging Frontiers, Limitations and Future Directions*
University of Miami, 12/2013 – *Vascular Cognitive Impairment in Context of the Aging Brain*

Eric Porges, PhD, Post-Doctoral Fellow

Interaction of Pain and Pleasure Networks. Presented at the annual meeting of the Cognitive Neuroscience Society in San Francisco, CA (4/16/13)

Talia Seider, BA, Graduate Student

11/ 2012: Memory declines more rapidly with age in HIV infected adults. McKnight Poster Reception at the Society for Neuroscience. San Diego, CA.

Vonetta Dotson, PhD, Assistant Professor, CAM Scholar and Josh Kirton, MS, Graduate Student

Dotson, V.M., Kirton, J.W., Sozda, C.N., Perlstein, W.M., Anton, S. & Manini, T. (2013, November). *An fMRI study of sex differences in memory encoding and working memory in older adults*. Paper to be presented at the 2013 Society for Neuroscience conference in San Diego, CA.

Szymkowicz, S.M., **Kirton, J.W.**, Sozda, C.N., Perlstein, W.M. & **Dotson, V.M.** (2013, November). *Effect of aerobic exercise on memory encoding in older adults with a history of depression: An fMRI pilot study*. Poster to be presented at the 2013 Society for Neuroscience conference in San Diego, CA.

Szymkowicz, S. M., **Kirton, J. W.**, Sozda, C. N., Perlstein, W. M., & **Dotson, V. M.** (2013, November). *Effect of aerobic exercise on memory encoding in older adults with a history of depression: An fMRI pilot study*. Poster to be presented at the 6th annual McKnight Brain Research Foundation Poster Reception at Society for Neuroscience (SfN), San Diego, CA.

Szymkowicz, S. M., **Kirton, J. W.**, Sozda, C. N., & **Dotson, V. M.** (2013, October). *Preliminary results from the Physical Activity for Mood and Memory (PAMM) study*. Poster presented at the 4th annual Spotlight on Research in Aging exhibition, University of Florida, Gainesville, FL.

Kirton, J. W., Sozda, C. N., Perlstein, W. M., Manini, T. M., Anton, S. D. and **Dotson, V. M.** (2013, February). *Differences in brain activity in men and women for working memory but not memory encoding*. Poster presented at the Institution for Learning in retirement Student Research on Aging Exposition Gainesville, FL.

Adam J. Woods, PhD, Assistant Professor, CAM Scholar

Course Director: NYC Neuromodulation 2013 Non-invasive Brain Stimulation Practical Course (93 students)
Invited speaker at the UF Information Technology Research Computing Day 2013 (11/7/13): Research Computing Infrastructure for Image Processing of the Brain
Invited attendee to the UC Davis Summit on Transcranial Direct Current Stimulation (Sept 5, 2013)
Invited speaker to the NYC Neuromaduation 2013 Conference (Nov 22-23, 2013) – Multimodal combinations of fMRI and tDCS: Frontiers and Challenges
Presented poster at IoA Spotlight on Aging Research 9/9/13 "Targeting Space, Time, and Causality in the Human Brain using Multimodal Neuroimaging"
Presented research talk at the 42nd Southeastern Magnetic Resonance Conference in Tallahassee Florida; "Exploring structure-function relationships using parallel BOLD fMRI and Transcranial Direct Current Stimulation;" 10/11/13-10/13/13

Natalie Ebner, PhD, Assistant Professor, CAM Scholar

Tasdemir-Ozdes, A., Bluck, S. B., & **Ebner, N. C.** (November, 2013). *Effects of mental time travel on healthy lifestyle choices in young and older adults: The role of valence*. Poster at the Society for the Study of Human Development 8th Biennial Meeting, Fort Lauderdale, FL, USA.

Westberg, L., Zettergren, A., Lovén, J., Svärd, J., Milding, J., Johansson, D., **Ebner, N. C.**, & Fischer, H. (November, 2013). *Association between an oxytocin receptor gene variant and face recognition as well as related amygdala activation*. Poster at the Society for Social Neuroscience, San Diego, CA, USA.

Lin, T., Johnson, M. K., Ankudowich, E., & **Ebner, N. C.** (September, 2013). *Self vs. Others: Behavioral and Neural Evidence of the Self-Positivity Effect in Young and Older Adults*. Poster at the 4th Annual Spotlight on Aging Research, Gainesville, FL, USA.

Tasdemir-Ozdes, A., & **Ebner, N. C.** (July, 2013). *Effect of mental time travel on lifestyle decisions: Does valence matter?* Talk at the International Academic Conference on Social Sciences, Istanbul, Turkey.

Högman, L., Svärd, J., Högman, W., **Ebner, N. C.**, Makower, I., & Fischer, H. (July, 2013). *Age-differences in brain and behavior during recognition facial expressions at longer and shorter durations*. Poster at the 13th European Congress of Psychology, Stockholm, Sweden.

Ebner, N. C., Maura, G., Westberg, L, & Fischer, H. (June, 2013). *Associations of the oxytocin receptor gene (OXTR) polymorphisms with brain response during reading of facial emotions in young and older adults*. Poster at the Clinical and Translational Science Institute (CTSI) Research Day, Gainesville, FL, USA.

John Williamson, PhD, Assistant Professor, CAM Scholar

Kesayan T, **Williamson JB**, Falchook AD, Okun MS, Malaty IA, Rodriguez R, White KD, Hauser RA, Heilman KM. *Abnormal tactile pressure perception in Parkinson's disease: A perceptual grasp*. Poster Presented at the 2013 annual meeting of the American Academy of Neurology, San Diego.

Falchook AD, Salazar L, Johnson EM, Morales MC, **Williamson JB**, Fischler I, Heilman KM. *Estimation of eye level: Normal egocentric vertical attention biases*. Poster Presented at the 2013 annual meeting of the American Academy of Neurology, San Diego.

Behforuzi H, Burtis B, **Williamson JB**, Stamps JJ, Heilman KM. *Impaired initial vowel versus consonant word fluency in dementia of the Alzheimer type*. Poster Presented at the 2013 annual meeting of the American Academy of Neurology, San Diego.

Acosta L, Haque S, Estalilla D, Szeles D, Appel H, Fischler I, Austin J, Heilman K, **Williamson, J.** *Mindfulness-based stress reduction and creativity*. resented at the 2013 International Neuropsychological Society Annual Conference, Hawaii.

Harciarek M, **Williamson JB**, Burtis DB, Haque S, Heilman KM. *Putaminal ipsilesional neglect*. Presented at 2012 International Neuropsychological Society Midyear Meeting, Oslo, Norway.

Harciarek M, **Williamson JB**, Biedunkiewicz B, Lichodziejewaska-niemirko M, Debska-Slizien A, Rutkowski B. *Reno-cerebrovascular disease: A model for cognitive decline in patients treated with dialysis.* Presented at 2012 International Neuropsychological Society Midyear Meeting, Oslo, Norway.

Harciarek M, **Williamson JB**, Biedunkiewicz B, Lichodziejewaska-niemirko M, Debska-Slizien A, Rutkowski B. *Hypertension And Blood Urea Nitrogen Independently Predict Progression Of Executive Problems In Dialized Patients With End-Stage Renal Disease*. Presented at 2012 International Neuropsychological Society Midyear Meeting, Oslo, Norway.

Kesayan T, Falchook AD, **Williamson JB**, White K, Skidmore F, Heilman KM. *Disordered tactile force perception in Parkinson disease*. Presented at the 64th Annual Meeting of the American Academy of Neurology, New Orleans, LA, April 2012.

Falchook A, Mosquera D, Finney GR, **Williamson JB**, Heilman KM. *Conceptual apraxia in Alzheimer disease: Impaired mechanical knowledge with preserved tool selection associative knowledge*. Presented at the 64th Annual Meeting of the American Academy of Neurology, New Orleans, LA, April 2012.

Burtis, D.B., **Williamson, J.B.**, Haque, S., Harciarek, M., Heilman, K.M. *Disengagement Neglect*. Presented at the 64th Annual Meeting of the American Academy of Neurology, New Orleans, LA, April 2012.

Williamson, J.B., Haque, S., Burtis, D.B., Heilman, K.M. *Ipsilesional Neglect in Right Hemispace with Right Hemisphere Strokes*. Presented at the 64th Annual Meeting of the American Academy of Neurology, New Orleans, LA, April 2012.

Haque, S., **Williamson, J.B.**, Burtis, D.B., Estalilla, D., Heilman, K.M. *Proximity Dependent Attentional Biases in Patients with Chronic Stroke*. Presented at the 64th Annual Meeting of the American Academy of Neurology, New Orleans, LA, April 2012.***

Salazar-Bejarano, L., Jaffer, M., Burtis, D.B., **Williamson, J.B.**, Isham, R., Heilman, K.M. *Speed of Global versus Focal Processing*. Presented at the 64th Annual Meeting of the American Academy of Neurology, New Orleans, LA, April 2012.

Jaffer, M., Salazar-Bejarano, L., Burtis, D.B., **Williamson, J.B.**, Isham, R., Heilman, K.M. *Processing During Focal versus Global Attention*. Presented at the 64th Annual Meeting of the American Academy of Neurology, New Orleans, LA, April 2012.

Williamson JB, Burtis BD, Haque S, Harciarek M, Estalilla D, Heilman KM. *Chronic left parietal but not chronic right hemisphere lesions are associated with ipsilesional spatial bias*. Presented at 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA February 2012.

Cohen ML, **Williamson JB**, Kwon JC, Schwartz B, Salazar L, Heilman KM. *Parkinson patients' impaired disengagement from focal attention impairs the allocation of global attention*. Presented at 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA February 2012.

Burtis DB, Wang C, Ding M, Heilman KM, **Williamson JB**. *Constrained monocular viewing (CMV) and its effects on the autonomic nervous system*. Presented at 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA February 2012.

Susveri K, Falchook AD, **Williamson JB**, Heilman KM. *Right up there: Hemispatial and hand asymmetries of attitudinal pseudoneglect*. Presented at 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA February 2012.

Claunch JB, Falchook AD, **Williamson JB**, Fischler I, Jones EM, Baum JB, Heilman KM. *Remembered spaces and famous faces influence vertical line bisections*. Presented at 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA February 2012.

Claunch JD, Falchook AD, **Williamson JB**. Fischler I, Jones EM, Baum JB, Heilman KM. *The highs and lows of attentional disengagement during vertical line bisections*. Presented at 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA February 2012.
Falchook AD, Mosqueara DM, Finney GR, **Williamson JB**, Heilman KM. *Conceptual apraxia in Alzheimer disease: Impaired mechanical knowledge with preserved tool selection associative knowledge*. Presented at 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA February 2012.
Burtis DB, Wang C, Mo J, Ding M, **Williamson JB**, Heilman KM. *Electrophysiological correlates of constrained monocular viewing*. Presented at 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA February 2012.
Srivastava M, Falchook AD, **Williamson JB**, Heilman KM. *Focal vertical attention and hemispheric hand bias: Who has the upper hand?* Presented at 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA February 2012.
Srivastava A, Falchook AD, **Williamson JB**, Heilman KM. T*he upward bias in vertical line bisection and quadrisection*. Presented at 40th Annual Meeting of the International Neuropsychological Society, Montreal, CA February 2012.

Buford, Thomas PhD, Assistant Professor

A supplemental benefit to ACE inhibitor use for seniors with hypertension? University of Florida, Institute on Aging. Interdisciplinary Seminar Series, Gainesville, FL. 9/30/2013
A supplemental benefit to ACE inhibitor use for seniors with hypertension? Geriatric Research Education and Clinical Center, Central Arkansas Veterans Healthcare System, Little Rock, AR. 8/8/13.
A supplemental benefit to ACE inhibitor use for seniors with hypertension? Geriatric Research Education and Clinical Center, North Florida/South Georgia Veterans Health System, Gainesville, FL. 3/13/13.

PRESENTATIONS TO THE COMMUNITY (NON-SCIENTIFIC MEETINGS):

Ron Cohen, PhD – Gainesville Senior Recreational Center, *The Aging Brain*

Kim Foli, B.S.- The Active Brain Study & Current Trends in Brain Research. Many educational and recruitment oriented talks have been given in the Gainesville and Jacksonville communities to support The ACTIVE BRAIN Study/ LIFE Ancillary Study. This includes educational talks to the LIFE Study participants in Gainesville and Jacksonville, and to such places as Alachua County Senior Recreational Center, Oak Hammock Retirement Community, The Village Retirement Community and other local venues such as UF Alumni Retired Faculty Meeting, and the UF Medical Guild. There has been overwhelming recruitment response to these talks and other novel recruitment and advertising approaches, which has enabled the us to successfully screen and fill a database of 200+ prospective research participants interested participating in a variety of ways with the CAM-CTRP, and supporting the research Vision and Mission of CAM-CTRP.

Strickland-Hughes, C. M., & Ebner, N. C. (December, 2012). Social memory and aging. Institute for Learning in Retirement at Oak Hammock & at the PrimeTime Institute at the Senior Recreation Center, Institute of Aging Senior Health Series, University of Florida, Gainesville, FL, USA.

AWARDS:

Adam J. Woods, Ph.D., nominated as a junior fellow to the World Academy of Art and Science, 2013

FACULTY BIOGRAPHICAL SKETCHES: See page 67

TRAINEES AND RECRUITMENT:

Recruitment efforts have been successful, and are ongoing for development of the CAM-CTRP team of Faculty, Post Docs, Pre Docs and others being mentored.

Vonetta Dotson, PhD, is an Assistant Professor in the Department of Clinical and Health Psychology (CHP) at the University of Florida, with a joint appointment in the Department of Neuroscience at the University of Florida. She is also a Claude C. Pepper scholar. She received her Ph.D. from CHP in 2006 with a specialization in neuropsychology and a certificate in gerontology. She completed her postdoctoral training in the Laboratory of Personality and Cognition in the National Institute on Aging Intramural Research Program under the mentorship of Drs. Susan Resnick and Alan Zonderman. Her research focuses on studying the interaction of psychological disorders such as depression with cognitive and brain aging using both neuroimaging and behavioral techniques. Her more recent work focuses on the impact of aerobic exercise on depression-related cognitive and brain changes in older adults.

Natalie Ebner, PhD, is an Assistant Professor in the Department of Psychology at University of Florida since 2011. She is Adjunct Faculty at Cognitive Aging and Memory Clinical Translational Research Program (CAM-CTRP) since 2013. She received her Ph.D. in 2005 in Psychology with a particular focus on lifespan development and aging from the Free University of Berlin in Germany. She completed post-doctoral fellowships at the Max Planck Institute for Human Development in Berlin, Germany, and at Yale University, where she also worked as Associate Research Scientist before joining the faculty at University of Florida. Dr. Ebner's faculty mentors are Dr. Ron Cohen, Dr. Julia Graber, Dr. Tom Foster, and Dr. Michael Marsiske.

Dr. Ebner's research is at the intersection of cognitive, social, and developmental psychology, with a particular focus on age-related changes in cognitive processing of social and emotional information and on development and interplay of motivation, emotion, and cognition in adulthood. In particular, Dr. Ebner examines how emotional (e.g., faces displaying different emotion expressions, positive and negative personality traits) and self-relevant information (e.g., related to one's own age, personal goals and agendas, age stereotypes, etc.) affect attention, decision-making, and memory, how and why this may change across the lifespan. She uses a multi-methods approach that combines convergent measures, including self-report, behavior observation, eye tracking, genetics, hormonal markers, and functional neuroimaging techniques, with the aim to integrate introspective, behavioral, and neuropsychological data.

The two most current project that Dr. Ebner is engaged in in collaboration with researchers from the CAM-CTRB are (a) a set of studies on the short-term and long-term effects of intranasal oxytocin on cognition, physical health, and socioemotional functioning in aging, and (b) a study on neural dysregulation related to emotion processing in aging using real-time fMRI.

Adam J. Woods, PhD has joined the team from a fellowship at Penn State as an Assistant Professor. His active program of research investigates precursors and neuroimaging-based biomarkers of cognitive frailty in older adults. He has a strong background with multi-disciplinary neuroscience methodologies (MRI/fMRI, electrophysiology, non-invasive brain stimulation), extensive experience with aging-related disorders, and past research with neurological diseases. His present research investigates markers and mechanisms of susceptibility to cognitive impairment following acute illness/injury (urinary tract infection, knee replacement surgery, etc.). This work uses modern neuroimaging and biomarkers methods to investigate mechanisms of cognitive frailty in older adults. He is currently outfitting an impressive Faraday Cage for many future research studies involving EEG on the aging brain.

Florida Opportunity Scholars Mentor Program – 5 undergraduate research assistants

Course Director, the Clinical Neuroscience of Aging online graduate course for the Dept. of Aging and Geriatric Research Masters and Certificate Program.

John Williamson, PhD is funded through the Alzheimer's Foundation collaborating with Kenneth Heilman, MD in the education of behavioral neurology and neuropsychology/neuroscience fellows and students in research methods and content related to diseases of aging. He is the director of a stroke neuropsychology clinic through the University of Florida Department of Clinical and Health Psychology. Our service has expanded to include neurodegenerative diseases (early and moderate stage) in collaboration with behavioral neurology. John recently (July 2013) joined the CAM team. "We have quickly developed an exciting program of collaborative projects involving multiple UF departments and the VAMC. The support of the McKnight Brain Research Foundation has enabled us to be bold in our vision and I am expecting great things moving forward."

Eric Porges, PhD, from University of Chicago has joined the team in August of 2013, as a Post-Doctoral Fellow. Prior to his arrival, Eric studied individual differences in physiological response to social stressors, using both peripheral and central measures of nervous system response. He is currently involved in a number of projects at the CAM-CTRP, including but not limited to the ACTIVE

BRAIN Study, where he is implementing the functional neuroimaging tasks, setting up a Semi-automated neuroimaging pipeline to expedite analysis of data collected in this study and others, and planning a K-award submission.

Tiffany Cummings, PsyD, has come to UF as a Post-Doctoral Fellow, with a three-fold educational opportunity. She is equally supported by CAM-CTRP, PHHP-Clinical and Health Psychology and Dept. of Psychiatry. She has been tasked with assisting in the development of the Brain Wellness Clinic initiative at multi sites, including the IOA-Senior Care Clinic and the Movement Disorders Center for Neurorestoration.

Talia Seider, BA, Talia is a second year graduate student in the neuropsychology track in the department of Clinical and Health Psychology. Her interests are cerebrovascular disease effects on cognition, neuroimaging, HIV, and aging. She is working on quantification of white matter hyperintensities in a cohort with HIV and studying their effect on cognitive functioning in the context of aging.

Amanda Garcia, MS, Amanda is a third year graduate student in the neuropsychology track in the department of Clinical and Health Psychology. Dr. Cohen is serving as her primary mentor for her dissertation. She has interest and background in the cognitive neuroscience of semantic processes and language, and also in functional neuroimaging, including FMRI. She will be conducting research in the CAM-CTRP on normal age-associated changes in semantic brain networks as measured by FMRI.

Vaughn Bryant, MS, Vaughn is currently a 1st year doctoral student in the program in Clinical and Health Psychology. His current mentors are Dr. Ronald Cohen and Dr Nicole Whitehead. Currently, Vaughn is working with Drs. Cohen, Cook (Epidemiology) and Whitehead, on projects for the SHARC(Southern HIV and Alcohol Research Consortium) and Neurocognitive working group, which involve addressing neurocognitive issues in people living with HIV. Vaughn is particularly interested in the neuropsychiatric symptoms of apathy and depression, specifically, how these neuropsychiatric symptoms affect cognitive performance and neuroimaging results.

Joshua Kirton, MS is a fourth year doctoral student in Clinical Neuropsychology working with Vonetta Dotson and Ronald Cohen. His research interest includes neuroimaging in aging and depression. He is currently working on research to quantify regional white matter hyperintensities in older adult and examine their relationship to depressive symptom dimensions. He is also engaged in fMRI research on a variety of cognitive aging and depression projects.

Undergraduate Volunteers: CAM-CTRP has 7 of the very brightest and best qualified undergraduate students serving as research assistants. Dr. Cohen mentors 2 of these, and Dr. Woods mentors 5.

Faculty recruitment: Efforts were made for Richard Briggs, Ph.D., from Southwestern Medical Center, Dallas, Texas. This position would have been co-funded by the CAM-CTRP and VA Medical Center. Dr. Briggs decided to take a position in Atlanta Georgia that was willing to provide tenure on hire.

There is an intensive recruitment effort underway for an M.D. or Ph.D., RO1 funded candidate to join the team. The recruitment expertise of Hawkins and Merrit, Inc., have been retained to spearhead this national candidate search.

Dr. Xiang Gao, M.D., a physician researcher from Harvard University with an established NIH track record will be interviewed in early December for a CAM-CTRP faculty position. Dr. Gao has multiple areas of interest of relevance to cognitive aging, most notably the effects of cerebral vascular disease on the aging brain. He also has clinical trial research experience.

In addition, two prospective candidates will be visiting and interviewing in mid-December, Dr. James Morris, Ph.D., and Dr. Jessica Connelly, Ph.D., from Virginia. They are a married couple that may bring extensive neuroimaging research and genomic experience to help fulfill the mission of CAM-CTRP.

CLINICAL /TRANSLATIONAL PROGRAMS:

The LIFE-ARISE Grant Submission (1RO1AG046134-01) – This study will significantly advance the field of Alzheimer's disease prevention in an understudied high risk frail population not currently targeted in any other large randomized clinical trial. LIFE –ARISE will provide conclusive evidence whether physical activity effectively improves a comprehensive array of neuroimaging, cognitive and biological markers of AD. This trial will have a major public health and policy impact regarding the benefits of physical activity for AD prevention in frail older adults.

The PCORI (Patient-Centered Outcomes Research Institute) Grant Submission – A $17 million dollar collaboration proposal from CTSI was initiated for funding related to areas of Patient Centered Outcomes Research. The CAM-CTRP (Cohen,Woods) was invited to collaborate with the Pepper Center (Manini, Anton) to develop Physical and Cognitive Frailty Assessments, that would be used as an initial screening within all health care provider centers in North Florida. This submission is awaiting results for funding.

ADRC – (Alzheimer's Disease Research Center) Grant submission – (Todd Golde, Ph.D., and Ron Cohen, Ph.D.,) This proposal involved collaboration between UF and Mt. Sinai in Miami, to develop an Alzheimer's Disease Research Center. Cohen was invited to be Co-I for several aspects of the project including a neuroimaging core. Unfortunately, the was not funded, but will likely be resubmitted.

Cognitive Aging Drug Development – CAM-CTRP (Cohen et al.,) **and ARML** (Foster, Bizon) have initiated efforts to identify promising compounds worthy of clinical trials, to examine possible effects on improving cognitive function, performance and brain health. Four classes of compounds have been identified, and initial organizational efforts have been taken to plan out trials needed for compounds within each class.

Neuroimaging Users Group Consortium – (Woods, Cohen, Porges et.al) Adam Woods has taken the lead on collaborating with the Administration of AMRIS (Long, Mareci, Lai) to self-start and develop a Neuroimaging User Group to facilitate human clinical translational research involving AMRIS 3T MR system. A total of 64 multidisciplinary MR users have opted into the group list-serve, and 40+ attended the first Users Group meeting in mid-November, 2013. It was determined that subgroups would be formed as a result of the identified areas of development, to focus efforts on specific needs of neuroimaging investigators across the campus.

Areas of special interest so far include:

1. **Sequence Bank** – A compilation of common MR sequences (eg: DTI, MPRAGE, BOLD etc.) available to all UF 3T MRI users to facilitate cross lab and project collaborations. These data are intended to foster acquisition of large data sets that will allow the CAM-CTRP and other UF investigators to address a variety of aging and brain related studies.
2. **Standard Operating Procedures and Organization of MR Suite** – To establish a working order for use of the 3T AMRIS facilities to assist investigators in making maximal use of all available resources.
3. **Acquisition of Arterial Spin Labeling** – Group organized to facilitate the acquisition of Phillips ASL sequences for multiple MR users. The acquisition of ASL will foster the inclusion of advanced MR methodology and numerous ongoing and planned grant submissions and opportunities.

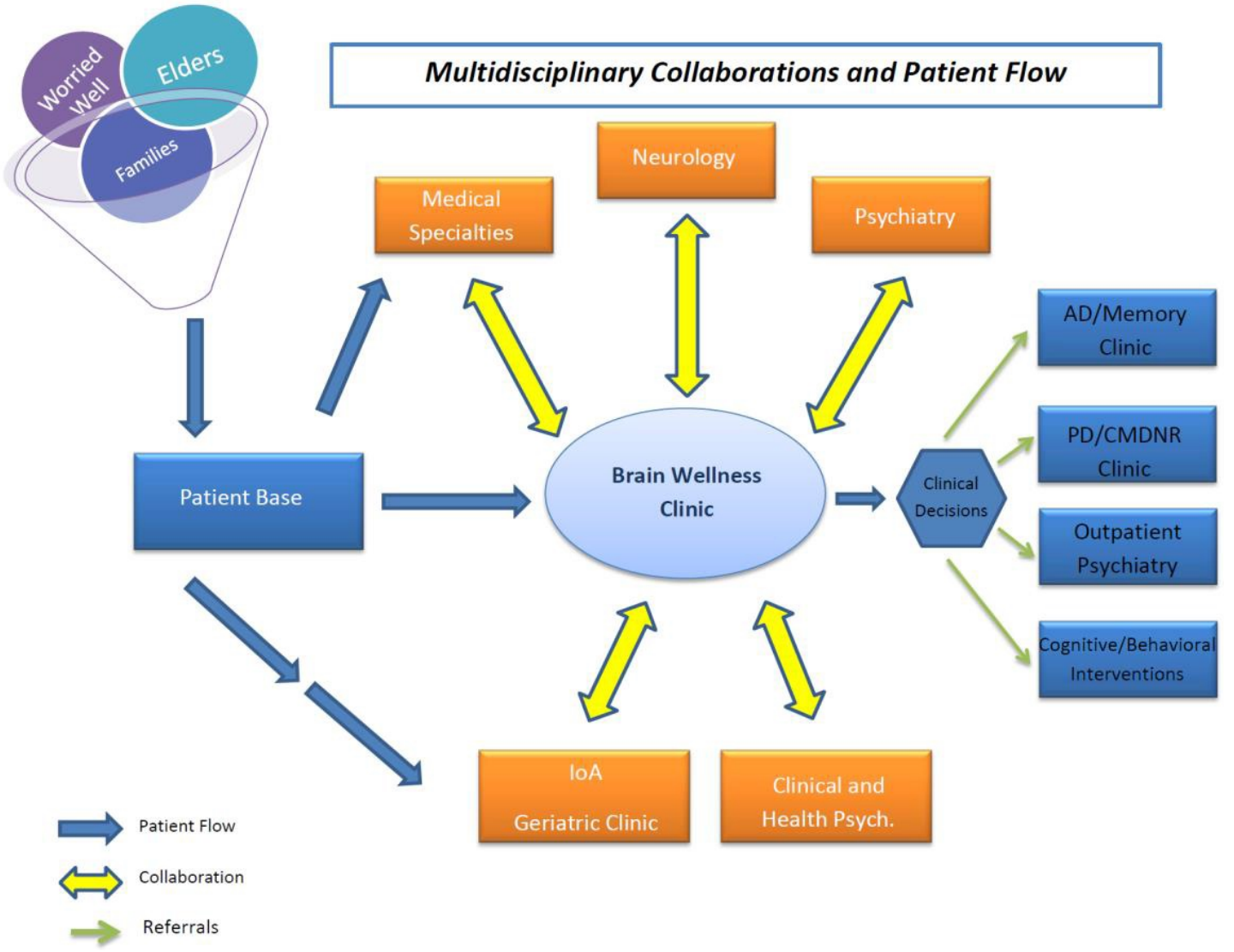
TECHNOLOGY TRANSFER: NA

BUDGET UPDATE: See page 56

EDUCATIONAL PROGRAMS FOCUSING ON AGE RELATED MEMORY LOSS:

CAM-CTRP has initiated a Brain Wellness Program, housed in the 1st floor of the new CTRB-IOA Senior Care clinic. It will serve as an interface between clinical geriatric and clinical research programs of IOA, provide appropriate screenings, information on potential

interventions for brain wellness and referrals. This program will be integrated with parallel Brain Wellness clinics under the direction of Dawn Bowers, Ph.D., at the Movement Disorders Center for Neurorestoration.



T-32 Training Grant in Development – (Cohen) Submission scheduled for May 2014. Program will support 6 Post-Doctoral Fellows at a time, with 2 new fellows recruited annually for a 2 year rotation. The program will focus on neuroscience of cognitive and physical aging. We will train Post Doc Fellows in research methods and provide a valuable and unique educational experience, directed at the aging brain, including opportunities to learn neuroimaging, electrophysiology approaches, other neuroscientific methods, epidemiology, biostatistics, and to obtain exposure to clinical trials, and clinical translational research.

Monthly CAM-CTRP Neuroimaging Seminar Series – (Woods) – This seminar series is intended to provide a University wide forum for presentation of state of the art neuroimaging research and methodology. This series will fill an educational gap at the University of Florida where currently there is no educational structure in place to disseminate this widely used neuroscientific modality. This talk series will feature a monthly speaker, and lunch for attendees.

Non-Invasive Brain Stimulation Practical Course – (Woods) Dr. Woods is the course director of an annual non-invasive brain stimulation practical course, taught at the NYC Neuromodulation Conference. This course provides over 100 clinicians and researchers per year with practical knowledge of transcranial direct current stimulation techniques. This technique is a novel tool for interventions aimed at slowing aging related cognitive decline. This topic serves as a central point in the educational structure of the practical course.

COLLABORATIONS WITH MCKNIGHT INSTITUTES, INSTITUTIONS, RESEARCH PROGRAMS, AND OTHERS:

A. **Inter-Institute neuroimaging initiative** – described previously.

B. **ARML/ CAM-CTRP clinical translational initiatives**; this collaborative effort between the McKnight ARML and CAM-CTRP is focusing on bringing promising compounds that may benefit cognitive aging to clinical trials.

C. **CAM-CTRP/ AMRIS neuroimaging initiatives**; efforts are underway to develop a NIPYP (neuroimaging analysis pipeline) that will facilitate the processing and preliminary analysis of multimodal neuroimaging data obtained by the CAM-CTRP, and other AMRIS investigators. Also, the initiation of a neuroimaging user group reflects this collaboration (see above).

D. **Integration of Memory Disorders Clinic data**, including IRB approved coherent records review, and analysis of MR data via the HiPerGator Computing System – Glenn Finney, M.D., Dept. of Neurology, Adam J. Woods, Ph.D., Ron Cohen, Ph.D.,

E. **Study of Semantic Networks** – Kenneth Heilman, M.D., Steve Nadeau, M.D., Robert Cook, M.D., Amanda Garcia, M.S

F. **Obesity and Type 2 Diabetes, Bariatric Surgery effects on brain function** – NIH RO1 Grant Submission July, 2013, Perfect Score received 11/25/2013

G. **Effect on Exercise on memory in Geriatric Depression; fMRI pilot study** – Vonetta Dotson, Ph.D.,

COLLABORATIVE PROGRAMS WITH NON-MCKNIGHT INSTITUTES, INSTITUTIONS AND RESEARCH PROGRAMS:

These grant proposals involve collaboration with core and affiliated CAM-CTRP faculty, as well as investigators from other departments in the university and the VA Medical Center, as well as other university collaborations.

A. **Heart Failure and the aging brain**, – Kenneth Heilman, M.D., Adam Falchook, M.D., John Williamson, Ph.D., Ron Cohen, Ph.D. – Extension of ongoing line of research that Dr. Cohen has been involved in over past 2 decades.

B. **Resynchronization of Heart Failure and Cognition in aging** – (to be submitted) Kenneth Heilman, M.D., John Williamson, Ph.D., Ron Cohen, Ph.D., Michael Jansen, M.D., James Hill, M.D. (cardiologists at University of Florida)

C. **HIV and the Aging Brain** – Robert Cook, M.D., Ron Cohen, Ph.D. – NIH RO1 Grant Submission Dec. 5, 2013

ONGOING COLLABORATIONS AMONG UF AND BROWN UNIVERSITY, INCLUDING GUNDSTADT AND GROUP FROM KENT STATE, BRICKMAN AND GROUP FROM COLUMBIA UNIVERSITY.

D. **Alcohol and HIV: Biobehavioral interactions and intervention** – Ron Cohen, Ph.D., Collaborations with investigators from Brown University and Tufts

E. **Cognitive Effects of Cardiac Rehabilitation in Heart Failure** – Ron Cohen, Ph.D., and collaborations with Gundstadt and group from Kent State.

F. **Predicting Brain Changes in HIV/AIDS** – to be submitted: Continued work with Brad Navia and group from Tufts, Suzanne DeLaMonte from Brown University and Paul Thompson from UCLA.

G. **ENIGMA – Center for Worldwide Medicine, Imaging and Genomics** – Ron Cohen Ph.D., with Paul Thompson from UCLA and Brad Navia from Tufts.

H. **Mindfulness Training to improve adherence behaviors in Heart Failure outpatients** – Continued collaboration with Beth Brock at Brown University and University of Massachusetts Medical Center.

I. **P50** – University of Florida – Mt. Sinai Medical Center AD Research Center

J. **Southern HIV Alcohol Research Consortium (SHARC)** (Cohen) – Robert Cook, M.D., and other collaborators at the UF CTSI

K. **American Heart Association Research Innovation Grant** – (Mark, Woods) Hovering: A Novel Index of Executive Function Accessible by Patients with Aphasia (14IRG18150025), submitted 07/16/13, Role: Statistical Consultant

L. **V Foundation Grant**, (submitted) (Woods) Collaboration with the UF Cancer Institute, improving the management of the older breast cancer patients with locally advanced disease.

M. **Obesity and Type II Diabetes** – Collaborations among Kfir Ben-David M.D., UF Surgery, Kenneth Cusi, M.D., Diabetes Center of Excellence, Christina Mc Crae Ph.D., UF Sleep Research Lab, Ron Cohen, Ph.D., CAM-CTRP

BRIEFLY DESCRIBE PLANS FOR FUTURE RESEARCH AND OR CLINICAL INITIATIVES:

The proposed pilot studies will create enough pilot data for future RO1 projects over the next several years. Development of the novel compounds for clinical trial interventions will also be a major area of effort in the future.

IF APPLICABLE, PLEASE PROVIDE ENDOWMENT INVESTMENT RESULTS FOR THE REPORT PERIOD: See page 62

WHERE ANY FUNDS USED FOR A PROHIBITED PURPOSE DURING THE REPORT PERIOD? No

DO YOU RECOMMEND ANY MODIFICATIONS TO THE PURPOSE OR MANDATES IN THE GIFT AGREEMENT? No

DID ALL ACTIVITIES DURING THE REPORT PERIOD FURTHER THE PURPOSE? Yes

NEGATIVE EVENTS (LOSS OF PERSONNEL, SPACE, BUDGET): No

ADDITIONAL COMMENTS: See letter on page 37

SIGNATURE, DATE AND TITLE OF PERSON SUBMITTING THE REPORT:

Ronald Cohen, PhD, ABPP, ABCN
Professor, Aging, Neurology, and Psychiatry
Director, CAM-CTRP

Faculty Biographical Sketches

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Jennifer L. Bizon	Associate Professor
eRA COMMONS USER NAME (credential, e.g., agency login) jbizon	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of North Carolina at Chapel Hill	BS	1993	Psychology
University of California, Irvine	PhD	1998	Neurobiology and Behavior
Johns Hopkins University	Post-doc	1998-2002	Neuroscience

A. Personal Statement

My research program is broadly focused on understanding brain aging and its implications for cognitive functions, including learning, memory, and executive processes. Our central approach involves integrating neuroanatomical, biochemical, and/or pharmacological techniques with cognitive/behavioral variables to better understand how aging alters corticolimbic inhibitory and neuromodulatory circuits, and how such alterations contribute to decline of function across multiple cognitive domains. We are particularly interested in how changes in these systems contribute to age-related decline of executive functions, including working memory, cognitive flexibility, and decision making. A key element of our approach involves the consideration of individual differences in cognitive aging, which can be leveraged to identify and to better understand the relevant cognitive and neural mechanisms that underlie both impaired and successful cognitive outcomes. Our ultimate goal is to target effective compensatory strategies and to develop new approaches for promoting successful cognitive aging.

B. Positions and Honors

1993	Research Assistant at University of North Carolina at Chapel Hill
1993-1998	Graduate Student Assistant, University of California, Irvine, Laboratory of Dr. Christine Gall
1998-2003	Postdoctoral Fellow, Johns Hopkins University, Laboratory of Dr. Michela Gallagher
2002-2004	Assistant Research Scientist, Dept. of Psychology, Johns Hopkins University
2004-2010	Assistant Professor of Psychology, Texas A&M University
2004-2010	Faculty of Neuroscience, Texas A&M University
2010-present	Associate Professor of Neuroscience and Psychiatry, University of Florida College of Medicine
2011-present	Co-director of Neuroscience Graduate Program, University of Florida College of Medicine

Honors and Professional Activities

Graduated with Highest Honors (Psychology) UNC-Chapel Hill (1993)
Individual NRSA, NIMH F31 pre-doctoral award (1995-1998)
Individual NRSA, NIA F32 post-doctoral award (2001-2003)
Leadership and Service Award, Faculty of Neuroscience, Texas A&M University (2008)
Montague Center for Teaching Excellence Award (2008), College of Liberal Arts, Texas A&M University
Editor, Animal Models of Human Cognitive Aging (2008), *Humana (Wiley) Press*
Editorial Board, *Neurobiology of Aging* (2008-present)
Advisory Board, Alzheimer's Drug Discovery Foundation (2010-present)
NIH Special Emphasis Review Panel (ZAG1 ZIJ-5), Bethesda, MD (2009)
NSF Review Panel (Modulatory Brain Systems), Rockville, MD (2011)
NIH Review Panel (CNNT) Washington, DC (2010, 2011)
NIH Review Panel (CDIN) Washington, DC (2012)
NIH Review Panel (F30A) Washington, DC (Feb, June 2013)
NIH Review Panel (F30B) Washington, DC (Nov 2013)

Ad Hoc Reviewer for National Science Foundation (2009-present)
McKnight Cognitive Test Battery Working Group (2011-present)

C. Selected Peer-reviewed Publications (2013):

Adolescent Risk Taking, Cocaine Self-Administration, and Striatal Dopamine Signaling. Mitchell MR, Weiss VG, Beas BS, Morgan D, **Bizon JL**, Setlow B. Neuropsychopharmacology. 2013 Oct 22. doi: 10.1038/npp.2013.295.

Centrally administered angiotensin-(1-7) increases the survival of stroke prone spontaneously hypertensive rats. Regenhardt RW, Mecca AP, Desland F, Ritucci-Chinni PF, Ludin JA, Greenstein D, Banuelos C, **Bizon JL**, Reinhard MK, Sumners C. *Exp Physiol*. 2013 Oct 18.

Characterization of age-related changes in synaptic transmission onto F344 rat basal forebrain cholinergic neurons using a reduced synaptic preparation. Griffith WH, Dubois DW, Fincher A, Peebles KA, **Bizon JL**, Murchison DA. *J Neurophysiol*. 2013 Oct 16.

Beas BS, Setlow B, **Bizon JL**. (2013) Distinct manifestations of executive decline in aged rats. *Neurobiology of Aging*. 34(9): 164-174.doi: 10.1016/j.neurobiolaging.2013.03.019.

Simon NW, Beas BS, Montgomery KS, Haberman RP, **Bizon JL**, Setlow B. (2013) Prefrontal cortical-striatal dopamine receptor mRNA expression predicts distinct forms of impulsivity. *European Journal of Neuroscience* 37(11): 1779-88. doi: 10.1111/ejn.12191.

Mendez IA, Damborsky JC, Winzer-Serhan UH, **Bizon JL**, Setlow B (2013) A4β2 and α7 nicotinic acetylcholine receptor binding predicts choice preference in two cost benefit decision-making tasks. *Neuroscience*. 230:121-31. doi: 10.1016/j.neuroscience.2012.10.067.

Bañuelos, C, LaSarge, CL, McQuail, JA, Hartman, JA, Gilbert, RJ, Ormerod, BK, **Bizon, JL** Age-related changes in basal forebrain cholingergic and GABAergic neuron number: Relationship with spatial impairment. (2013) *Neurobiology of Aging*. 34(3):845-62. doi: 10.1016/j.neurobiolaging.2012.06.013.

(Under Review)

Yoder, W. M., Setlow, B., **Bizon, J. L.**, & Smith, D. W. Characterizing olfactory perceptual similarity using carbon chain discrimination in behaviorally-trained Fischer 344 rats. Under Revision at *Chemical Senses*.

Shimp, K. M.*, Mitchell, M. R.*, Beas, B. S.*, **Bizon, J. L.**, & Setlow, B. Affective and cognitive mechanisms of risky decision making. Under Revision at *Neurobiology of Learning and Memory*, Special Issue on Memory and Decision Making.

Beas, B. S.*, Setlow, B., Samanez-Larkin, G. R., & **Bizon, J. L.** Decision making in animal models of cognitive aging: a cross-species comparison of rodents and humans. Invited for Special Issue of Neurobiology of Learning and Memory on Memory and Decision Making. Currently Under Review.

Bañuelos, C.*, Beas, B. S.*, McQuail, J. A., Gilbert, R. J., Frazier, C. J., Setlow, B., & **Bizon, J. L.** Altered GABAergic signaling contributes to age-related impairments in working memory. Under Review.

D. Research Support:

Ongoing:

R01 DA024671 (B. Setlow PI, **Bizon** co-PI) 4/1/09-3/31/14 15% effort
National Institute on Drug Abuse
"Neural mechanisms of enduring cocaine effects on impulsive choice"
The goal of this project is to understand the long-term effects of cocaine use on decision making and to begin to elucidate the neurobiology associated with impulsivity resulting from psychostimulant drug use. No overlap.

5R37AG036800-03 (Foster PI, **Bizon**, co-I) 6/1/14-6/1/17 20% effort
National Institute on Aging
"Signaling cascades and memory deficits during aging"
The goal of this project is to understand the influence of Ca2+ signaling on spatial and working memory deficits that emerge in normal aging. No Overlap.

R01 AG029421 (**Jennifer L. Bizon**, PI) 8/1/07-6/30/13 35% effort
National Institute on Aging
"Neural Mechanisms of Age-related cognitive decline" (title change)
The goal of this project is to determine the contributions of GABAergic mechanisms in prefrontal cortex and hippocampus to age-related cognitive decline.

Initial Review Impact Score 23, Percentile 16, A1 is Pending.

Completed:

F31-AG037286-01 (Karienn Montgomery student. Bizon sponsor) 8/1/10-8/1/12 n/a
National Institute of Aging
Transfer Learning in Mice: Implications for improved diagnosis and treatment of Alzheimer's Disease
The goal of this study is to design novel behavioral assessments that are very sensitive to age-related pathology and that are highly translational.

R01-NS041548 (Grau PI, Bizon, co-I) 4/07-3/11 15% effort
National Institute of Neurological Disorder and Diseases
"Learning within the spinal cord: clinical implications"
The goal of this grant is to study the role of BDNF in spinal cord learning. No overlap.

R01-DA13188 (PJ Wellman PI, Bizon co-I) 8/01/07-6/30/10 15% effort
National Institute of Drug Abuse
"Heavy Metal and Drug Self-Administration: Mechanisms"
The goal of this project is to determine how exposure to heavy metals (lead, cadmium) during development affects vulnerability to drug abuse during adulthood.

F31- NS059324 (Candi Lynn LaSarge student, Bizon sponsor) 6/1/08- 12/1/10 n/a
National Institute of Neurological Disorders and Stroke
"The Role of Basal Forebrain in Mild Cognitive Impairment"
The goal of the project under this training fellowship is to determine how changes in basal forebrain anatomy are related to cognitive dysfunction in aging.

R01-AA012386 (G Frye PI, Bizon co-I) 8/1/08-8/1/10 10% effort
National Institute on Alcohol Abuse and Alcoholism
"CNS Development GABAARs and Vulnerability to Ethanol"
The goal of this project is to determine how developmental exposure to alcohol affects basal forebrain neuronal function and cognition later in life.

F31- DA023331 (NW Simon student, Bizon co-sponsor) 2/1/08-2/1/10 n/a
National Institute on Drug Abuse
"Long-term cocaine effects on impulsive choice and orbitofrontal cortex activity"
The goal of the project under this training fellowship is to determine how chronic cocaine exposure affects impulsive decision-making and orbitofrontal cortex function.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Dawn Bowers, Ph.D.	Professor, Clinical & Health Psychology
eRA COMMONS USER NAME (credential, e.g., agency login) dbowers	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Emory University, Atlanta GA		1968-1970	Psychology
University of Florida, Gainesville FL	B.A.	08/1972	Psychology
University of Florida, Gainesville FL	M.S.	12/1974	Clinical Psych/Neuropsy
University of Florida, Gainesville FL	Ph.D.	12/1978	Clinical Psych/Neuropsy
University of Florida, Gainesville FL	Post-doc	12/1979	Behavioral Neurology

A. Personal Statement

I am a university professor and a clinical neuropsychologist-cognitive neuroscientist. I have longstanding research and clinical expertise in cognitive and emotional changes that are associated with neurologic disease and aging, particularly apathy, depression, memory and executive function. Current research focuses on emotion regulation and executive function, psychophysiologic signatures of apathy and depression, and interactive effects of cognitive training and exercise in cohorts of elderly adults. I have been a funded researcher for many years, including two recently completed clinical trials one for treatment of apathy using rTMS and another for treatment of "'masked faces" in individuals with Parkinson disease. My Cognitive Neuroscience Laboratory at the McKnight Brain Institute includes four doctoral students, who are using various tools (startle, pupillometry, ERP, computational modeling, advanced statistical approaches) to better understand mechanisms that underlie emotional and cognitive changes in older adults including those with dopaminergic depletion disorders. As such, I have experimental tools/approaches and statistical expertise that can help facilitate hypothesis-driven research including such as the important innovative approach to execise/cognitive training being proposed in this project.

B. Positions and Honors

Positions & Employment

1976-1977	Teaching Fellow in Neurology, Boston University College of Medicine
1976-1977	Internship in Clinical Psychology/Neuropsychology, Boston VAMC
1976-1977	Externship in Geriatric Neuropsychology, Framingham Heart Study, MA
1979	Post-doctoral Fellowship, Behavioral Neurology, UF College of Medicine
1980- 1998	Associate Professor in Neurology [Assistant 1980-85], UF College of Medicine
1984-1998	Neuropsychologist, State of Florida Memory Disorders Clinic
1998-	Professor of Clinical & Health Psychology [Associate 1998-2002]
1998-	Director, Cognitive Neuroscience Laboratory, UF McKnight Brain Institute
2006-	Division Chief, Neuropsychology Area, Dept. Clinical & Health Psychology
2006-2009	UF Foundation Research Professor
2012	Fellow, American Psychological Association, Division 40 (Neuropsychology)
2012-15	Board of Governors, International Neuropsychological Society
2013	Fellow, American Board of Professional Psychology-Clinical Neuropsychology

Other Experience & Professional Memberships

2012-	Merit Review Panel for Mental Health and Behavioral Sciences – B (MHBB) Department of Veterans Affairs
2011-	Member, NIH SBBIR2013/01 ZRG1 ETTN-K (10) B – Small Business: Clinical Clinical Neurophysiology, Devices, Neuroprosthetics, & Biosensors
5/ 2012	Panel Member, NIH Review of LRP proposals
2011-12	Ad hoc Member, Special Emphasis Panel, Clinical and Imaging Translations Study Section (ZRG1 DTCS Y(81)].
2009-10	Ad hoc Member, NIH Adult Psychopathology & Disorders of Aging Study Section
2006	Member, NIH Special Emphasis Panel (ZRR1 BT-801), Interdisciplinary Research Consortium

2005	Member, NIH Special Emphasis Panel (2006/01) Cognition and Perception Study Section
2004-05	Ad hoc Member, NIH Biobehavioral Mechanisms of Emotion, Stress, and Health Study Section
2000-	Editorial Boards, The Clinical Neuropsychologist, Journal of International Neuropsychological Society
1999-2003	Special Review Panel, Minority Research Infrastructure Support Program (MRISP), NIMH
1995-1998	Member, Merit Review Committee, Mental Health &d Behavioral Science, Dept. Veterans Affairs

Membership American Psychological Association (Divisions 12 and 40), International Neuropsychology Society, American Academy of Neurology, Society for Neuroscience, Cognitive Neuroscience Society

Journal Reviews: *Neuropsychologia, Lancet, Neurology, New England Journal of Medicine, Cortex, Movement Disorders, Journal of International Neuropsychological Society, The Clinical Neuropsychologist, J. Neurology, Neuropsychiatry, & Neurosurgery, Neuropsychology, Neuropsychologia, J. Cognitive Neursocience, JCED, Parkinson Disease and Parkinsonism*

C. Selected Peer-reviewed Publications (2013)
(Students in italics)

Dietz, J., Jones, J., Bradley, M., Okun, M.S., Perlstein, W., **Bowers, D.** (2013). The late positive potential, emotion, and apathy in Parkinson's disease. *Neuropsychologia*. 51, 960-6.

Dietz, J., Noecker, A., McIntyre, C.C., *Mikos, A.*, **Bowers, D.**, Foote, K., Okun, M.S. (2013). Stimulation region within the GPI does not affect verbal fluency: Results from field modeling. *Brain Stimulation*. 6, 248-53

Zahodne, L.B., Marsiske, M.M., **Bowers, D.** (2013). A latent class analysis of psychological disturbance in Parkinson disease. *International Journal of Geriatric Psychiatry*. Oct;28(10):1054-60. doi: 10.1002 PMID:23307695

Jordan, L., Zahodne, L., Okun, M.S., **Bowers, D.** (2013). Hedonic and behavioral deficits associated with apathy in Parkinson's disease. *Movement Disorders*, 28(9):1301-4 [epub 2013 May]

Velez-Lago, F.M., Hardwick, A., Oyama, G., Thompson, A., Sporrer, J., Zeilman, P., Foote, K., **Bowers, D.**, Ward, H., Sanchez-Ramos, Okun, M. (2013). Differential and better response to chorea compared to dystonia in Huntington's Disease DBS. *Stereotactive Funct Neuroimaging*. 91, 129-133. [epub 2013 Jan 22].

Gullett, J., Price, C., *Nguyen, P.*; Okun, M., Bauer, R.; **Bowers, D.** (2013) Reliability of three Benton Judgment of Line Orientation Short Forms in idiopathic Parkinson's Disease. *The Clinical Neuropsychologist*. 27(7):1167-78

Jones, J., Jacobson, C., *Murphy, M.C.*, Price, C.E., Okun, M.S., **Bowers, D.** (2013, in press). Influence of hypertension on neurocognitive domains in non-demented Parkinson's disease patients. *Parkinson's Disease*

Price, C., *Tanner, J.*, Schmalfuss, I., Gearen, P., Dickey, D., Heilman, K.M., McDonaugh, D.L., Libon, D., Leonard, C., **Bowers, D.**, Monk, T. (2013, in press). Presurgery neuroanatomical biomarkers for postoperative cognitive decline after total knee arthroscopy in older adults. *Anesthesiology*

Okun, MS, Foote, K.D., Wu, S.S., Ward, H.E., **Bowers, D.**, Rodriguez, R.L., Malaty, I., Goodman, W.K., Gilbert, D.M., Walker, H.C., Mink, J.W., Merritt, S., Morishita, T., Sanchez, J.C. (2013). A Trial of Scheduled Deep Brain Stimulation for Tourette Syndrome: Moving Away From Continuous DBS Paradigms. *JAMA Neurology*. 70, 85-94

Libon, D., Swenson, R., Ashendorf, L., Bauer, R., **Bowers, D.** & Milberg, W. (2013, in press). Edith Kaplan and the Boston Process Approach. *Journal of International Neuropsychological Society*.

Nadeau, S., **Bowers, D.**, Jones, T., Wu, S., Triggs, W.J., Heilman, K.M. (2013, in press). Cognitive effects of treatment of depression with repetetive transcranial magnetic stimulation. *Cognitive & Behavioral Neurology*

Chapters
Bauer, R.M., **Bowers, D.** (2013). Intellectual Antecedents to the Boston Process Approach to Neuropsychological Assessment. In D. Libon (Ed.), *Boston Process Approach to Neuropsychological Assessment*. New York: Oxford University Press

Bowers, D., Jones, J., Dietz, J. (2013, in press). Assessment of Emotion. In J. Synder, Nussbaum, and Parsons, M. (eds). *Pocket Handbook of Neuropsychological Assessment*.

D. Research Support

Current

R01 NS082386 PI: Price 9/25/2013 -9/24/2018
White Matter Connectivity and PD Cognitive Phenotype
This grant examines several cognitive subtypes of PD in relation to white matter connectivity using diffusion tensor imaging.
Role: CO-I

R1NS079767 PI: **Bowers** 6/1/2012-12/30/2014
Emotion Regulation, Executive Function, and Parkinson Disease.
This grant tests whether Parkinson patients can learn to "upregulate" their emotional reactivity, as measured by electrophypsiological measures (LPP, ERP), and whether the ability to do so is related to executive functioning.
Role: PI

1 F31 NS073331-01 PI: Dietz 5/01/2011-11/30/2013
Psychophysiology of Emotion in Parkinson disease
This predoctoral NRSA examines temporal trajectory of psychophysiological and ERP changes associated with approach and avoidance in Parkinson disease.
Role: Mentor

Recently Completed

McKnight Brain Research Foundation PI: **Bowers** 11/01/2010-5/30/2013
Multimodal Platform for the Enhancement of Cognition in Normal Elderly
This study examines whether exercise predosing improves effects of cognitive training in older adults, the trajectory of change over time, and the extent to which pure "aerobic" vs exergames are more beneficial.

National Parkinson Foundation PI: Classen 7/01/2010 – 05/30/2012
The Role of Visual Attention in Driving Safety in Parkinson disease
This study examines the relationship between driving and various visuopercpetual/spatial indices of cognition.
Role: Co-I

1R34MH080764, PI: Okun 08/31/2009 -09/01/2012
Scheduled and Responsive Brain Stimulation for the Treatment of Tourette Syndrome.
This clinical trial examines the effectivess of a scheduled DBS protocol for treatment of symptoms in patients with intractable Tourettes syndrome.
Role: Co-I

R21-AG033284 Multiple PI: Altman & Hass 8/2/2010-8/1/2012
Language and Executive function in Parkinson's disease: Effects of dual task and exercise.
This project examines the influence of aerobic exercise and multi-tasking on language processing in patients with Parkinson disease.
Role: Co-I

R01-NS50633 PI: **Bowers** 12/01/04-11/30/09
Masked Facies in Parkinson Disease: Mechanism and Treatment
In this study, we evaluated a behavioral treatment approach for improving facial expressivity in patients with parkinson's disease using a double-blind sham-controlled randomized clinical.
Role: PI

Thomas W. Buford, PhD

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Buford, Thomas W.	Assistant Professor
eRA COMMONS USER NAME	Director, Health Promotion Center
tbuford	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Oklahoma Baptist University	BSE	2000-2004	Social Science
Oklahoma State University	MS	2004-2006	Exercise Physiology
Baylor University	PhD	2006-2009	Health Sciences (Interdisciplinary)
University of Florida	Scholar	2009-2011	Geriatrics/Clinical & Translational Science

A. Personal Statement

Dr. Buford, an exercise physiologist, will serve as the Principal Investigator for the proposed project. His specific research interest lies in identifying targeted interventions to prevent physical disability among high-risk older adults, including those with diabetes. During his graduate training, Dr. Buford received training in exercise physiology, skeletal muscle function, and nutritional biochemistry. After arriving at the University of Florida (UF), Dr. Buford was designated as a both a KL2 scholar within the Clinical and Translational Science Institute (CTSI) as well as a Pepper Scholar within the Claude D. Pepper Older Americans Independence Center (OAIC). During this time, Dr. Buford continued his development as a scientist through continued coursework. This coursework resulted in a post-graduate certificate in Translational Health Science and covered topics pertinent to the proposed research including research ethics, epidemiology, conduct of clinical and translational research, and design/management of clinical trials. This training laid a strong foundation for the expertise needed to conduct the proposed research. This unique position as a scholar supported by both the UF Claude D. Pepper Older Americans Independence Center (OAIC) and Clinical and Translational Science Institute (CTSI) provided him with a wealth of experiences learning from senior investigators and fellow junior colleagues through regular personal meetings and roundtable discussions. Additionally, Dr. Buford serves as a co-investigator on the NIH-funded, Phase 3 Lifestyle Intervention and Independence for Elders (LIFE) study and is in charge of overseeing the conduct of the interventions at the UF field site. This experience has provided Dr. Buford with first-hand working knowledge of how to oversee multidisciplinary research teams. I am currently responsible for overseeing conduct of the LIFE interventions at our field center. In addition, Dr. Buford has assembled a research team that includes essential experience and expertise in endocrinology, behavioral psychology, and geriatrics that is complimentary to his own. Thus, the research team is well-equipped to conduct the proposed research.

B. Positions and Honors

Positions and Employment

2012- Director, Health Promotion (Research) Center, Institute on Aging, Univ. of Florida
2012- Assistant Professor, Dept. of Aging and Geriatric Research, Univ. of Florida
2012- Adjunct Assistant Professor, Dept. of Applied Physiology and Kinesiology, College of Health and Human Performance, Univ. of Florida
2009-2011 Research Associate and Lecturer, Dept. of Aging and Geriatric Research, College of Medicine, Univ. of Florida
2006-2009 Research Assistant, Exercise and Biochemical Nutrition Laboratory, Baylor Univ.
2004-2006 Research Assistant, A.B. Harrison Human Performance Laboratory, Oklahoma State Univ.

Other Experience and Professional Memberships

2010 Ad Hoc Grant Review: UK Medical Research Council
2012 Ad Hoc Grant Review: South African Medical Research Council
2012-2013 Member: Clinical and Population Innovative Research Grants Review Committee American Heart Association
2003-2010 Member: National Strength and Conditioning Association
2004- Member: American College of Sports Medicine
2007- Member: American Physiological Society

2009- Member: Gerontological Society of America
Health Sciences Section
2010- Member: American Diabetes Association
2011- Member: American Heart Association
Council on Nutrition, Physical Activity, and Metabolism

Selected Honors

2013 Accepted Applicant, NIH Early Career Reviewer Program
2013 Selected Attendee, University of Michigan OAIC Annual Research Retreat
2010 Travel Scholarship, Claude D. Pepper Older Americans Independence Centers

National Meetings

2009 Outstanding Doctoral Student in Exercise, Nutrition, and Preventive Health, Baylor Univ.
2009 Student Manuscript Award, Texas Chapter, American College of Sports Medicine
2007 Challenge Scholarship, National Strength and Conditioning Association
2006 Graduate Research Excellence Award, Oklahoma State Univ.
2004 Summa Cum Laude graduate, Oklahoma Baptist Univ.

C. Selected peer-reviewed publications (of 40 peer-reviewed publications)

Most relevant to the current application

1. SA Anton, C Karabetian, K Naugle, **TW Buford**. Obesity and Diabetes as Accelerators of Functional Decline: Can Lifestyle Interventions Maintain Functional Status in High Risk Older Adults? *Exp. Gerontol.* (in press)
2. TM Manini, **TW Buford**, D Lott, K Vandenborne, MJ Daniels, J Knaggs, H Patel, M Pahor, MG Perri, SD Anton. Effect of dietary restriction and exercise on lower extremity tissue compartments in obese older women: A pilot study. *J Gerontol A Biol Sci Med Sci.* (in press). PMID: 23682155.
3. JR Nocera, **TW Buford**, TM Manini, K Naugle, C Leeuwenburgh, M Pahor, SD Anton, MG Perri. The Impact of Behavioral Intervention on Obesity Mediated Declines in Mobility Function: Implications for Longevity. *J Aging Res.* 2011: 392510. PMID: 22013527.
4. **TW Buford**, DJ Lott, E Marzetti, SE Wohlgemuth, K Vandenborne, M Pahor, C Leeuwenburgh, TM Manini. Age-related differences in Lower Extremity Tissue Compartments and Associations with Physical Function in Older Adults. *Exp Gerontol*. 47(1): 38-44. 2012. PMID: 22015325
5. **TW Buford**, SJ Rossi, DB Smith, A Warren. A comparison of periodization models during nine weeks with equated volume and intensity for strength. *J. Strength Cond. Res.* 21(4): 1245-1250. 2007. PMID: 18076234

Other publications of importance to the field

6. AM Joseph, PJ Adhihetty, **TW Buford**, SE Wohlgemuth, HA Lees, LMD Nguyen, JM Aranda, B Sandesara, M Pahor, TM Manini, E Marzetti, C Leeuwenburgh. The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals. *Aging Cell*. 11(5): 801-809. 2012. PMID: 22681576
7. E Marzetti, R Calvani, M Cesari, **TW Buford**, M Lorenzi, BJ Behnke, C Leeuwenburgh. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. *Int J. Biochem Cell Biol*. (in press)
8. **TW Buford**, TM Manini, FC Hsu, M Cesari, SD Anton, S Nayfield, RS Stafford, TS Church, M Pahor, CS Carter, for the LIFE Research Group. ACE inhibitor use by older adults is associated with improved functional responses to exercise. *J Am Geriatr Soc*. 60(7): 1244-1252. 2012. PMID: 2272632.
9. **TW Buford**, MD Roberts, TS Church. Toward exercise as personalized medicine. *Sports Med*. (in press).
10. E Marzetti, SE Wohlgemuth, HA Lees, TM Manini, **TW Buford**, JM Aranda, R Calvani, G Capuani, M Marsiske, R Bernabei, M Pahor, C Leeuwenburgh. Skeletal muscle apoptotic signaling predicts thigh muscle volume and gait speed in community-dwelling older persons: an exploratory study. *PLoS ONE*. 7(2): e32829. 2012. PMID: 22389725.
11. **TW Buford**, SD Anton, AR Judge, E Marzetti, SE Wohlgemuth, CC Carter, C Leeuwenburgh, M Pahor, TM Manini. Models of Accelerated Sarcopenia: Critical Pieces for Solving the Puzzle of Age-Related Muscle Atrophy. *Ageing Res Rev*. 9(4): 369-383. 2010. PMID: 20438881
12. **TW Buford**, MB Cooke, DS Willoughby. Resistance Exercise-Induced Changes of Inflammatory Gene Expression within Human Skeletal Muscle. *Eur J Appl Physiol*. 107(4): 463-471. 2009. PMID: 19669788
13. **TW Buford**, MB Cooke, TM Manini, C Leeuwenburgh, DS Willoughby. Effects of Age and Sedentary Lifestyle on Skeletal Muscle NFkB Signaling in Males. *J Gerontol A Biol Sci Med Sci*. 65(5): 532-537. 2010. PMID: 20045871
14. **TW Buford**, MB Cooke, BD Shelmadine, GM Hudson, LL Redd, DS Willoughby. Differential gene expression of FoxO1, ID1, and ID3 between young and older men and associations with muscle mass and function. *Aging Clin Exper Res*. 23(3): 170-174. 2011. PMID: 21993163.

15. **TW Buford**, MB Cooke, BD Shelmadine, GM Hudson, L Redd, DS Willoughby. Effects of Eccentric Treadmill Exercise on Inflammatory Gene Expression in Human Skeletal Muscle. *Appl Physiol Nutr Metab*. 34(4):745-753. 2009. PMID: 19767811

D. Research Support

Ongoing

13SDG17080033 (Buford) 7/1/2013-6/30/2017
American Heart Association
Multi-modal intervention to reduce cardiovascular risk among hypertensive older adults
The objective of this project is to compare the efficacy of physical exercise for improving physical function among hypertensive older adults when given in concert with differing classes of antihypertensive medications.
Role: Principal Investigator

2P30AG028740-S (Buford) 8/1/13-7/31/15
NIH/NIA
ACE inhibitors Combined with Exercise for Seniors – Mechanisms
The objective of this project is to determine the impact of combined antihypertensive therapy and physical exercise on cardiopulmonary function and indices of skeletal muscle function in hypertensive older adults.
Role: Principal Investigator

2P30AG028740 (Pahor) 4/1/2012- 3/31/2017
NIH/NIA
Claude D. Pepper Older Americans Independence Center (OAIC)
The major goals of this program are to assess the mechanisms leading to sarcopenia and functional decline, and to develop and test interventions for the treatment and prevention of physical disability in older adults.
Roles: Co-Investigator, Clinical Research Core; Junior Scholar, Research Career Development Core

1UO1AG022376-01 (Pahor) 09/01/09-08/31/15
NIH/NIA
Physical exercise to prevent disability – LIFE
The major goal of this project is to determine by conducting a Phase 3 randomized, controlled trial (RCT) whether physical exercise prevents major mobility disability in older persons.
Role: Co-Investigator

PS00089402 (Buford) 05/23/13-5/22/14
Abbott Nutrition, Abbott Laboratories
This study is a randomized, double-blinded, controlled trial of an oral nutritional supplement containing AN 777 in older hospitalized patients.
Role: Site Principal Investigator

GDF8/REGN1033-HV-Phase1-SC-1223 (Pahor) 9/3/2013-9/2/2014
Regeneron Pharmaceuticals
This study is a randomized double-blind, placebo-controlled, muticenter study to further evaluate the safety and efficacy of REGN1033, a monoclonal antibody which inhibits myostatin, with and without exercise, in elderly subjects 65 and older.
Role: Sub-Investigator

Completed (last three years)

1P30AG028740-S (Leeuwenburgh) 4/1/2007-3/31/2013
NIH/NIA
Skeletal Muscle Apoptosis and Physical Performance, Oxidative RNA/DNA Damage and Repair in Aged Human Muscle
The major goal of this longitudinal study is to assess the role of myocellular apoptosis and RNA/DNA damage in the progression of human sarcopenia.
Role: Co-PI

1KL2RR029888-S (Nelson) 8/16/09-8/15/12
NIH/NCRR
KL2 Scholar Award
The major goal of this award is to advance the PI's potential as a biomedical scientist by providing protected time to complete post-graduate coursework and seed funding to initiate a research program.
Role: Junior Scholar

1P30AG028740 (Pahor) 4/1/2007-3/31/2012
NIH/NIA
Claude D. Pepper Older Americans Independence Center (OAIC)
The major goals of this program are to assess the mechanisms leading to sarcopenia and functional decline, and to develop and test interventions for the treatment and prevention of physical disability in older adults.
Roles: Co-Investigator, Clinical Research Core; Junior Scholar, Research Career Development Core

Proposal 37268 (Buford) 11/31/09-11/30/11
Merck and Co., Inc.
Role of Skeletal Muscle Blood Flow in Regeneration and Sarcopenia
This overall goal of this investigator-initiated project is to find novel biomarkers, specifically focused on muscle regenerative capacity, as targets for novel therapeutic interventions to combat sarcopenia.
Role: Principal Investigator

No grant # assigned (Buford) 3/31/10-4/20/11
American College of Sports Medicine
Graded Vascular Occlusion and KAATSU Exercise on Skeletal Muscle Regenerative Signaling
The overall goal of this pilot project was to compare the molecular changes induced in skeletal muscle following resistance exercise combined with blood flow restriction to changes following standard resistance exercise.
Role: Principal Investigator

1P30AG028740-S (Manini) 4/1/2009-3/31/2010
NIH/NIA
Molecular mechanisms of skeletal muscle loss in HIV-infected older persons (OAIC supplement)
The overall goal of this project is to evaluate the feasibility of conducting a case-control study to identify disease-specific and therapy-related factors associated with muscle fatigue and sarcopenia in older adults with HIV infection.
Role: Co-Investigator

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Dr. Sara N. Burke	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) SARA BURKE	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Oregon, Eugene, OR, USA	B.Sc./M.Sc.	12/2000	Psychology
University of Arizona, Tucson, AZ, USA	Ph.D.	05/2009	Neuroscience
University of Arizona, Tucson, AZ, USA	Postdoctoral	09/2013	Neurobiology of Aging

A. Personal Statement

The principal aim of my research is to investigate how medial temporal lobe structures involved in memory and high-level sensory perception are altered during normal aging. Age-associated cognitive impairments do not result from alterations to brain structures in isolation. Therefore, to fully understand cognitive aging, it is critical to examine how brain areas interact. A powerful tool for pin-pointing disruptions in the complex neural systems that produce cognitive dysfunction during normal aging is the careful analysis of behavior. Therefore, all of my past and present research projects have begun with an extensive cognitive test battery, including tests of spatial memory, working memory, stimulus recognition and sensory perception. Following, a careful characterization of behavior, the primary methods I use to assay the neurobiological basis of age-associated cognitive decline are single-cell imaging techniques and in vivo ensemble recordings from behaving rats. A strength of this approach is that the neurobiology of age-related memory loss is examined at multiple levels. Behavioral analysis along with advanced imaging and physiological techniques provides a multiplicative understanding of the locus of circuit disruptions by linking specific physiological features to cognitive performance.

B. Positions and Honors

Positions and Employment

1997-1999	Undergraduate Research Assistant in Dr. Richard Marrocco's Visual-Attention laboratory (U of O)
1999-2000	Graduate Research Associate in Dr. Richard Marrocco's Visual-Attention laboratory (U of O)
2000-2002	Research Associate in Dr. Alvin Eisner's Visual Adaptation laboratory (Oregon Health & Science University, Portland, OR)
2002-2009	Graduate Research Associate in Dr. Carol Banes Neural Systems, Memory and Aging Laboratory (U of Arizona)
2003-2004	Graduate Teaching Assistant for MSB407: Cellular, Molecular Neuroscience (U of Arizona)
2006-2011	Teaching Assistant for NRSC4/524: Gerontology (University of Arizona)
2009-2013	Postdoctoral Research Associate in Evelyn F. McKnight Brain Institute (U of Arizona)
Since 10/2013	Assistant Professor, Department of Neuroscience, University of Florida

Awards/Honors

1999	Phi Beta Kappa, inducted
	Departmental honors in Psychology, University of Oregon
	Magna Cum Laude, University of Oregon
2002-2004	Recipient of National Institute of Health Training Grant
2006	Recipient of the Society for Neuroscience Travel Award
2006-2009	Recipient of the Ruth L. Kirschstein National Research Service Award
2008	Recipient of the D.B. Marquis Behavioral Neuroscience Award
2010	Recipient of the D.B. Marquis Behavioral Neuroscience Award

Committees and Service

2008	Mentor and small group leader for University of Arizona Undergraduate Biology Research Program
2010-2011	Society for Neuroscience Membership Survey Advisory Group
2010-2011	Mentor for the University of Arizona Assurance Program

C. Selected Peer-reviewed Publications

past 12 months

1. Hartzell AL, **Burke SN**, Hoang LT, Lister JP, Rodriguez CN, Barnes CA (2013). Transcription of the immediate-early gene Arc in CA1 of the hippocampus reveals activity differences along the proximodistal Axis that are attenuated by advanced age. *Journal of Neuroscience*, 33(8):3424-33. PMID: 23426670; PMCID: PMC3711759.

2. **Burke SN**, Maurer AP, Nematollahi S, Uprety A, Wallace JL, Barnes CA (2013). Advanced age has dissociative effects on dual functions of the perirhinal cortex. *Accepted pending revisions, Journal of Neuroscience*.

3. **Burke SN**, Thome A, Plange K, Engle JR, Trouard TP, Gothard KM, Barnes CA (2013). Orbitofrontal cortex and basolateral amygdala volume show a dissociable relationship with reward devaluation in young and aged monkeys. *Accepted pending revisions, Journal of Neuroscience*.

4. Maurer AP, Lester AW, **Burke SN**, Ferng J, Barnes CA (2013). Back to the Future: Preserved hippocampal network activity during reverse ambulation. *Under review, Nature Neuroscience*.

Additional publications of importance to the field (in chronological order)

1. Stewart CE, **Burke S**, Marrocco RT. (2000). Cholinergic modulation of covert orienting in the rat. *Psychopharmacology*, 155, 210-218. PMID: 11401012.

2. Chawla MK, Lin G, Olson K, Vazdarjanova A, **Burke SN**, McNaughton BL, Worley PF, Guzowski JF, Roysam B, Barnes CA (2004). 3D-catFISH: A system for automated quantitative three-dimensional compartmental analysis of temporal gene transcription activity imaged by fluorescence *in situ* hybridization. *Journal of Neuroscience Methods*, 139(1):13-24. PMID: 15351517.

3. Eisner A, **Burke SN**, Toomey MD (2004). Visual sensitivity across the menstrual cycle. *Visual Neuroscience*, 21, 513-531. PMID: 15579218.

4. **Burke SN**, Chawla MK, Penner MR, Crowell BE, Worley PF, Barnes CA, McNaughton BL (2005). Differential encoding of behavior and spatial context in deep and superficial layers of the neocortex. *Neuron* 45, 667-674. PMID: 15748843.

5. **Burke SN**, Barnes CA (2006). Neural plasticity in the ageing brain. *Nature Reviews Neuroscience*, 7, 30-40. PMID: 16371948.

6. Maurer AP, Cowen SL, **Burke SN**, Barnes CA, McNaughton BL (2006). Phase precession in hippocampal interneurons showing strong functional coupling to individual pyramidal cells. *Journal of Neuroscience*, 26, 13485-13492. PMID: 17192431.

7. Maurer AP, Cowen SL, **Burke SN**, Barnes CA, McNaughton BL (2006). Organization of hippocampal cell assemblies based on theta phase precession. *Hippocampus*, 16, 785-794. PMID: 16921501.

8. **Burke SN**, Maurer AP, Zhiyoung Y, Navratilova Z, Barnes CA (2008). Glutamate receptor-mediated restoration of experience-dependent place field expansion plasticity in aged rats. *Behavioral Neuroscience*, 122(3), 535-548. PMID: 18513124 ; PMCID: PMC2773228.

9. Gerrard JL, **Burke SN**, McNaughton BL, Barnes CA. (2008). Sequence reactivation in the hippocampus is impaired in aged rats. *Journal of Neuroscience*, 28(31):7883-90. PMID: 18667620; PMCID: PMC2703197.

10. **Burke SN**, Wallace JL, Nematollahi S, Uprety AR and Barnes CA (2010). Pattern separation deficits may contribute to age-associated recognition deficits. *Behavioral Neuroscience*, 24(5): 559-573. PMID: 20939657; PMCID: PMC3071152.

11. **Burke SN** and Barnes CA (2010). Senescent synapses and hippocampal circuit dynamics. *Trends in Neurosciences*, 33(3): 153-61. PMID: 20071039; PMCID: PMC3076741.

12. **Burke SN**, Maurer AP, Nematollahi S, Uprety AR, Wallace JL and Barnes CA (2011). The influence of objects on place field expression and size in distal hippocampal CA1. *Hippocampus*, 21(7):783-801. PMID: 21365714; PMCID: PMC3314262.

13. **Burke SN**, Maurer AP, Hartzell AL, Nematollahi S, Uprety A, Wallace JL and Barnes CA (2012). Representation of three-dimensional objects by the rat perirhinal cortex. *Hippocampus*, 22(10):2032-44. PMID: 22987680; PMCID: PMC3447635.

14. **Burke SN**, Hartzell AL, Lister JP, Hoang LT, Barnes CA (2012). Layer V perirhinal cortical ensemble activity during object exploration: a comparison between young and aged rats. *Hippocampus*, 22(10):2080-93. PMID: 22987683; PMCID: PMC3523702.

15. **Burke SN**, Ryan L, Barnes CA (2012). Characterizing cognitive aging of recognition memory and related processes in animal models and in humans. *Frontiers in Aging Neuroscience*, 4(15). PMID: 22988437; PMCID: PMC3439640.

16. Maurer AP, **Burke SN**, Lipa P, Skaggs WE, Barnes CA (2012). Greater running speeds result in altered hippocampal phase sequence dynamics. *Hippocampus*, 22(4):737-47. PMID: 21538659; PMCID: PMC3367321.

17. Takehara-Nishiuchi K, Insel N, Hoang LT, Wagner Z, Olson K, Chawla MK, **Burke SN**, Barnes CA (2012). Activation patterns in superficial layers of neocortex change between experiences independent of behavior, environment, or the hippocampus. *Cerebral Cortex*, 23(9):2225-34. PMID: 22806267; PMCID: PMC3733063.

18. **Burke SN**, Maurer AP, Cowen SL & Barnes CA (2013). Perirhinal cortical interneurons exhibit reduced firing rates with advanced age. *Society for Neuroscience Abstracts*, 43.

19. Plange K, Engle JR, **Burke SN**, Gray DT, Barnes CA (2013). Changes in sensory function are correlated with cognitive impairments in bonnet macaques. *Society for Neuroscience Abstracts*, 43.

20. Chance FS, Maurer AP, **Burke SN**, Barnes CA (2013). Dual input component models of CA1 activity in young and aged rats. *Society for Neuroscience Abstracts*, 43.

21. Lester AW, Maurer AP., **Burke SN**, Hoang LT, Barnes CA (2013). Preserved neural dynamics during reverse locomotion. *Society for Neuroscience Abstracts*, 43.

D. Research Support for the Past 3 Years

Current

Institutional Startup Funds 10/01/2013 – 6/30/2016

Completed Support

NIH – F31 NS054465 01/2007 – 01/2009

Aging and Neural Ensembles in the Perirhinal Cortex

The major goal of this project was to investigate the neurobiology of age-associated impairments in object recognition using high-density single cell recordings and single-cell imaging in young and old rats.

Role: Primary investigator under the mentorship of Carol A. Barnes.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Cohen, Ronald A.	Professor
eRA COMMONS USER NAME (credential, e.g., agency login) rcohen1	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Tulane University	BSc	06/76	Psychology
Louisiana State University	Ph.D.	08/82	Psychology
UCLA Medical Center: Neuropsychiatric Institute	Internship	07/82	Psychology
University of Florida	Fellowship	07/83	Neuropsychology

A. Personal Statement

I joined the faculty of the Institute on Aging and McKnight Brain Institute at the University of Florida, where I am the director of a new Cognitive Aging and Memory-Clinical Translational Research Program. This division's research on cognitive aging integrates neurocognitive, neuroimaging, and laboratory biomarker approaches. Until this year, I have been a professor at Brown University, where I co-directed the Memory Disorders Program for a number of years. I have conducted clinical and cognitive neuroscience research and directed a clinical program aimed at the assessment of neurodegenerative diseases, including Alzheimer's, and vascular dementia, and normal aging. I have an extensive background in clinical and cognitive neuroscience and also neuroimaging, with specific expertise in attention-executive functioning and its relationship to learning and memory. A major line of research for me over the past two decades has been vascular and metabolic factors affecting cognitive function in specific clinical populations in the context of aging, a focus which converges with the aims of the current study. I have published I have published over 190 peer-reviewed articles, and numerous book chapters on topics related to this project. Besides co-editing several books on topics related to areas of clinical neuropsychological research, I authored "Neuropsychology of Attention" in 1993 which was the first book on this topic in the field, and is now being published as a second edition. I recently published "Brain Imaging in Behavioral Medicine and Clinical Neuroscience", which will be the first to address the use of neuroimaging methods for studying various problems in behavioral medicine along with clinical neuroscience. I have published numerous papers based on cognitive, neuroimaging and laboratory biomarkers analyses of data from studies of AD, vascular dementia, cardiovascular disease, and risk factors relevant to this study. I am a co-PI on a number of NIH supported projects, and have a track record as a PI on past NIH supported projects as well. I have decades of NIH research support to study attention, executive function and the brain.

In my role as director of the Cognitive Aging and Memory-Clinical Translational Research Program at UF, I am in an excellent position to serve as PI and Co-I on many new pilot projects, and NIH sponsored studies, providing expertise and support related to MCI/AD and mechanisms of the aging brain.

B. Positions and Honors

1992-1993	Associate Professor of Neurology, Univ. Mass. Medical School
1993-1996	Assistant Professor, Psychiatry-Human Behavior, Brown University
1993-2008	Director, Neuropsychology: The Miriam Hospital, Providence, RI
1996-2004	Associate Professor, Psychiatry-Human Behavior, Brown University
2002-2011	Permanent Member, NIH – BMIO Study Section
2008-2012	Director, Neuropsychological Research, The Miriam Hospital
1998-Current	Editorial Boards: Journal of the International Neuropsychological Society; Brain Imaging and Behavior; The Clinical Neuropsychologist, Stroke, JCRP
2002-Current	Member, Executive Committee, Brown University, Magnetic Resonance Foundation
2004-Current	Professor, Brain Sciences Program, Brown University
2004-Current	Professor of Psychiatry and Human Behavior, Brown University
2012-Current	Director, Center for Cognitive Aging and Memory, University of Florida
2012-Current	Evelyn McKnight Endowed Professor, Departments of Neurology, Psychiatry and Aging, University of Florida

C. Selected Peer-reviewed Publications (selected from 196 peer-reviewed publications)

Most relevant to the current application

1. Stopa EG, Butala P, Salloway S, Johanson CE, Gonzalez L, Tavares R, Hovanesian V, Hulette CM, Vitek MP, **Cohen RA**.(2008). Cerebral cortical arteriolar angiopathy, vascular beta-amyloid, smooth muscle actin, Braak stage, and APOE genotype. *Stroke*, 39(3):814-21.
2. **Cohen RA**, Poppas A, Forman DE, Hoth KF, Haley AP, Gunstad J, Jefferson AL, Tate DF, Paul RH, Sweet LH, Ono M, Jerskey BA, Gerhard-Herman M. (2009). Vascular and cognitive functions associated with cardiovascular disease in the elderly. *J Clin Exp Neuropsychol*, 31:96-110. PMC 2739675.
3. Ott BR, Cohen RA, Gongvatana A, et al. (2010). Brain ventricular volume and cerebrospinal fluid biomarkers of Alzheimer's disease. *J Alzheimers Dis*., 20(2):647-657. PMCID: PMC 3078034.
4. Gongvatana A, Harezlak J, Buchthal S, et al. Progressive cerebral injury in the setting of chronic HIV infection and antiretroviral therapy. *J Neurovirol*. Apr 24 2013.
5. Paul RH, Ernst T, Brickman AM, **Cohen RA**, et al. Relative sensitivity of magnetic resonance spectroscopy and quantitative magnetic resonance imaging to cognitive function among nondemented individuals infected with HIV. *J Int Neuropsychol Soc*. Sep 2008;14(5):725-733.
6. Zahodne LB, Gongvatana A, **Cohen RA**, Ott BR, Tremont G. Are Apathy and Depression Independently Associated With Longitudinal Trajectories of Cortical Atrophy in Mild Cognitive Impairment? *Am J Geriatr Psychiatry*. Apr 28 2013.

Additional publications supporting study concept, hypothesis and methods (chronological order)

7. Brickman, A.M., M.E. Zimmerman, R.H. Paul, S.M. Grieve, D.F. Tate, **Cohen RA**, L.M. Williams, C.R, Clark, and E. Gordon. (2006). Regional white matter and neuropsychological functioning across the adult lifespan. *BiolPsychiatry*, 60(5): 444-53.
8. Jefferson, A.L., D. Cahn-Weiner, P. Boyle, R.H. Paul, D.J. Moser, N. Gordon, **Cohen RA**. (2006). Cognitive predictors of functional decline in vascular dementia. *Int J Geriatr Psychiatry*, 21(8):752-4.
9. Zimmerman, M.E., A.M. Brickman, R.H. Paul, S.M. Grieve, D.F. Tate, J. Gunstad, **Cohen RA**, et al. (2006). The relationship between frontal gray matter volume and cognition varies across the healthy adult lifespan. *Am J Geriatr Psychiatry*, 14(10): 823-833.
10. Zhu T, Zhong J, Hu R, Cohen RA, et al. Patterns of white matter injury in HIV infection after partial immune reconstitution: a DTI tract-based spatial statistics study. *J Neurovirol*. Feb 2013;19(1):10-23.
11. Dewey J, Hana G, Russell T, et al. Reliability and validity of MRI-based automated volumetry software relative to auto-assisted manual measurement of subcortical structures in HIV-infected patients from a multisite study. *Neuroimage*. Jul 15 2010;51(4):1334-1344.
12. Paskavitz, JF, Sweet, LH, Helmer, KG, Rao SM, **Cohen, RA**. (2009). Recruitment and stabilization of brain activation within a working memory task; a FMRI study. *Brain Imaging and Behavior*, 4(1):5-21.
13. **Cohen RA**, Harezlak J, Gongvatana A, et al. (2010). Cerebral metabolite abnormalities in human immunodeficiency virus are associated with cortical and subcortical volumes. *J Neurovirol*.,16(6):435-444.
14. Okonkwo OC, **Cohen RA**, Gunstad J, Tremont G, Alosco ML, Poppas A. (2010). Longitudinal trajectories of cognitive decline among older adults with cardiovascular disease. *Cerebrovascular Disease*, 0(4):362-373. PMC 3014862.
15. Okonkwo OC, **Cohen RA**, Gunstad J, Poppas A. (2011). Cardiac output, blood pressure variability, and cognitive decline in geriatric cardiac patients. *J Cardiopulm Rehabil Prev*., 3195):290-7. PMC 3171573.
16. **Cohen RA**, de la Monte S, Gongvatana A, et al. (2011). Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning. *J Neuroimmunol*., 233(1-2):204-210. PMC 3074016.
17. Alosco ML, Spitznagel MB, Raz N, **Cohen RA**, Sweet LH, van Dulmen M, Cobert LH, Josephson R, Waechter D, Hughes J, Rosneck J, Gunstad J. (2012). Cognitive reserve moderates the association between heart failure and cognitive impairment. *J Clin Exp Neuropsychol*, 34(1):1-10. PMID 22034987.

D. Research Support

Ongoing Research Support

5 R01 MH074368-05 **(Ronald Cohen, PI)** 09/30/06–08/31/13
"Age Effects on HIV-Associated Brain Dysfunction" (No Cost Extension)
The goal of this project is to achieve greater understanding of how HIV infection interacts with aging to cause brain abnormalities that affect neurocognitive functioning. Dr. Cohen oversees this entire project.
Role: Principal Investigator

5 R01 HL089311-04 (John Gunstad, PI) 09/15/08-11/30/12
NHLBI/Subcontract from Kent State
"Cognitive Benefits of Cardiac Rehabilitation in Heart Failure"
The main goal of this project will be to study CVD and its effects on the brain, and particularly how cardiac rehabilitation and the

effects of vascular conditioning are influenced by the vascular CVD and systemic vascular disease factors.
Role: Principal Investigator of Subcontract

5U01 CA1503878-03 (Rena Wing, PI) 09/28/09-08/31/14
"Increasing Sleep Duration: A Novel Approach to Weight Control"
The purpose of the project is to translate the basic science on sleep duration into a novel intervention to reduce obesity and obesity-related co-morbidities.
Role: Co-Investigator

5 R34 DA031057-02 **(Ron Cohen, PI)** 09/30/10-08/31/13
"Improving Adherence and Cognition in Substance-Using HIV Patients"
Substance abuse in the context of HIV infection is a major problem that affects clinical outcome and interferes with adherence to treatment regimens. This study examines the value of a computer-based cognitive training program (Vigorous Mind) to enhance attention and executive functioning as a means of improving organizational and planning ability and ultimately treatment adherence. The study focuses on further development of the program for use in this population and initial testing to determine its acceptability and whether a larger scale clinical trial is warranted.
Role: Principal Investigator

5 P01 AA019072-02 (Peter Monti, PI) 09/30/10-08/31/15
"Alcohol and HIV: Biobehavioral Interactions and Intervention"
This study focuses on the interactive effects of HIV and alcohol use on metabolic-vascular disturbances underlying brain dysfunction.
Role: Principal Investigator of Substudy

Completed Research Support

5 R01 NS036524-10 (Brad Navia, PI) 05/23/05-04/30/10
NINDS/Subcontract from Tufts University
"Proton MRS Studies of Cerebral Injury in HIV Infection"
The major goals of this project are to examine the MRS and MRI correlates of cognitive function in the context of antiretroviral therapy.
Role: PI of Subcontract

3 R01 NS036524-07S1 (Brad Navia, PI) 07/01/06-04/30/10
NINDS/Subcontract from Tufts University
"Brain Morphometric Studies of Cerebral Injury in HIV Infection"
(Supplement to "Proton MRS Studies of Cerebral Injury in HIV Infection")
Role: Principal Investigator of Subcontract

5 P50 CA084719-11 (Jeanne McCaffery, PI of sub) 09/30/99-07/31/10
NCI/Subcontract from Butler Hospital
"Nicotine Dependence: Phenotype, Endophenotype & Contexts"
The major goal is to characterize the relationship of cigarette smoking to fMRI responses on smoking related tasks. Dr. Cohen's role is to provide expertise related to the functional imaging analyses and interpretation of data from these paradigms.
Role: Co-Investigator

5 R01 HL084178-03 (Lawrence Sweet, PI) 01/25/07-11/30/11
NHLBI/Subcontract from Butler Hospital
"Hemodynamic and Cognitive Function in Cardiovascular Disease"
This study aims at characterizing the relationship between cerebral hypoperfusion and abnormalities of BOLD on FMRI in association with working memory and attention performance among patients with heart failure.
Role: Principal Investigator of Subcontract

5 R01 DA020725-03 (Tara White, PI) 10/01/07-05/31/11
NIDA/Subcontract from Brown University
"Imaging Individual Differences in Amphetamine Effects"
This study examines the relationship between personality factors and response to risk and award following intake of amphetamines.
Role: Principal Investigator of Subcontract

2 R56 DK075119-05A1 (John Gunstad, PI) 09/01/06-08/31/12
NIDDK/Subcontract from Kent State
"Extended Effects of Bariatric Surgery on Cognitive Function"
This study examines the effects obesity and rapid loss of weight associated with bariatric surgery.
Role: Principal Investigator of Subcontract

PENDING
1R01DK099334 07/01/2013-06/30/2018 3.60 CM
National Institutes of Health $2,074,460
Obesity and type-2 diabetes: Bariatric surgery effects of brain function
The proposed prospective longitudinal study will examine whether cerebral metabolic and vascular dysfunction, including glucose/insulin disturbances (co-morbid diabetes) underlie obesity-associated cognitive dysfunction, and whether significant weight loss and diabetes remission following bariatric surgery reduces these disturbances.
Role: PI

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Vonetta M. Dotson	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) dotsonv	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
St. Mary's University	B.A.	5/99	Psychology
University of Florida	M.S., Ph.D.	5/02, 8/06	Psychology (Clinical)
James A. Haley Veterans Hospital	N/A	7/06-8/06	Predoctoral Internship
NIA Intramural Research Program	Postdoctoral	8/06-7/09	Cognitive Neuroscience of Aging and Depression

A. Personal Statement

Vonetta Dotson is an Assistant Professor in the Department of Clinical and Health Psychology (CHP) at the University of Florida, with a joint appointment in the Department of Neuroscience at the University of Florida. She is also a Claude C. Pepper scholar. She received her Ph.D. from CHP in 2006 with a specialization in neuropsychology and a certificate in gerontology. She completed her postdoctoral training in the Laboratory of Personality and Cognition in the National Institute on Aging Intramural Research Program under the mentorship of Drs. Susan Resnick and Alan Zonderman. Her research focuses on studying the interaction of psychological disorders such as depression with cognitive and brain aging using both neuroimaging and behavioral techniques. Her more recent work focuses on the impact of aerobic exercise on depression-related cognitive and brain changes in older adults.

B. Positions and Honors

Positions and Employment

2006-2009 Postdoctoral Fellow, Laboratory of Personality and Cognition, National Institute on Aging Intramural Research Program, Baltimore, MD

8/2009-present Assistant Professor, Department of Clinical and Health Psychology, University of Florida, Gainesville, FL
Affiliate Faculty, Department of Neuroscience, University of Florida, Gainesville, FL

Awards/Honors

1997 ACCD Foundation Scholars Award
1997-1999 Dean's List, St. Mary's University
1998-1999 The National Dean's List
2000-2004 University of Florida Graduate Minority Fellowship
2003-2005 University of Florida Institute on Aging Trainee
2004-2005 National Institute on Aging funded Predoctoral Fellow
2004 Recipient of National Institute on Aging Technical Assistance Workshop travel fellowship
2005 Accepted into the Society for Neuroscience's Neuroscience Scholars Program
2006 Accepted to attend the American Psychological Association's Advanced Training Institute on Functional Magnetic Resonance Imaging
2006 Recipient of the Institute for Learning in Retirement Graduate Aging Research Award
2007 Accepted to attend the American Psychological Association's Advanced Training Institute on Structural Equation Modeling for Longitudinal Research
2007 Recipient of National Institute on Aging Summer Institute on Aging Research travel fellowship
2010 Claude D. Pepper Affiliated Scholar
2012 Claude D. Pepper Scholar

Licensure: Licensed psychologist, State of Florida, License No. PY 8055

Professional Memberships: Society for Neuroscience, International Neuropsychological Society, American Psychological Association

B. Peer-reviewed publications or manuscripts in press (in chronological order)

1. Perlstein, W.M., Larson, M.J., **Dotson, V.M.**, & Kelly, G.K. (2006). Temporal dissociation of components of cognitive control dysfunction in severe TBI: ERPs and the cued-Stroop task. *Neuropsychologia*, 44(2), 260-274. PMID: 15979655

2. Larson, M.J., Perlstein, W.M., Stigge-Kaufmann, D., Kelly, G.K., & **Dotson, V.M.** (2006). Affective context induced modulation of the error-related negativity. *Neuroreport*, 17(3), 329-33. PMID: 16462607

3. **Dotson, V.M.**, Singletary, F.S., Fuller, R., Koehler, S., Bacon Moore, A., Rothi, L.J.G., & Crosson, B. (2008). Treatment of word-finding deficits in fluent aphasia through the manipulation of spatial attention: Preliminary findings. *Aphasiology*, 22(1), 103–113.

4. **Dotson, V.M.**, Schinka, J.A., Brown, L, Borenstein, A.R., & Mortimer, J.A. (2008). Characteristics of the Florida Cognitive Activities Scale in Older African Americans. *Assessment*, 15(1), 72-77. PMID: 18258733

5. **Dotson, V.M.**, Resnick, S.M., & Zonderman, A.B. (2008). Differential Association of Baseline, Concurrent, and Chronic Depressive Symptoms with Cognitive Decline in Older Adults. *American Journal of Geriatric Psychiatry*, 16, 318-330. PMID: 18378557

6. **Dotson, V.M.**, Kitner-Triolo, M., Evans, M.K., & Zonderman, A.B. (2008). Literacy-based normative data for low socioeconomic status African Americans. *The Clinical Neuropsychologist*, 22, 989–1017. PMID: 18609322

7. Pedraza, O., **Dotson, V.M.**, Willis, F.B., Graff-Radford, N.R., and Lucas, J.A. (2009). Internal Consistency and Test-Retest Reliability of the Geriatric Depression Scale-Short Form in African American Older Adults. *Journal of Psychopathology and Behavioral Assessment*, 31(4), 412-416. PMID: 20161488

8. **Dotson, V.M.**, Kitner-Triolo, M., Evans, M.K., & Zonderman, A.B. (2009). Effects of Race and Socioeconomic Status on the Relative Influence of Education and Literacy on Cognitive Functioning. *JINS*, 15, 580-589. PMID: 19573276

9. **Dotson, V.M.**, Beason-Held, L., Kraut, M.A., & Resnick, S.M. (2009). Longitudinal Study of Chronic Depressive Symptoms and Regional Cerebral Blood Flow in Older Men and Women. *International Journal of Geriatric Psychiatry*, 24(8), 809-19. PMID: 19484709

10. **Dotson, V.M.**, Davatzikos, C., Kraut, M.A., & Resnick, S.M. (2009). Depressive Symptoms and Brain Volumes in Older Adults: A Longitudinal MRI Study. *Journal of Psychiatry and Neuroscience*, 34(5), 367-375. PMID: 19721847

11. **Dotson, V.M.**, Zonderman, A.B., Davatzikos, C., Kraut, M.A., & Resnick, S.M. (2009). Frontal Atrophy and Immediate Memory Deficits in Older Adults with a History of Elevated Depressive Symptoms. *Brain Imaging and Behavior*, 3, 358–369. PMID: 20161651

12. **Dotson, V.M.**, Baydoun, M.A., & Zonderman, A.B. (2010). Recurrent depressive symptoms and the incidence of dementia and MCI. *Neurology*, 75, 27-34. PMID: 20603482

13. Sutin, A. R., Beason-Held, L. L., **Dotson, V. M.**, Resnick, S. M., & Costa, P. T. (2010). The neural correlates of neuroticism differ by sex and prospectively mediate depressive symptoms among older women. *Journal of Affective Disorders*, 127, 241-7. PMID: 20599276

14. Goveas, J.S., Espeland, M.A., Hogan, P., **Dotson, V. M.**, Tarima, S., Coker, L.H., Ockene, J., Brunner, R., Woods, N.F., Wassertheil-Smoller, S., Kotchen, J.M., Resnick, S. (2011). Depressive symptoms, brain volumes and subclinical cerebrovascular disease in postmenopausal women: the Women's Health Initiative MRI Study. *Journal of Affective Disorders*, 132, 275–284. PMID: 21349587

15. **Dotson, V.M.**, Zonderman, A.B., Kraut, M.A., & Resnick, S.M. (2013). Temporal Relationships between Depressive Symptoms and White Matter Hyperintensities in Older Men and Women. *International Journal of Geriatric Psychiatry*, 28, 66–74. DOI: 10.1002/gps.3791.

16. **Dotson, V.M.**, Sozda, C.N., Marsiske, M., & Perlstein, W.M. (2013). Within-session Practice Eliminates Age Differences in Cognitive Control. *Aging, Neuropsychology and Cognition: A Journal on Normal and Dysfunctional Development*, 20 (5), 522-531. DOI:10.1080/13825585.2012.736469.

17. Kirton, J. W., Resnick, S. M., Davatzikos, C. Kraut, M. A. & **Dotson, V. M.** (2013). Depressive Symptoms, Symptom Dimensions and White Matter Lesion Volume in Older Adults: A Longitudinal Study. *American Journal of Geriatric Psychiatry*. DOI: 10.1016/j.jagp.2013.10.005.

C. Research Support

Physical, Cognitive and Mental Health in Social Context
Principal Investigator: Michael Marsiske, Ph.D.
5T32AG020499-07
NIH/NIA
Role: Research Fellow/Trainee
2004 - 2005

Double Jeopardy: Cognitive Decline in Depression and Aging
Principle Investigator: Vonetta M. Dotson, Ph.D.
AG024539-01
NIH/NIA
Role: PI
9/04 - 6/06

Effect of Exercise on Memory in Geriatric Depression: An fMRI Pilot Study
Principal Investigator: Vonetta M. Dotson, Ph.D.
McKnight Brain Research Foundation
Role: PI
3/11-8/13

Diversity Supplement to the Lifestyle Interventions and Independence for Elders (LIFE) Study (PI)
Principle Investigator: Marco Pahor, M.D.
U01 AG022376
NIH/NIA
Role: PI for diversity supplement
2/12-2/14

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Natalie C. Ebner	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) NATALIE.EBNER	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Free University Berlin, Berlin, Germany	B.A.	04/1998	Psychology
Free University Berlin, Berlin, Germany	M.A.	03/2001	Psychology
Free University Berlin & Max Planck Institute for Human Development, Berlin, Germany	Ph.D.	04/2005	Psychology
Max Planck Institute for Human Development, Berlin, Germany	Postdoctoral	06/2007	Psychology
Yale University, New Haven, USA	Postdoctoral	07/2010	Psychology

A. Personal Statement

My laboratory primarily focuses on cognitive, social, and affective experimental aging research using behavioral, eye-tracking, and neuroimaging techniques.

B. Positions and Honors

Positions

2001-2005 Predoctoral Fellow, Free University Berlin & Max Planck Institute for Human Development, Berlin, Germany
2005-2007 Postdoctoral Fellow, Max Planck Institute for Human Development, Berlin, Germany
2007-2010 Postdoctoral Fellow, Department of Psychology, Yale University, New Haven, USA
2010-2011 Associate Research Scientist, Department of Psychology, Yale University, New Haven, USA
08/2011- Assistant Professor, Department of Psychology, University of Florida, Gainesville, USA
06-2013- Adjunct Faculty at Cognitive Aging and Memory Clinical Translational Research Program; CAM-CTRP, University of Florida, Gainesville, USA

Other Experience and Professional Memberships

2000- Member, German Psychological Association
2003- Member, American Psychological Association
2003- Member, Society for Personality and Social Psychology
2008- Member, Association for Psychological Science
2008- Member, Social and Affective Neuroscience Society
2010- Member, Society for Social Neuroscience
2012- Member, Cognitive Neuroscience Society
2009 Reviewer for Retirement Research Foundation Doctoral Dissertation Award in the Psychology of Aging (American Psychological Association)
2012- Reviewer for the Swiss National Fond
2012- Early Career Reviewer (ECR) at the Center for Scientific Review (CSR), National Institute of Health

Awards

2003 Student Research Award, American Psychological Association (Division 20)
2004 Graduate Student Poster Award, Society for Personality and Social Psychology
2006 Heinz-Heckhausen-Jungwissenschaftlerpreis (Young Research Scientist Award), German Psychological Association

C. Selected Peer-reviewed Publications

Most relevant to the current application (in chronological order)

1. **Ebner, N. C.**, Maura, G., MacDonald, K., Westberg, L., & Fischer, H. (2013). Oxytocin and socioemotional aging – Current knowledge and future trends. [Research topic] Frontiers in Human Neuroscience, 7(487), 1-14. DOI: 10.3389/fnhum.2013.00487
2. **Ebner, N. C.**, Johnson, M. R., Rieckmann, A., Durbin, K., Johnson, M. K., & Fischer, H. (in press). Processing own-age vs. other-age faces: Neuro-behavioral correlates and effects of emotion. *NeuroImage*.

3. **Ebner, N. C.**, Johnson, M. K., & Fischer, H. (2012). Neural mechanisms of reading facial emotions in young and older adults. *Frontiers in Psychology*, 3(223), 1-19. DOI: 10.3389/fpsyg.2012.00223.
4. **Ebner, N. C.**, Gluth, S., Johnson, M. R., Raye, C. L., Mitchell, K. M., & Johnson, M. K. (2011). Medial prefrontal cortex activity when thinking about others depends on their age. [Special issue] *Neurocase*, 17, 260-269. DOI:10.1080/13554794.2010.536953. NIHMS ID: NIHMS251257
5. **Ebner, N. C.**, He, Y., Fichtenholtz, H. M., McCarthy, G., & Johnson, M. K. (2010). Electrophysiological correlates of processing faces of younger and older individuals. Social Cognitive and Affective Neuroscience. Advance online publication. DOI:10.1093/scan/nsq074. *PMC Journal* – in process
6. **Ebner, N. C.**, He, Y., & Johnson, M. K. (2011). Age and emotion affect how we look at a face: Visual scan patterns differ for own-age versus other-age emotional faces. [Special section] *Cognition & Emotion*. Advance online publication. DOI:10.1080/02699931.2010.540817. NIHMS ID: NIHMS303333
7. Riediger, M., Voelkle, M., **Ebner, N. C.**, & Lindenberger, U. (2011). Beyond "happy, angry, or sad?": Age-of-poser and Age-of-rater effects on multi-dimensional emotion perception. [Special section] *Cognition & Emotion*. Advance online publication. DOI:10.1080/02699931.2010.540812
8. **Ebner, N. C.**, & Johnson, M. K. (2010). Age-group differences in interference from young and older emotional faces. *Cognition & Emotion*, 24, 1095-1116. DOI:10.1080/02699930903128395. PMCID: PMC3030265
9. **Ebner, N. C.**, Riediger, M., & Lindenberger, U. (2010). FACES—A database of facial expressions in young, middle-aged, and older women and men: Development and validation. *Behavior Research Methods*, 42, 351-362. DOI:10.3758/BRM.42.1.351. PMID: 20160315
10. **Ebner, N. C.**, & Johnson, M. K. (2009). Young and older emotional faces: Are there age-group differences in expression identification and memory? *Emotion*, 9, 329-339. DOI: 10.1037/a0015179. PMCID: PMC2859895
11. Mitchell, K. J., Raye, C. L., **Ebner, N. C.**, Tubridy, S. M., Frankel, H., & Johnson, M. K. (2009). Age-group differences in medial cortex activity associated with thinking about self-relevant agendas. *Psychology and Aging*, 24, 438-449. DOI:10.1037/a0015181. PMCID: PMC2859896
12. **Ebner, N. C.** (2008). Age of face matters: Age-group differences in ratings for young and old faces. *Behavior Research Methods*, 40, 130-136. DOI:10.3758/BRM.40.1.130. PMID: 18411535

Additional recent publications of importance to the field (in chronological order)

1. Lovén, J., Svärd, J., **Ebner, N. C.**, Herlitz, A., & Fischer, H., (2013). Face gender modulates women's brain activity during face encoding. *Social Cognitive and Affective Neuroscience*. [Epub ahead of print]
2. Voelkle, M. C., **Ebner, N. C.**, Lindenberger, U., & Riediger, M. (2013). Here we go again: Anticipatory and reactive mood responses to recurring unpleasant situations throughout adulthood. *Emotion*, 13(3), 424-433. DOI: 10.1037/a0031351
3. West, R. L., **Ebner, N. C.**, & Hastings, E. C. (2012). Linking goals and aging: Experimental and life-span approaches. In E. A. Locke & G. P. Latham (Eds.), *New developments in goal setting and task performance*. London, UK: Routledge Academic.
4. Voelkle, M. C., **Ebner, N. C.**, Lindenberger, U., & Riediger, M. (2011). Let me guess how old you are: Effects of age, gender, and facial expression on perceptions of age. *Psychology & Aging*. Advance online publication. DOI: 10.1037/a0025065. PMID: 21895379
5. Gluth, S., **Ebner, N. C.**, & Schmiedek, F. (2010). Attitudes toward younger and older adults: The German Aging Semantic Differential. *International Journal of Behavioral Development*, 34, 147-158. DOI:10.1177/0165025409350947.
6. **Ebner, N. C.**, Riediger, M., & Lindenberger, U. (2009). Schema reliance for developmental goals increases from early to late adulthood: Improvement for the young, loss prevention for the old. *Psychology and Aging*, 24, 310-323. DOI:10.1037/a0015430. PMID: 19485650
7. **Ebner, N. C.**, Freund, A. M., & Baltes, P. B. (2006). Developmental changes in personal goal orientation from young to late adulthood: From striving for gains to maintenance and prevention of losses. *Psychology and Aging*, 21, 664-678. DOI:10.1037/0882-7974.21.4.664. PMID: 17201488

D. Ongoing Research Support

NIH/NIAAA (1R01AA022456-01)
Ebner (**co-I; 5%**; PI: Dr. Sara Jo Nixon)
10/01/13-09/01/2017 ($1,600,000)
Neurobehavioral and Emotional Deficits in Male and Female Alcoholics
The goal of this project is to examine gender differences in deficits in cognitive and emotional functioning in alcoholics.

Swedish Research Council
Ebner (**co-PI; 5%**; PI: Dr. Hakan Fischer)
11/01/13-10/01/2017 ($480,000)
Effects of Oxytocin on Socioemotional Aging: Studies on Brain Function and Behavior.

The goal of this project is to examine the effects of intranasal oxytocin administration on socioemotional functioning from a brain-behavior perspective.

University of Florida Claude D. Pepper Older Americans Independence Center (sponsor: NIH/NIA)
Ebner (PI; 5%)
08/01/13-07/01/2015 ($65,000)
Effects of Oxytocin on Physical and Cognitive Functioning in the Elders
The goal of clinical trial is to examine the effects of intranasal oxytocin administration on cognition, health, and socioemotional functioning in aging over time.

University of Florida University of Florida McKnight Brain Institute
Ebner (PI; 0.1%)
11/01/13 ($1,000)
Improving Neural Dysregulation in Advanced Age: A Neurofeedback Approach
The goal of this project is to explore age differences in emotional dysregulation using a neurofeedback approach.

University of Florida University of Florida McKnight Brain Institute
Ebner (**co-I; 0.5%**; PI: Dr. Adam Woods)
11/01/13 ($59,000)
Acquiring Human Whole-Brain Phosphorous Magnetic Resonance Imaging Capabilities in the McKnight Brain Institute
The goal of this project is to implement a system for Human Whole-Brain Phosphorous Magnetic Resonance Imaging

University of Florida Clinical and Translational Science Institute (CTSI) Pilot Project Award (sponsor: NIH/NCATS Clinical and Translational Science Award to the University of Florida UL1 TR000064)
Ebner (**PI; 5%**)
01/01/13-12/31/13 ($20,000)
Neuro-behavioral effects of oxytocin on decisions of trust in aging
The goal of this project is to determine neuroendocrine and socio-behavioral effects of oxytocin on decisions of trust in aging.

Scientific Research Network on Decision Neuroscience and Aging (SRNDNA) Pilot Project Award (sponsor: NIH/NIA)
Ebner (PI; 5%)
08/01/13-7/31/14 ($29,800)
Effects of oxytocin on health-related decision making in aging
The goal of this project is to determine neuroendocrine and socio-behavioral effects of oxytocin on health-related decision making in aging.

Completed Research Support
Department of Psychology 2011 Michael L. & Judith D. Woodruff Research Competition Grant
Ebner (PI; 5%)
08/15/11-06/02/13 ($6,000)
Neural mechanisms of social memory in young and older adults
The goal of this project is to determine the neural correlates for older adults' increased schema reliance and to examine whether self-relevance of information counteracts memory biases arising from schemas.

DFG EB 436/1-1 (sponsor: German Science Foundation)
Ebner (PI; 100%)
07/01/07-06/30/10
Motivational orientation in adulthood
The goal of this project was to assess behavioral and neural correlates of age-related differences in processing motivationally and socially relevant information

Thomas Foster, PhD

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Thomas Foster	Professor of Neuroscience
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Arizona, Tucson AZ	BS	1981	Psychology
Bowman Gray, School of Medicine, W-S, NC	PhD	1987	Physio/Pharm
University of Colorado, Boulder CO	Postdoctoral	1991	Neurophysiology and behavior

A. Personal Statement

My research focuses on understanding brain mechanisms of aging and their relationship with age-related cognitive decline. My long-term goal is the amelioration of memory deficits associated with aging. My research program utilizes a combination of behavioral characterization with biochemical, molecular, and electrophysiological techniques and treatments (behavioral, pharmacological, and viral) to obtain a vertically integrated perspective on neural aging, from the molecular to the cognitive level. I have been continuously funded through NIH as a principle investigator since 1992 and my work includes 103 publications on memory mechanisms and the aging brain. As part of this work we are funded to examine electrophysiological and transcriptional markers of aging in relation to hippocampal function. Our published research demonstrates that age-related memory impairments are linked to changes in cell excitability (i.e. afterhyperpolarization), synaptic plasticity, and altered gene expression. We have previously examined variability in cell excitability during aging in relation to cognitive decline. We have published a number of papers examining the regulation of gene expression in hippocampal tissue during aging, including descriptions of regional differences. Recent work points to altered redox signaling in mediating senescent physiology. Other major projects in the lab examine the role of estrogen receptors in protecting against age-related cognitive decline.

B. Position and Honors

Positions and Employment

Assistant Professor, 1991-1992 Dept. Psych. University of Connecticut
Assistant Professor, 1992-1998, Dept. Psych. University of Virginia
Associate Professor, 1998-2003, Dept. Pharmacology, University of Kentucky Medical School
Associate Professor, 2003-2006, Dept Neurosci, University of Florida
Professor 2006-present, Dept Neurosci, University of Florida

Academic Honors and Awards

National Advisory Council on Aging NIH Method to Extend Research in Time (MERIT) Award (2011)
McKnight Chair for Research on Aging and Memory, University of Florida 2003-present
Member of the planning Committee for the Cognitive Aging Summits I & II 2006-present
Associate Editor Frontiers in Aging Neuroscience 2009-present
Member for > 10 NIH Special Emphasis Review Panels (2001-2011)
Member, NIH IFCN-7 Study Section 1999-2004
Shannon Investigators Award, 1992

C. Selected Peer-reviewed Publications

Publications in peer reviewed journals accepted or published in 2013.

1. Brim BL, Haskell R, Awedikian R, Ellinwood NM, Jin L, Kumar A, **Foster TC**, Magnusson KR. Memory in aged mice is rescued by enhanced expression of the GluN2B subunit of the NMDA receptor. *Behav Brain Res* 2013; 238:211-226. **PM:23103326**

2. Speisman RB, Kumar A, Rani A, Pastoriza JM, Severance JE, **Foster TC**, Ormerod BK. Environmental enrichment restores neurogenesis and rapid acquisition in aged rats. *Neurobiol Aging* 2013; 34(1):263-274. **PM:22795793**

3. Speisman RB, Kumar A, Rani A, **Foster TC**, Ormerod BK. Daily exercise improves memory, stimulates hippocampal neurogenesis and modulates immune and neuroimmune cytokines in aging rats. *Brain Behav Immun* 2013; 28:25-43. **PM:23078985**

4. Han X, Aenlle KK, Bean LA, Rani A, Semple-Rowland SL, Kumar A, and **Foster TC**. Role of estrogen receptor alpha and beta in preserving hippocampal function during aging. *Journal of Neuroscience* 2013, 33: 2671-2683. **PMID: 23392694.**

5. Kumar A and **Foster TC**. Linking redox regulation of NMDAR synaptic function to cognitive decline during aging. *Journal of Neuroscience* 2013; 33: 15710-15715. **PMID: 24089479**

6. Boye SL, Peshenko IV, Huang WC, Min SH, McDoom I, Kay CN, Liu X, Dyka FM, **Foster TC**, Umino Y, Karan S, Jacobson SG, Baehr W, Dizhoor AM, Hauswirth W, Boye SE. AAV-mediated gene therapy in the guanylate cyclase (RetGC1/RetGC2) double knockout mouse model of Leber congenital amaurosis. *Hum Gene Ther* 2013. **PM:23210611**

7. Lee WH, Kumar A, Rani A, **Foster TC**. Dissociating oxidative damage and memory: NMDAR-redox regulation of memory during normal aging. *Neurobiol Aging* 2013, in press 12/9/2013.

8. Bean, LA, Ianov, L, **Foster, TC** Estrogen Receptors, the Hippocampus, and Memory. *The Neuroscientist* 2013, in press 12/17/2013.

D. Research Support

Ongoing Research Support

R01 AG037984 Foster (PI) 9/15/2010 to 7/31/2016
This project will examine the hypothesis that the ratio of ERα/ERβ interacts with the level of E2 during aging to regulate memory and transcription of genes for neuroprotection and synaptogenesis.
Role: PI

R37 AG036800 Foster (PI) 10/05/2010 to 08/31/2014
The major goals of this project are to examine the hypothesis that age-related changes in NMDA receptor function impair signaling cascades, which lead to impaired transcription and memory deficits.
Role: PI

UF Opportunity Grant Foster (co-PI) 2012 to 2013
Genomic Bases of Differential Aging in Hippocampal Circuits: Single Cell Approaches
Research Completed

R01 AG14979 Foster (PI) 6/01/07 to 5/31/12
The major goals of this project are to examine the hypothesis that age-related changes in oxidative stress mediate changes in Ca2+ homeostasis, neuroplasticity, and memory deficits.
Role: PI

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Manini, Todd M.	Assistant Professor
eRA COMMONS USER NAME tmanini	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Ohio University, (Athens, OH)	BS	1997	Biology
Syracuse University, (Syracuse, NY)	MS	2000	Exercise Physiology
Syracuse University, (Syracuse, NY)	Ph.D.	2004	Exercise Physiology
National Institute on Aging	Fellowship	2006	Epidemiology

A. Personal Statement

Dr. Manini, a New and Early Career Investigator, will be the Principal Investigator of this project. He possesses the background knowledge in neuromuscular physiology to lead the study and research team. He completed his graduate degree in Exercise Physiology at Syracuse University where he conducted studies on neuromuscular function in a variety of populations. This work led to 14 manuscripts published in premier journals that showcase research on the neuromuscular system (e.g. J. of Applied Physiology, Archives of Physical Medicine & rehabilitation, etc.). He then completed a fellowship at the National Institute on Aging Intramural Laboratory of Epidemiology, Demography and Biometry. During his fellowship he was mentored by Dr. Tamara Harris, a leading NIH-funded researcher in the area of prognostic indicators for prevention of physical and cognitive disability in older adults. The current proposal marks an integration of his backgrounds in neuromuscular physiology and post-hospital functional limitation that is uniquely suited to lead the project. This proposal also parallels his current work where he is the recent recipient of an Exploratory Grant (R21) that studies the effects of a neural task-specific training in pre-clinically disabled older adults. He is also conducting observational pilot studies in populations that suffer from muscle weakness (HIV, Fatigued, Breast Cancer). Such studies are closely linked with the proposed work to investigate neural factors relating to muscle weakness and will provide a transition of knowledge to patient populations who experience muscle weakness.

B. Positions and Honors

Positions and Employment

1997-2001	Graduate assistant, Syracuse University, Syracuse, NY
2002-2003	Adjunct faculty, Syracuse University, Syracuse, NY
2003-2004	Graduate Student Fellowship, Syracuse University, Syracuse, NY
2004-2006	Post-Doctoral Fellowship, National Institute on Aging, Bethesda, MD
2006-2007	Research Assistant Professor, University of Florida, Gainesville, FL
2007-	Assistant Professor (Tenure-Track), University of Florida, Gainesville, FL

Other Experience and Professional Memberships

Referee:	Journal of the American Medical Association (JAMA), Journals of Gerontology: Biological & Medical Science, Journal of the American Geriatrics Society, Biomed Central: Geriatrics, British Medical Journal, Aging Clinical and Experimental Research, Medicine Science in Sports and Exercise, AJP: Regulatory, Integrative and Comparative Physiology, International Journal of Sport Psychology.
Member:	Gerontological Society of America, American Physiological Society, American College of Sports Medicine
NIH Study section:	2007 ZAG1 ZIJ-7 NIA Thrombosis RFA review, ARRA stage 1 grant reviewer
NIH Study section:	ZAG1 ZIJ-M1 Special Emphasis Panel SRG
Grant Reviewer:	Longevity Consortium
Symposia Chair:	Gerontological Society of America and American College of Sports Medicine
Additional Training:	Genetics and genomics strategies in aging research workshop (2007), Bench to Bedside Idiopathic fatigue and aging (2008), Mitochondrial Respirometry (2009), Microarray analysis and interpretation (2008)

Honors

1998-99	Sidney Young Student Research Award: Two time recipient
2003	Syracuse University: Creative Grant Competition Award
2003	Mid-Atlantic Regional American College of Sports Medicine: Presidents award
2005	Maxwell School of Citizenship and Public Affairs: Certificate of Advanced studies in Gerontology
2005	Gerontological Society of America: Austin Bloch Post-Doctoral Award
2005	Syracuse University doctoral prize & Certificate of University Teaching
2010	University of Florida Assistant Professor Excellence Award
2011	Keynote speaker for Quebec network for research on aging. Title: Sarcopenia ≠ Dynapenia
2011	Outstanding presentation award granted to Torrance Higgins (Mentee of Manini TM) at the Annual Conference of the Institute for Learning in Retirement. Student Research on Aging Symposium. Evaluation of Self Efficacy and Anxiety on the Use of Compensatory Strategies
2011	UF College of Medicine Exemplary Teachers Award
2011	Fellow of the American College of Sports Medicine

C. Selected Peer-reviewed Publications (Selected from 94 peer-reviewed publications, * Senior / Corresponding author)

Most relevant to the current application

1. **Manini TM***, Clark BC. Dynapenia & Aging: An Update. *Journals of Gerontology: Biological and Medical Sciences*. Epub March 28th, 2011. PMID: 21444359.
2. Clark BC, **Manini TM***. Sarcopenia ≠ Dynapenia. *Journals of Gerontology: Biological and Medical Sciences*. Vol 63(8) 829-834, 2008. PMID: 18772470
3. Clark BC & **Manini TM***. What is Dynapenia? Invited review for the *Journal of Nutrition*. In press
4. Clark BC, **Manini TM**, Bolanowski S, Ploutz-Snyder L. Adaptations in human neuromuscular function following prolonged unweighting: Part II. Neurological properties & motor imagery efficacy. *Journal of Applied Physiology*, 101: 256-263, 2006. PMID: 16514003.
5. **Manini TM***, Visser M, Won-Park S, Patel K, Strotmeyer E, Chen H, Goodpaster B, De Rekeneire N, Newman AB, Simonsick EM, Kritchevsky SB, Ryder K, Schwartz S, Harris TB. Knee extension strength cutpoints for maintaining mobility. *Journal of the American Geriatrics Society*. 55(3): 451-7, 2007. PMID: 17341251.

Additional recent publications of importance to the field

1. **Manini TM*** & Clark BC. Functional consequences of sarcopenia and dynapenia in the elderly. *Current Opinion in Clinical Nutrition and Metabolic Care*. Vol 13(3): 271-6. 2010. PMCID: PMC2895460, PMID: 20154609.
2. Clark BC, Pierce JR, **Manini TM** and Ploutz-Snyder LL. Effect of prolonged unweighting of human skeletal muscle on neuromotor force control. *European Journal of Applied Physiology*. 100 (1): 53-62, 2007. PMID: 17287986.
3. Clark BC, **Manini TM**, Hoffman RL, Russ DW. Restoration of voluntary muscle strength following 3-weeks of cast immobilization is suppressed in women compared to men. Archives of Physical Medicine and Rehabilitation. 90(1): 178-80, 2009. PMID: 19154845.
4. Clark BC, **Manini TM**, NR Ordway and LL Ploutz-Snyder. Leg muscle activity during walking with assistive devices at varying levels of weight-bearing. *Archives of Physical Medicine & Rehabilitation*. Vol 85 (9): 1555-1560, 2004. PMID: 15375835.
5. **Manini TM***, Clark BC, Nalls MA, Goodpaster BH, Ploutz-Snyder LL, Harris TB. Reduced physical activity increases inter-muscular adipose tissue in healthy young adults. *American Journal of Clinical Nutrition*. 31(3): 217-24, 2007. PMID: 17284732.
6. **Manini TM***, Everhart J, Patel V, Schoeller D, Colbert L, Visser M, Tylavsky F, Bauer D, Goodpaster B, Harris T. Daily activity energy expenditure and mortality among older adults. *JAMA*. 2006;296:171-179. PMID: 16835422.
7. **Manini, TM***, Baldwin, S.L., Ordway, N.R., Ploutz-Snyder, R.J., & Ploutz-Snyder, L.L. (2005) Knee extensor isometric unsteadiness does not predict functional limitation in older adults. *American Journal of Physical Medicine and Rehabilitation*. 2005;84(2), 112-121. PMID: 15668559.
8. Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB, Velasquez-Mieyer P, Boudreau R, **Manini TM**, Newman AB, Goodpaster BH. Longitudinal study of muscle strength, quality and adipose tissue infiltration. *American J of Clinical Nutrition*. Vol 90 (6): 1579-85. 2009. PMCID: PMC2777469, PMID: 19864405.
9. **Manini, TM***, Clark, B.C., Tracy, B.L., Burke, J., & Ploutz-Snyder, L.L. (2005). Resistance or functional training improves knee extensor movement variability in functionally limited older adults. European Journal of Applied Physiology, 95(5-6), 436-446. PMID: 16193338.
10. **Manini, TM***, Marko, M., VanArnam, T., Cook, S., Fernhall, B., Burke, J., & Ploutz-Snyder, L. (2007) Efficacy of Resistance and task-specific exercise in older adults who modify tasks of everyday life. *Journals of Gerontology: Medical Sciences*, 62(6), 616-623. PMID: 17595417.

D. Research Support

Ongoing Research Support

NIH/NIA R01AG042525 7/01/13-06/31/18

Metabolic cost of daily activities in older adults

This study will determine the age-related differences in metabolic cost of common daily activities. We will also evaluate the impact that functional impairment has on the metabolic cost of performing daily activities. The study will provide a new understanding of the true metabolic intensity of performing daily tasks in older adults.

Role: Principal Investigator

NIH/NIA 1 UO1 AG022376-05 09/01/09-08/31/15

The LIFE Study

This is a multi-site Phase III randomized controlled trial of physical activity to prevent major mobility disability and cognitive decline in older adults. The results from the trial will definitively determine whether a physical activity intervention conducted over 4 years can prevent many age-related disabilities.

Role: Principal Investigator of the Florida Field Center (Study PI: Pahor)

NIH/NHLBI Women's Health Initiative Extension Study 09/01/10-08/31/15

Contracts: N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221.

The primary goal of this project is to continue follow-up of the original cohort of the Women's health Initiative that began in 1994. A secondary goal is to conduct a second wave data collection surveys. Early stage investigators will be introduced to the WHI study, initiate secondary data analyses and collaborate on ancillary proposals.

Role: Co-Investigator and Early Stage Investigator (Regional PI: Shumaker)

NIH/NIA P30AG028740 6/1/12-3/31/17

Claude D. Pepper Older Americans Independence Center (OAIC)

This is the 2012-2017 refunded UF OAIC where Dr. Manini is a Co-Investigator. The major goals of this program are to assess the mechanisms leading to sarcopenia and functional decline, and to develop and test interventions for the treatment and prevention of physical disability in older adults.

Role: Co-Investigator

NIH/NIA 1R15AG040700 8/01/12-8/01/15

Comparative effects of resistance training protocols in older adults at risk of mobility disability

The proposed research will determine the comparative effectiveness resistance training regimens on older adults' muscle strength and size, their ability to perform everyday tasks (functional capacity), and their quality of life.

Role: Co-Investigator (PI: Summer Cook)

NIH/NCATS UL1 TR000064 4/01/12-4/01/14

Comorbidity Indices, Physical Function, and "Iatrogenic" Disability

This study was awarded through the clinical and Translational Science Award to the University of Florida. The Integrated Data Repository (IDR) is a large-scale "database" collecting and organizing information from across the UF Academic Health Center to support improved care and research. This project will utilize the IDR to study the onset and recovery of mobility limitation of elders admitted to the hospital.

Role: Principal Investigator

NIH/NIA R15AG040700 10/01/12-9/31/15

Comparative effects of resistance training protocols in older adults at risk of mobility disability

The proposed research will determine the comparative effectiveness resistance training regimens on older adults' muscle strength and size, their ability to perform everyday tasks (functional capacity), and their quality of life.

Role: Co-Investigator

NIH/NIA 5T32AG020499 05/01/11-04/30/14

Physical, cognitive and mental health in a social context

The purpose of this program is to train predoctoral researchers in biobehavioral and social approaches to aging, and to prepare them for settings including traditional disciplinary departments, clinical research environments, and multidisciplinary gerontology programs.

Role: Primary Mentor to Torrance Higgins (PI: Marsiske)

Regeneron Pharmaceuticals 06/01/13-06/01/14

A randomized, double-blind, placebo-controlled, parallel group, multicenter study of the safety and bioeffect of regn1033 with and without exercise in health subjects.

REGN1033 is a fully human monoclonal antibody that binds to myostatin and inhibits its function. This "proof of mechanism" study is planned to further evaluate the safety and tolerability of REGN1033, assess potential effects of REGN1033 on lean mass, muscle strength, and cardiac structure and function.

Role: Co-Principal Investigator

Research Support Completed During the Last Three Years

NIH/NIA R21 AG031974-01A209 09/01/09-08/30/12

Task-Specific Exercise for the Clinically Disabled

The major goals of this project are to determine the short and long-term responses of task-specific exercise (exercises that simulate daily living) in the pre-clinically disabled and to explore mechanisms of adaptation following task-specific exercise.

Role: Principal Investigator

NIH/NIA 1 P30 AG028740-S3 10/01/09-12/31/11

Mitochondrial function and fatigue in the elderly

This pilot study will supplement the current OAIC and is geared toward studying fatigue in the elderly and whether mitochondrial dysfunction contributes to the prevalence of fatigue in the elderly.

Role: Principal Investigator

Michael Marsiske, PhD

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Marsiske, Michael	Associate Professor, Dept. of Clinical and Health Psychology, University of Florida
eRA COMMONS USER NAME (credential, e.g., agency login) MMARSISKE	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Toronto, Toronto, ON, Canada	B.Sc.	05/87	Psychology
Pennsylvania State University, University Park, PA	M.S.	12/90	Human Development & Fam Studies
Pennsylvania State University, University Park, PA	Ph.D.	12/92	Human Development & Fam Studies
Max Planck Institute for Human Development, Berlin, Germany	Post-doc.	08/95	Psychology & Human Development

A. Personal statement

Dr. Marsiske is an Associate Professor with a background in cognitive psychology and cognitive neuroscience. Substantively, Dr. Marsiske's area of expertise is in the area of cognitive function in the context of aging. Funded projects have included the ACTIVE clinical trial, a ten-year controlled trial of cognitive interventions for older adults, with up to six waves of longitudinal follow up. Other recent studies have included a Robert Wood Johnson Foundation study of computer games as a cognitive intervention for older adults, and McKnight Brain Research foundation study of the unique and combined effects of cognitive training and cognitive engagement on the mental performance of very old adults. Marsiske also has served as Training Director of the NIA-funded predoctoral institutional training T32 program "Physical, Cognitive and Mental Health in Social Context" since 2003. Since 1996, he has also served as instructor of four graduate-level data analysis courses, including a course in multivariate methods and a course in growth modeling/survival analyses. Dr. Marsiske is also the Core Leader for the Recruitment, Retention and Adherence Core of the University of Florida NIA-funded Pepper Center. In this role, he has overseen the screening of over 8,000 older adults, and has successfully met recruitment goals for almost 20 large and small clinical trials. He also oversees the participant retention process for the Pepper Center, and has developed the local retention protocol.

B. Positions and Honors

Positions

1992-1995	Postdoctoral Research Fellow, Center for Psychology and Human Development, Max Planck Institute for Human Development and Education
2000-2003	Associate Director for Research, Institute on Aging; Associate Professor of Health Policy and Epidemiology, and Clinical and Health Psychology; Joint Professor of Psychology, UF
2003	Interim Director, Institute on Aging; Associate Professor of Clinical and Health Psychology; Joint Professor of Psychology, UF
1995-present	Assistant Professor, Institute of Gerontology and Department of Psychology, Wayne State University (Adjunct status since 2000)
2003-present	Associate Professor of Clinical and Health Psychology; Joint Professor of Psychology, UF
2007-present	Affiliate Faculty, Department of Epidemiology and Biostatistics, UF

Other Experience and Professional Memberships

1987-present	American Psychological Association (*Student affiliate 1987-1992*; Member 1992-present)
1988-present	Gerontological Society of America
1992-present	American Psychological Society
1995-present	Member, Executive Committee, Division on Adult Development and Aging, American Psychol. Association
2001-2003	Member, NIH Peer Review, NIA-S (Behavioral and Social Science of Aging)
2003	Member, Editorial Board, Journal of Gerontology: Psychological Sciences
2004	Member, Editorial Board, Aging, Neuropsychology and Cognition
2003-2005	Chair, NIH Peer Review, NIA-S (Behavioral and Social Science of Aging)
2005	Member, NIH Peer Review, Special Emphasis Panel (HRS/AHEAD)

2007	Member, NIH Peer Review, Special Emphasis Panel (Program Project), NIA
2003, 2009	Member, NIH Peer Review, Special Emphasis Panel (Roybal Centers)
2008-2009	American Society on Aging
2009	Member, NIH Peer Review, Special Emphasis Panel, Recovery Act Career Awards, RC2-SEP1 review
2009	Member, NIH Peer Review, Special Emphasis Panel, Research and Research Infrastructure "Grand Opportunities" (RC2).
2009	Member, NIH Peer Review, Special Emphasis Panel (Alzheimer's Disease Clinical Trials Special Emphasis Panel (BBBP-N[52]), National Institute on Aging, SBIR/STTR
1992-2010	International Society for the Study of Behavioral Development
2008, 2010	Member, NIH Peer Review, Special Emphasis Panel (P50 Supplement), NIA
2006, 2010, 2011	Member, NIH Peer Review, Special Emphasis Panel (T32), NIA
2012-2015	Chair-Elect, Membership Committee, Gerontological Society of America

Honors

1994	Recipient of Fellowship for Summer Institute on Successful Midlife Development from the MacArthur Foundation Research Network on Successful Midlife Development
1997	Recipient, 1997 Springer Award for Early Career Achievement in Research on Adult Development and Aging, Division 20 (Adult Development and Aging), American Psychological Association
2002	Fellow, Gerontological Society of America
2008, 2009	Recipient, Research Mentorship Award (for Statistics, Research Design and Measurement and Multivariate Statistics), Department of Clinical and Health Psychology, UF
2003, 2005, 2006, 2009, 2011	Recipient, Audrey Schumacher Award for Teaching Excellence (for Statistics, Research Design and Measurement and Multivariate Statistics), Department of Clinical and Health Psychology, UF
2011-2014	University of Florida Research Foundation Professorship

C. Selected Peer-reviewed Publications (2013)

(Students in italics)

Belchior, P., **Marsiske, M.**, *Sisco, S. M.*, *Yam, A.*, Bavelier, D., Ball, K., & Mann, W. C. (2013). Video game training to improve selective visual attention in older adults. *Computers in Human Behavior*, 29(4), 1318-1324. PMID: Pending, PMCID: Pending, NIHMSID: 492651, DOI http://dx.doi.org/10.1016/j.chb.2013.01.034, (PIF = 2.476).

Cook, S. E., *Sisco, S. M.*, & **Marsiske, M.** (2013, in press). Dual-task effects of simulated lane navigation and story recall in older adults with and without memory impairment. *Aging, Neuropsychology, and Cognition*, PMID: 23043546 PMCID: Pending, NIHMSID: 492857, DOI http://dx.doi.org/10.1080/13825585.2012.725459, (PIF = 1.715).

Dotson, V. M., Sozda, C. N., **Marsiske, M.**, & Perlstein, W. M. (2013, in press). Within-session practice eliminates age differences in cognitive control. *Aging, Neuropsychology, and Cognition*, PMID: 23116428 PMCID: PMC3655128, DOI http://dx.doi.org/10.1080/13825585.2012.736469, (PIF = 1.715).

Dzierzewski, J. M., Buman, M. P., Giacobbi, P. R., Roberts, B. L., *Aiken Morgan, A.*, **Marsiske, M.**, & McCrae, C. S. (2013, in press) Exercise and Sleep in Community-Dwelling Older Adults: Evidence for a Reciprocal Relationship. *Journal of Sleep Research*. PMID: pending, PMCID: pending, NIHMSID: 503190, DOI: pending, (PIF = 3.813).

Dzierzewski, J. M., **Marsiske, M.**, *Aiken Morgan, A.*, *Buman, M. P.*, Giacobbi Jr., P. R., Roberts, B., & McCrae, C. S. (2013, in press). Cognitive inconsistency and practice-related learning in older adults. *The Journal of Gerontopsychology and Geriatric Psychiatry*, PMID: pending PMCID: pending, NIHMSID: 501549, DOI: pending, (PIF = 0.28** approx).

Giacobbi, P. R., Jr., *Buman, M. P.*, *Dzierzewski, J.*, *Aiken-Morgan, A. T.*, Roberts, B., **Marsiske, M.**, Knutson, N., & Smith-McCrae, C. (2013, in press). Content and perceived utility of mental imagery by older adults in a peer-delivered physical activity intervention. *Journal of Applied Sport Psychology*. PMID: Pending PMCID: Pending, NIHMSID: 493068, DOI pending, (PIF = 1.547).f

Gross, A. L., Brandt, J., Bandeen-Roche, K., Carlson, M. C., Stuart, E. A., **Marsiske, M.**, & Rebok, G. R. (2013, in press). Do older adults use the Method of Loci? Results from the ACTIVE Study. *Experimental Aging Research*. PMID: Pending, PMCID: Pending, NIHMSID: 493534, DOI pending, (PIF = 1.306).

Gross, A. L., Rebok, G. W., Brandt, J., Tommet, D., **Marsiske, M.**, & Jones, R. N. (2013). Modeling Learning and Memory Using Verbal Learning Tests: Results from ACTIVE. *Journals of Gerontology: Psychological Sciences*, 68(2), 153-167. PMID: 22929389, PMCID: Pending, NIHMSID: Pending, DOI http://dx.doi.org/ 10.1093/geronb/gbs053, (PIF = 3.169).

Hekler, E.B., *Buman, M.P.*, Poothakandiyil, N., Rivera, D.E., *Dzierzewski, J.M.*, *Aiken Morgan, A. T.*, McCrae, C.S., Roberts, B.L., **Marsiske, M.**, & Giacobbi, Jr. P.R. (2013, in press) Exploring behavioral markers of long-term physical activity maintenance: A case study of system identification modeling within a behavioral intervention. *Health Education & Behavior*. PMCID: Pending, NIHMSID: 493611, DOI pending, (PIF = 1.536).

Jones, R. N., **Marsiske, M.**, Ball, K., Rebok, G., Willis, S. L., Morris, J. N., & Tennstedt, S. L. (2013, in press). The ACTIVE cognitive training interventions and trajectories of performance among older adults. *Journal of aging and health*. PMID: 23103453, PMCID: Pending, NIHMSID: 447584, DOI http://dx.doi.org/10.1177/0898264312461938, (PIF = 1.936).

Marsh, A. P., Kennedy, K., Lovato, L., Castro, C., Domanchuk, K., Glynn, N. W., McDavitt, E., Rodate, R., **Marsiske, M.**, McGloin, J., Groessl, E. J., Pahor, M., & Guralnik, J. M. (2013, in press) Lifestyle Interventions and Independence for Elders (LIFE) Study: Recruitment and baseline characteristics *Journal of Gerontology: Medical Sciences*. PMID: 23716501 PMCID: Pending, NIHMSID: pending, DOI http://dx.doi.org/10.1093/gerona/glt064, (PIF = 4.598).

Marsiske, M., *Dzierzewski, J. M.*, *Thomas, K. R.*, Kasten, L., Jones, R., Johnson, K., Willis, S. L., Ball, K., & Rebok, G. W. (2013, in press) Race-related Disparities in Five-year Cognitive Change in Untrained ACTIVE Participants. *Journal of Aging and Health*. PMID: Pending, PMCID: Pending, NIHMSID: 501124, DOI pending, (PIF = 1.936).

Nocera, J., Stegemoller, E. L., Malaty, I., Okun, M., **Marsiske, M.**, & Hass, C. (2013). Using the Timed Up and Go Test in a clinical setting to predict falling in Parkinson's Disease. Archives of Physical Medicine and Rehabilitation. *Psychiatry*. PMID: 23473700 PMCID: Pending, NIHMSID: pending, DOI http://dx.doi.org/10.1016/j.apmr.2013.02.020, (PIF = 2.655).

Rexroth, D. F., **Marsiske, M.**, Rebok, G. W., Tennstedt, S. L., Xu, Y., & Unverzagt, F. W. (2013, in press). Relationship of Demographic and Health Factors to Cognition in Older Adults in the ACTIVE Study. (2013, in press) *Journal of Aging and Health*. PMID: Pending, PMCID: Pending, NIHMSID: 470068, DOI pending, (PIF = 1.936).

Roncoroni, J., *Nghiem, K.*, *Wall, W.*, **Marsiske, M.**, Tucker, C. M. (2013, in press). Validation of a patient-centered culturally sensitive clinic environment inventory using a national sample of adult patients, *Journal of Transcultural Nursing*. PMCID: Pending, NIHMSID: pending, DOI pending, (PIF = 0.933).

Sisco, S. M., **Marsiske, M**, Gross, A. L., & Rebok, G. W. (2013, in press). The Influence of Cognitive Training on Older Adults' Recall for Short Stories. *Journal of Aging and Health*. PMID: Pending, PMCID: Pending, NIHMSID: 470077, DOI pending, (PIF = 1.936).

Tucker, C. M., *Butler, A.*, *Kaye, L. B.*, *Nolan, S. E. M.*, *Flenar, D. J.*, **Marsiske, M.**, Bragg, M., Hoover, E., & Daly, K. (2013, in press) Impact of a culturally sensitive health self-empowerment workshop series on health behaviors/lifestyles, BMI, and blood pressure of culturally diverse overweight/obese adults. *American Journal of Lifestyle Medicine*. PMCID: Pending, NIHMSID: 494656, DOI pending, (PIF = not available).

Tucker, C. M., *Nghiem, K. N*, **Marsiske, M**, & Robinson, A. C. (2013, in press) Validation of a patient-centered culturally sensitive health care provider inventory using a national sample of adult patients. *Patient Education and Counseling*. PMCID: Pending, NIHMSID: 493652, DOI pending, (PIF = 2.929).

Yam, A & **Marsiske, M.** (2013, in press). Cognitive Longitudinal Predictors of Older Adults' Self-Reported IADL Function. *Journal of Aging and Health*. PMID: Pending, PMCID: Pending, NIHMSID: 492578, DOI pending, (PIF = 1.936).

Zahodne, L. B., **Marsiske, M.**, & Bowers, D. (2013). A latent class analysis of psychological disturbance in Parkinson's disease. *International journal of geriatric psychiatry*. PMID: 23307695 PMCID: PMC3656148, NIHMSID: 492614, DOI http://dx.doi.org/10.1002/gps.3927, (PIF = 2.419).

Zlatar, Z. Z., Towler, S., McGregor, K. M., *Dzierzewski, J. M.*, Bauer, A., Phan, S., Cohen, M., **Marsiske, M.**, Manini, T. M., & Crosson, B. (2013). Functional language networks in sedentary and physically active older adults. *Journal of the International Neuropsychological Society*, 19, 1-10. PMID: 2345843; PMCID: PMC3691286, NIHMSID: 493121, DOI: http://dx.doi.org/10.1017/S1355617713000246, (PIF = 3.445).

D. Research Support

Ongoing Research Support

T32 AG020499 (Marsiske) 05/01/2013-04/30/2018

National Institute on Aging

Physical, Cognitive and Mental Health in Social Context

The major goals of this project are to train pre-doctoral researchers in the behavioral theories, methodologies and analyses needed to address questions of health, independence and functioning in older adults.

U01 AG022376 (Pahor) 09/01/2009-08/31/2015
National Institute on Aging
The LIFE Study
The major goals of this project are to investigate the effects of physical activity on mobility and independence in sedentary and frail adults aged 70 and older.

P30 AG028740 06/01/2007-03/31/2017
(Pahor; Marsiske Core Leader)
National Institute on Aging
Claude Denson Pepper Older Americans Independence Center
The major goals of this project are to provide infrastructure (administration, recruitment, clinical/pilot/developmental research support, biostatistics/data management) for research on the overarching themes of Sarcopenia and Disability

Number pending (Levy) 10/01/2013-09/30/2016
Veteran's Administration
Virtual Environments for Therapeutic Solutions (VETS) mTBI/PTSD Phase II
The major goals of this project are to develop a set of virtual environments (e.g., grocery store) to facilitate testing of, and intervention with, veterans with mild TBI and PTSD in the area of adaptive functional cognition

Completed Research Support (completed in the last three years only)
U01 AG014276 (Marsiske) 05/01/2008-03/31/2013
National Institute on Aging
ACTIVE Phase III: UF/WSU Field Site
The major goals of this project are to investigate the long term effects of cognitive training on everyday functioning, independence and well-being in older adults.

No number assigned 11/01/2010-04/30/2013
(Bowers; Marsiske Co-PI)
McKnight Brain Institute
VITAL: Village Interactive Training and Learning Study
The major goals of this project are to investigate the effects of physical exercise pre-dosing on cognitive plasticity (cognitive training responsiveness) in older adults.

T32 AG020499 (Marsiske) 05/01/2008-04/30/2013
National Institute on Aging
Physical, Cognitive and Mental Health in Social Context
The major goals of this project are to train pre-doctoral researchers in the behavioral theories, methodologies and analyses needed to address questions of health, independence and functioning in older adults.

R21 AG031974 (Manini) 09/15/2009-08/31/2011
National Institute on Aging
Task Specific Exercise for the Clinically Disabled
The major goals of this project are to investigate whether task-specific (ecologically valid) exercise has differential effects on the prevention of disability in older adults, relative to traditional aerobic/strength training.

No number assigned 02/01/2008-01/31/2012
(Anton/Manini)
McKnight Brain Institute
Resveratrol supplementation to improve memory and physical dysfunction in older adults
The major goals of this project are to investigate the effects of resveratrol supplementation on cognitive performance and inflammatory markers in older adults.

64441 (Belchior/Marsiske) 05/01/2008-07/31/2010
Robert Wood Johnson Foundation
Action video games to improve everyday cognitive function in older adults
The major goals of this project are to investigate the effect of an action video game-based intervention on the visual attention and processing of older adults

F31 AG034002 (Sisco) 01/01/2010-12/31/2011
National Institute on Aging
Neighborhood Influences In Cognitive Level And Training Gains In The ACTIVE Study
The major goals of this NRSA predoctoral training grant are to investigate whether neighborhood characteristics (socioeconomic position, facilities supporting health and psychological function) of ACTIVE participants are associated with their baseline cognitive function and/or response to initial training.

F31 AG032802 05/21/2009-05/20/2011
(Dzierzewski, co-mentor McCrae)
National Institute on Aging
Predicting Cognitive Inconsistency From Physical Activity And Sleep In Late-Life
The major goals of this NRSA predoctoral training grant are to investigate the coupling of cognition, sleep and activity engagement over an 18-week period in a sample of sedentary midlife and older adults.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Dr. Brandi K. Ormerod	Associate Professor
eRA COMMONS USER NAME (credential, e.g., agency login) BORMEROD	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Queen's University, Kingston, ON, Canada	B.Sc.	1998	Biopsychology
University of British Columbia, BC, Canada	Ph.D.	2003	Neuroscience
Stanford University, Stanford, CA, USA	Postdoctoral	2006	Stem Cell Sciences

A. Personal Statement

The goal of my research program is to understand how ongoing neurogenesis contributes to olfactory system and hippocampal integrity, how age- or disease-associated changes in neurogenesis impact cognition and how to exploit endogenous and transplantable neural progenitor cells for neural repair. We employ a multidisciplinary approach to address these questions. In collaboration with Dr. Tom Foster's laboratory we have discovered that exposure to an enriched environment or daily exercise can rejuvenate hippocampal neurogenesis and hippocampus-dependent spatial memory, perhaps by modulating cytokines in the blood and brain. With the generous support of the McKnight Brain Institute – Age-related Memory Loss Panel, we are expanding this work to test whether olfactory neurogenesis declines coincidentally with hippocampal neurogenesis in aged rats or whether the declines are region-specific and associated with distinct cognitive impairments and region-specific inflammatory biomarkers along with Dr. Jennifer Bizon.

B. Positions and Honors

Positions and Employment

1996-1998 Undergraduate Research Assistant in Dr. Beninger's Behavioral Pharm Laboratory (Queen's)
1997-1998 Undergraduate Research Assistant in Dr. Weisman's Avian Bioaccoustics Laboratory (Queen's)
1997-1998 Undergraduate Teaching Assistant for 4th yr Behavioral Pharmacology (Queen's University)
1998-2003 Teaching assistant and laboratory instructor for 5 different graduate and undergrad courses at UBC
1998-2003 Graduate Research Assistant in Dr. Liisa Galea's Behavioral Neuroendocrinology Lab (UBC)
2003-2006 Postdoctoral Stem Cell Researcher, Dr. Theo Palmer's Stem Cell Lab, Stanford University
Since 11/2006 - Assistant Professor, Biomedical Engineering Dept, University of Florida
- Developed 6 courses (4 graduate/2 undergraduate)

Since 11/2011 – Joint Faculty, Neuroscience Dept, University of Florida

Awards/Honors

1998 Faculty of Graduate Studies Travel Award (UBC; CDN$400)
1999 Natural Sciences and Engineering Research Council of Canada Scholarship A (UBC; $34,600)
2001 Natural Sciences and Engineering Research Council of Canada Scholarship B (UBC; $38,400)
2000 Killam Predoctoral Fellowship (UBC; CDN$44,000 - $24,000 top-up accepted)
2001 Killam Predoctoral Fellowship Travel Award (UBC; CDN$1,500)
2001 Alzheimers Society of Canada Predoctoral Fellowship (UBC; CDN$44,000 – declined)
2001 Invited to introduce UBC president Dr. Martha Piper at the first Nobel Awardee Michael Smith Honorary "Women at the Frontiers of EXXcellence" Conference opening ceremony
2002 UBC Brain Research Centre "3D Microscopy of Living Cells Course" scholarship (US$2,250)
2003 Society for Neuroscience Chapters Travel Award (US$735)
2003 Michael J. Fox Foundation Postdoctoral Fellowship (US$78,000)
2003 Natural Sci and Eng Research Council of Canada Post Doc Fellowship (Stanford; $40,000)
2003 NIH CHOC Human Embryonic Stem Cell Course (Burnham Inst; Scholarship Bursary; $1,500)
2004-2006 Chair of the Stanford Brain Food Bimonthly Seminar Series
Since 2007 UF College of Engineering Faculty Track Graduate Student Mentor

Committees and Service

2007	Scientific Consultant on Aging and Cloning to the American Federation for Aging Research
Since 2007	Maryland Funded TEDCO Stem Cell Competition Peer Review Committee
Since 2007	Ad Hoc Reviewer U Washington Alzheimer's Disease Research Center Competition
2008/9	UF Biomedical Engineering Faculty Search Committee
2008/9	UF Neuroscience Faculty Search Committee
Since 2009	Ad Hoc Reviewer for the National Science Foundation – Integrative Organismal Systems / BIO
Since 2010	Ad Hoc Reviewer for the US-Israel Binational Science Foundation
Since 2010	Ad Hoc Reviewer Agency for Science, Technology and Research (Korea)
Since 2011	Reviewing Editor for Frontiers in Aging Neuroscience
Since 2013	New York State Department of Health and the Empire State Stem Cell Board NYSTEM program
Since 2013	Editorial Board Advances in Neuroscience
Since 2013	NSF Career proposal review committee

C. Peer-reviewed Publications

1. Asokan A., Ball A.G., Laird C., Hermer L., and *Ormerod BK* (under review). Desvenlafaxine may accelerate neuronal maturation in the dentate gyri of adult male rats. *Neuroscience*.

2. Qia X, Shana Z, Jia Y, Guerra V, Alexander JC, **Ormerod BK**, Bruijnzeel AW (under review) Sustained AAV-mediated overexpression of CRF in the central amygdala diminishes the depressive-like state associated with nicotine withdrawal in rats. *Molecular Psychiatry*.

3. Hajihashemi MZ, Zhang T, **Ormerod BK**, Jiang H (under review). Non-invasive detection of seizure activity using time-series analysis of light scattering images in a rat model of generalized seizure. **Neural Engineering**.

4. Maden, M., Manwell L.A., **Ormerod B.K.** (2013). Proliferation zones in the axolotl brain and regeneration in the telencephalon. *Neural Development*, 8:1-15. PMID: 23327114; PMCID: 3554517.

5. Speisman, RB, Kumar A, Rani A, Pastoriza JM, Severance JE, Foster TC and **Ormerod BK** (2013). Environmental enrichment restores neurogenesis and rapid acquisition in aged rats. *Neurobiol Aging*. 34:263-274. PMID: 22795793; PMCID: 3480541.

6. Speisman RB, Kumar A, Rani A, Foster TC and **Ormerod BK** (2013). Daily exercise improves memory, stimulates hippocampal neurogenesis and modulates immune and neuroimmune cytokines in aging rats. *Brain, Behavior and Immunity*, 28:25-43. PMID: 23078985; PMCID: 3545095.

7. **Ormerod BK**, Hanft SJ, Asokan A, Haditsch U, Lee SW and Palmer TD (2013). PPARγ activation prevents impairments in spatial memory and neurogenesis following transient illness. *Brain, Behav Immun*, 29:28-38. PMID: 23108061; PMCID: 3570721.

8. Ogle,WO, Speisman, RB, and **Ormerod BK** (2013). Potential of treating age-related depression and cognitive decline with nutraceutical approaches: A mini-review. *Gerontology*, 59:23-31. PMID: 22947921; doi: 10.1159/000342208

9. Bañuelos, C, LaSarge, CL, McQuail J, Hartman JJ, Gilbert RJ, **Ormerod BK**, Bizon JL (2013). Age-related changes in rostral basal forebrain cholinergic and GABAergic projection neurons: relationship with spatial impairment. *Neurobiology of Aging*, 34:845-862. PMID: 22817834; PMCID: 3632262.

10. Lee SW, Haditsch U, Monje ML, Cord BJ, Guzman R, Kim S, Boettcher C, Priller J, **Ormerod BK** and Palmer TD (2013). Absence of CCL2 is sufficient to restore hippocampal neurogenesis following cranial irradiation. *Brain, Behavior and Immunity*, 30:33-44. PMID: 23041279; PMCID: 3556199.

11. Munikoti VV, Hoang-Minh, LB and **Ormerod BK** (2012). Enzymatic digestion improves the purity of harvested cerebral microvessels. *Journal of Neuroscience Methods* 207:80-85. JCR Impact Factor 2.100.

12. Stephens CL, Toda H., Palmer TD, DeMarse TB and **Ormerod BK** (2012). Adult neural progenitor cells reactivate superbursting in mature neural networks. *Experimental Neurology*, 234:20-30. PMID: 22198136; doi: 10.1016/j.expneurol.2011.12.009.

13. Bruijnzeel AW, Bauzo RM, Munikoti V, Rodrick GB, Yamada H, Fornal CA, **Ormerod BK**, Jacobs BL (2011). Tobacco smoke diminishes neurogenesis and promotes gliogenesis in the dentate gyrus of adolescent rats. *Brain Res*, 1413:32-42. PMID: 21840504; doi: 10.1016/j.brainres.2011.07.041.

14. Chen Z, Phillips LK, Gould E, Campisi J, Lee SW, **Ormerod BK**, Zwierzchoniewska M, Martinez OM, Palmer TD. (2011). MHC mismatch inhibits neurogenesis and neuron maturation in stem cell allografts. *PLoS One*. 6(3):e14787. PMID: 21479168; PMCID: 3068158.

15. Seifert AW, **Ormerod BK***, Cohn MJ* (2010). Sonic hedgehog regulates cell cycle kinetics during morphogenesis. *Nature Communications*. 1:1-9. *Corresponding Authors. PMID: 20975695; PMCID: 2964453.

16. Stratmann G, Sall JW, Rehan SA, May L, Rau V, McCulloch CE, **Ormerod BK**, Zusmer EJ, Bell JS, Lee, MT, Guggenheim J., Firouzian A, Dai R. (2009). Effect of hypercarbia and isoflurane on brain cell death and neurocognitive dysfunction in 7-day-old rats. *Anesthesiology*, 110:849-861. PMID: 19293696; doi: 10.1097/ALN.0b013e31819c7140.

17. Keravala A, **Ormerod B.K.**, Palmer TD, Calos M (2008). Long-term gene expression in mouse neural progenitor cells modified with PhiC31 integrase. *Journal of Neuroscience Methods*, 173:299-305.

18. **Ormerod BK.**, Palmer TD and Caldwell MA (2008). Neurodegeneration and Cell Replacement. *Philosophical Transactions of the Royal Society: Biological Sciences*, 363; 153-170. PMID: 17331894; PMCID: 2605492.

19. Buckwalter MS, Yamane M, Coleman BS, **Ormerod BK**, Chin JT, Palmer T, Wyss-Coray T (2006). Chronically increased transforming growth factor-beta1 strongly inhibits hippocampal neurogenesis in aged mice. *Am J Pathol*. 169:154-64. PMID: 16816369; PMCID: 1698757.

20. Nagy AI, **Ormerod BK**, Mazzucco C. and Galea LAM. (2006) Estradiol-Induced Enhancement in Cell Proliferation is mediated through Estrogen Receptors in the Dentate Gyrus of Adult Female Rats. *Drug Development Research*, 66; 1-8. Current JCR Impact Factor 1.109.

21. Hill MN, Patel S, Carrier EJ, Rademacher DJ, **Ormerod BK**, Hillard CJ, Gorzalka BB (2005) Downregulation of endocannabinoid signaling in the hippocampus following chronic unpredictable stress. *Neuropsychopharmacology*. 30:508-15 Current JCR Impact Factor 6.685.

22. **Ormerod BK**, Lee TT, Galea LA. (2004). Estradiol enhances neurogenesis in the dentate gyri of adult male meadow voles by increasing the survival of young granule neurons. *Neuroscience*, 128:645-54. PMID: 15381292.

23. **Ormerod BK**, Falconer EM and Galea LAM (2003). NMDA receptor activity and estradiol: Separate regulation of cell proliferation in the dentate gyrus of adult female meadow voles. *Endocrinology*, 179:155-163. PMID: 14596667.

24. **Ormerod BK** and Galea LAM (2003). Reproductive status influences the survival but not production of new cells in the dentate gyrus of adult male meadow voles. *Neurosci Letters*, 346:25-28. PMID: 12850539.

25. **Ormerod BK**, Lee TT-Y and Galea LAM (2003). Estradiol enhances but subsequently suppresses (via adrenal steroids) granule cell proliferation in the dentate gyrus of adult female rats. *J Neurobio* (now Developmental Biology), 55, 247-260. PMID: 12672021.

26. **Ormerod BK**, Beninger RJ (2002). Water maze versus radial maze: differential performance of rats in a spatial delayed match-to-position task and response to scopolamine. *Behav Brain Res*, 128, 139-152. PMID: 11796159.

27. **Ormerod BK** and Galea LAM (2001). Reproductive status regulates cell proliferation and survival in the dentate gyrus of adult female meadow voles: A possible role for estradiol. *Neurosci*, 102, 369-379. PMID: 11166123.

28. Galea LAM, Wide JK, Paine TA, Holmes MM, **Ormerod BK**, and Floresco SB (2001). High levels of estradiol disrupt conditioned placed preference learning, stimulus response learning and reference memory but have limited effects on working memory. *Behav Brain Res*, 126, 115-126. PMID: 11704257.

29. Beauchamp M., **Ormerod BK**, Jhamandas K, Boegman RJ and Beninger RJ (2000). Neurosteroids and reward: Allopregnanolone produces a conditioned place aversion in rats. *Pharm, Biochem, Behav*, 67, 29-35. PMID: 11113481.

30. Galea LAM, **Ormerod BK**, Sampath S, Kostaras X, Wilkie D.M. and Phelps M. (2000). Spatial working memory and hippocampal size across pregnancy in rats. *Hormones and Behavior*, 37, 86-95. PMID: 10712861.

D. Research Support for the Past 3 Years

Current

NIH R37 AG036800-03 – Foster (PI) 9/30/2010 – 8/31/2014

Signaling cascades and memory deficits during aging

The major goal of this MERIT award is to identify inflammatory and neuroinflammatory biomarkers that predict age-related changes in NMDAr signaling and hippocampus-dependent behavior in male rats. Dr. Ormerod's role on this award is to quantify circulating and central cytokines and chemokines across lifespan in male rats and relate them to measures of behavior in a rapid water maze task. No Overlap.

Role: Co-I (30% effort)

McKnight Brain Institute 6/30/2013-6/31/2014
Age-related Memory Loss Panel
Causes of and relationships between olfactory/hippocampal neurogenesis and age-related cognitive decline The major goal of this award is to quantify neurogenesis in samples already collected from young and aged male rats trained and tested in version of the water maze distinct from the one in the proposal. No Overlap.
Role: PI (10% effort)

DoD PR121769 – 09/2013 – 09/2016
Carney, King, Ormerod (Multiple PI)
Advancement of Somatostatin Gene Delivery for Disease Modification and Cognitive Sparing in Epilepsy
The major goal of this award is to investigate whether somatostatin expression increased through delivery with a viral vector minimizes seizure behavior through its effects on neuroinflammation and/or neurogenesis.
Role: Multiple PI (30% effort)

Pending
National Institute on Aging – Pending
5R37AG036800-03 – Foster (PI)
Signaling cascades and memory deficits during aging
The goal of this project is to understand the influence of Ca2+ signaling on spatial and working memory deficits that emerge in normal aging. No Overlap.
Role: Co-I (10% effort)

Completed Support
NSF – DGE-0802270 – 5/31/2010-5/31/2013
Rachel Speisman (student)
Using biomarkers to predict successful versus unsuccessful aging in rats.
The major goal of this award was to support the PhD student to identify biomarkers of age-related cognitive decline in male rats.
Role: Sponsor/Mentor

McKnight Brain Institute Age-related 6/1/2010 – 5/31/2012
Memory Loss Panel Award
Biomarkers of age-related cognitive decline
The major goal of this award is to identify immunomodulatory/neuroimmunomodulatory markers of age-related cognitive decline in rats.
Role: PI (10% effort)

NSERC/SSHERC/CIHR Canada Tri-Council 05/1/2011 – 08/1/2011
Michael Smith Foreign Study
Supplements Program
Laurie Manwell (Student)
Axolotl neurogenesis following brain injury
The major goal of this award was to support the PhD student to conduct her project at a foreign institution.
Role: Sponsor/Mentor

Ruth K. Broad Biomedical Research 6/1/2008 – 5/31/2010
Foundation Extramural Award
Neural stem cells and inflammation: Implications for Alzheimers disease
The major goal of this award is to understand how inflammation is transduced into neuroinflammation and to identify candidate inflammatory molecules that impact neural progenitor/stem cell behavior in young male mice.
Role: PI (30% effort)

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Matthew R. Sarkisian, Ph.D.	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) SARKISIAN01	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
Clemson University, Clemson, SC	B.S.	05/95	Biological Sciences
University of Connecticut, Storrs, CT	Ph.D.	12/01	Physiology and Neurobiology
Yale University, New Haven, CT	Postdoc	02/02-10/08	Neurobiology

A. Personal Statement

The goal of my research program is to better understand the molecular and cellular mechanisms that underlie both the development, function and plasticity of the cerebral cortex. Our studies focus on tiny hair-like structures called primary cilia, a type of 'cellular antenna' that extends from virtually all cell types in the cerebral cortex. We are exploring how cilia guide the development of different neural cell types, and the involvement of cilia in various age-related pathologies of the cortex ranging from deficits in intellectual capacity to aggressive brain tumors.

B. Positions and Honors

Positions and Employment

08/97-12/01	Graduate Student, Dept. of Physiology & Neurobiology, Univ. of Connecticut, Storrs, CT
02/02-01/08	Postdoctoral Associate/Fellow, Dept of Neurobiology, Yale Univ. School of Medicine, New Haven, CT
02/08-10/08	Associate Research Scientist, Dept of Neurobiology, Yale Univ. School of Medicine, New Haven, CT
10/2008-	Assistant Professor, Dept of Neuroscience, Univ. of Florida, Gainesville, FL

Honors and Research Awards

1995	George M. Savoy Junior Fellowship Award (Savoy Foundation for Epilepsy Research)
1996,2000	Armenian Students' Assoc. of America (ASA), Inc. Academic Scholarship
1999, 2000	University Predoctoral Fellowship, awarded by the UConn Neurosciences Steering Committee
2004-2005	James Hudson Brown-Alexander Brown Coxe Postdoctoral Fellowship (Yale University)
2006-2007	Eric W. Lothman Training Fellowship (Epilepsy Foundation of America Distinguished Postdoctoral Award)
2011,12,13	Recipient, Exemplary Teacher Award, University of Florida College of Medicine
2013	American Cancer Society Research Scholar

Professional and Memberships

1998-	Member of the Society for Neuroscience
2000-02,06	Member of the American Epilepsy Society
2007-09	Member of the New York Academy of Sciences
2010-	Member of the University of Florida Genetics Institute
2013-	Associate Member of the UF Heath Cancer Center

C. Selected Peer-Reviewed Publications *(from a total of 33 peer-reviewed publications)*:

1. **Sarkisian MR**, Tandon P, Liu Z, Yang Y, Hori A, Holmes GL, Stafstrom CE.(1997) Multiple kainic acid seizures in the immature and adult brain: ictal manifestations and long-term effects on learning and memory. *Epilepsia*, 38: 1157-1166.

2. **Sarkisian MR**, Rattan S, D'Mello S, LoTurco JJ (1999) Characterization of seizures in the flathead rat: a new genetic model of epilepsy in early postnatal development. *Epilepsia*, 40: 394-400.

3. **Sarkisian MR**, Frenkel M, Li W, Oborski JA, LoTurco JJ. (2001) Altered interneuron development in the cerebral cortex of the flathead mutant. *Cereb Cortex*, 11: 734-743.

4. **Sarkisian MR**, Li W, Di Cunto, F, D'Mello, SR, LoTurco JJ. (2002) Citron-kinase, a protein essential to cytokinesis in neuronal progenitors, is deleted in the flathead mutant rat. *J Neurosci*. 22: RC217 (1-5).

5. Li MO, **Sarkisian MR***, Mehal WZ, Rakic P, Flavell RA. (2003) Phosphatidylserine receptor is required for clearance of apoptotic cells. *Science* 302: 1560-1563.

6. Chi H, **Sarkisian MR***, Rakic P, Flavell RA. (2005) Loss of mitogen-activated protein kinase kinase kinase 4 (MEKK4) results in enhanced apoptosis and defective neural tube development. *Proc. Natl. Acad. Sci. (USA)* 102: 3846-3851.

7. **Sarkisian MR**, Bartley CB, Chi H, Nakamura F, Hashimoto-Torii K, Torii M, Flavell RA, Rakic P. (2006) MEKK4 signaling regulates filamin expression and neuronal migration. *Neuron* 52: 789-801.

8. Breunig JJ, **Sarkisian MR***, Arellano JI, Morozov YM, Ayoub A, Sojitra S, Wang B, Flavell RA, Rakic P, Town T. (2008) Primary cilia regulate hippocampal neurogenesis by mediating sonic hedgehog signaling. *Proc. Natl. Acad. Sci. (USA)* 105: 13126-13131.

9. **Sarkisian MR**, Bartley CM, Rakic P.(2008) Trouble making the first move: interpreting arrested neuronal migration in the cerebral cortex. *Trends Neurosci* 31: 54-61.

10. Anastas SB, Mueller D, Semple-Rowland SL, Breunig JJ, **Sarkisian MR§**. (2011) Failed cytokinesis of neural progenitors in citron kinase deficient rats leads to multi-ciliated neurons. *Cereb Cortex* 21: 338-344.

11. Wang Y, Yin X, Rosen G, Gabel L, Guadiana SM, **Sarkisian MR**, Galaburda AM, Loturco JJ. (2011) Dcdc2 knockout mice display exacerbated developmental disruptions following knockdown of doublecortin. *Neuroscience* 190: 398-408.

12. Arellano JI, Guadiana SM, Breunig JJ, Rakic P, **Sarkisian MR§**. (2012) Development and distribution of neuronal cilia in mouse neocortex. *J Comp Neurol* 520: 848-873.

13. **Sarkisian MR§**, Siebzehnrubl D (2012) Abnormal levels of Gadd45alpha in developing neocortex impair neurite outgrowth. *PLoS ONE* 7(9): e44207.

14. Guadiana SM, Semple-Rowland S, Daroszewski D, Madorsky I, Breunig JJ, Mykytyn K, **Sarkisian MR§**. (2013) Arborization of dendrites by developing neocortical neurons is dependent on primary cilia and type 3 adenylyl cyclase. *J Neurosci* 6; 2626-2638.

15. Siebzehnrubl FA, Silver DJ, Tugertimur B, Deleyrolle LP, Siebzehnrubl D, **Sarkisian MR**, Devers KG, Yachnis AT, Kupper MD, Neal D, Nabilsi NH, Kladde MP, Suslov O, Brabletz S, Brabletz T, Reynolds BA, Steindler DA. (2013) The ZEB1 pathway links glioblastoma initiation, invasion and chemoresistance. *EMBO Mol Med* 5: 1196-1212.

- **co-first author publication, §corresponding author*

D. Research Support

Ongoing Research Support

1) Source: **McKnight Brain Research Foundation at University of Florida**
   Type: Start-up funds
   Funding period: 10/03/08-10/02/14
   Role: PI

2) Source: **American Cancer Society**
   Title: "Targeting Therapy Resistant Cells in Glioblastoma"
   Funding period: 01/01/13-12/31/16
   Role: PI

3) Source: **Epilepsy Foundation of America**
   Title: Contribution of cilia defects to neuronal activity in developing cortex
   Funding period; 01/01/13-12/31/13
   Role: Mentor (Predoctoral fellowship to graduate student, Sarah Guadiana)

Completed Research Support

1) Source: American Cancer Society Chris DiMarco Institutional Research Grant Junior Investigator Award
   Title: "Towards Inhibiting Ciliogenesis to Prevent Glioblastoma"
   Funding Period: 12/01/10-11/30/11
   Role: PI

2) Source: **University of Florida McKnight Brain Institute Agency: Brain & Spinal Cord Injury Research Trust Fund (BSCIRTF)**
Title: "A Comparison of Pathogenic Processes in Acute Spinal Cord Injury and ALS"
Funding Period: 07/01/11-06/30/12
Role: Co-PI (with Dr. David Borchelt, Neuroscience)

3) Source: **University of Florida 2011 Research Opportunity Seed Fund Award from**
Title: "Mechanisms of Abnormal Brain Development in the VPA Model of Autism"
Funding Period: 05/01/11-04/30/13
Role: Co-PI (with Dr. Mark Lewis, Psychiatry)

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
John B Williamson	Assistant Professor
eRA COMMONS USER NAME (credential, e.g., agency login) WJOHNB	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
The Florida State University, FL	B.A.	1996	Psychology
Virginia Tech, Blacksburg, VA	M.S.	1999	Clinical Psychology
Virginia Tech, Blacksburg, VA	Ph.D.	2004	Clinical Psychology
University of Chicago	Internship Clinical Fellowship	2004	Neuropsychology
University of Illinois at Chicago	Research	2004-2006	Neuropsychology
University of Illinois at Chicago	Fellowship	2006-2008	Neuroscience

A. Personal Statement

I am a neuropsychologist. I am currently funded by a 5 year VA CDA-2 (K award equivalent) to examine the impact of chronic TBI on the development of PTSD continua symptoms, specifically disruptions in emotional cognition and physiology as they relate to changes in white matter integrity (e.g., uncinate fasciculus and anterior limb of the internal capsule). I was previously funded by an NIA F32 mechanism exploring similar issues in older patients with cerebrovascular disease. I currently have several aging projects underway including a normal aging project designed to assess changes in the salience of emotional memories with age. Further, I have submitted collaborative projects with David Clark, PhD on the impact of sensory feedback on fronto-subcortical resource allocation in walking. Under development are a series of grant projects geared at addressing autonomic/regional cerebral bloodflow impacts of modification of cardiac output on cognition/mood.

B. Positions and Honors

2012 – present	Assistant Professor Dept. of Neurology, University of Florida
2008 – present	Research Health Scientist Dept. of Veteran Affairs, Gainesville, FL
2008-2012	Research Assistant Professor Dept. of Neurology, University of Florida
2006 -2008	Research Fellow Depts. of Neurology and Psychiatry, University of Illinois
2004-2006	Clinical Fellow Dept. of Neurology, University of Illinois

C. Selected peer-reviewed publications (in reverse chronological order, 2012-2013)

1. Acosta LM, **Williamson JB**, Heilman KM. Agency and the Annunciation. *Journal of Religion and Health* 2013 [epub, ahead of print]. DOI 10.117/s10943-013-9724-y.
2. Behforuzi H., Burtis DB, **Williamson JB**, Stamps JJ, Heilman KM. Impaired initial vowel versus consonant letter-word fluency in dementia of the Alzheimer type. *Cognitive Neuroscience* 2013 (epub, ahead of print) 10.1080/17588929.2013.854200
3. Burtis DB, **Williamson JB**, Mishra M, Heilman KM. The blindside: Impact of monocular occlusion on spatial attention. *Journal of Clinical and Experimental Neuropsychology* 2013, in press.
4. Kabasakalian A, **Williamson JB**, Heilman KM. Hypometric allocentric and egocentric distance estimates in people with Parkinson's disease. *Cognitive and Behavioral Neurology* 2013.
5. **Williamson JB**, Lewis GF, Nyenhuis DL, Stebbins GT, Murphy C, Handelman M, Harden E, Heilman KM, Gorelick PB, Porges SW. The effects of cerebral white matter changes on cardiovascular responses to cognitive and physical activity in a stroke population. *Psychophysiology* 2012, in press.
6. Acosta, LMY, **Williamson JB**, Heilman KM. Which cheek did Jesus turn? *Religion, Brain & Behavior* 2012, in press.
7. Claunch J, Falchook A, **Williamson JB**, Fischler I, Jones E, Baum J, Heilman KM. Famous faces but not remembered spaces influence vertical line bisections. *Journal of Clinical and Experimental Neuropsychology* 2012, in press.
8. Falchook AD, Mosquera D, Finney GR, **Williamson JB**, Heilman KM. The relationship between semantic knowledge and conceptual apraxia in Alzheimer's disease. *Cognitive and Behavioral Neurology* 2012, in press.
9. Susveri K, Falchook A, **Williamson JB**, Heilman KM. Right up there: Hemispatial and hand asymmetries of altitudinal pseudoneglect. *Brain and Cognition* 2012, in press.

10. Harciarek M, **Williamson JB**, Haque S, Burtis D, Heilman KM. Ipsilateral neglect from a subcortical lesion: The effects of spatial position, distractors, and repeated trials. *Cognitive and Behavioral Neurology* 2012, 25, 42-49.
11. Harciarek M, **Williamson John B**, et al. Risk factors for selective cognitive decline in dialyzed patients with end stage renal disease: evidence from verbal fluency analysis. *Journal of the International Neuropsychological Society* 2012, 18, 162-167.

Research Support

2012-2017 1 LK2RX000707-01 CDA-2 (VA-K) *White matter changes and mild TBI: Emotional and autonomic consequences*. Funded by the Department of Veterans Affairs: **Williamson, Principal Investigator** Co-Is: Heilman, Porges, Crosson $898,188

2009-Present *Alzheimer's Disease Initiative (Heilman)* State of Florida, Dept. of Elder Affairs Memory Disorder Clinics. 1988 – Current Heilman, PI, **Williamson CO-I** ~$249,000/year

2012-2016 Merit Review Award. *Vertical Neglect.* Funded by the Department of Veterans Affairs: 1Heilman, PI. **Williamson Co-I**, ~$500,000

2008-2012 MHBB; 10. Merit Review Award. *Approach-Avoidance Spatial Neglect.* Funded by the Department of Veterans Affairs: Heilman, PI. **Williamson, Co-I** $456,000

2006 - 2008 1 F32 AG027648-01A1 *White matter integrity and autonomic stress response.* Funded by the National Institute of Aging; **Principal Investigator** $100,224

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Woods, Adam Joshua	Assistant Professor of Aging and Geriatrics Research
eRA COMMONS USER NAME (credential, e.g., agency login) AJWOODS	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Alabama at Birmingham	B.S.	05/03	Psychology
George Washington University	Ph.D.	05/10	Cognitive Neuroscience
University of Pennsylvania	Post-Doctoral	06/13	Cognitive Neuroscience

A. Personal Statement

Dr. Adam J. Woods is an Assistant Professor in the Department of Aging and Geriatric Research and the Cognitive Aging and Memory Clinical Translational Research Program in the Institute of Aging at the University of Florida. His active program of research investigates precursors and neuroimaging-based biomarkers of cognitive frailty in older adults. He has a strong background with multi-disciplinary neuroscience methodologies (MRI/fMRI, electrophysiology, non-invasive brain stimulation), extensive experience with aging-related disorders, and past research with neurological diseases. His present research investigates markers and mechanisms of susceptibility to cognitive impairment following acute illness/injury (urinary tract infection, knee replacement surgery, etc.). This work uses modern neuroimaging and biomarkers methods to investigate mechanisms of cognitive frailty in older adults.

B. Positions and Honors

Positions and Employment

2010-2013 Post-Doctoral Fellow, Department of Neurology, University of Pennsylvania, Philadelphia, PA
2013- Assistant Professor, Department of Aging and Geriatric Research, University of Florida, Gainesville, FL
2013- Cognitive Aging and Memory Clinical Translational Research Program Scholar, University of Florida, Gainesville, FL

Other Experience and Professional Memberships

2004- Member, American Psychological Association
2005- Member, Vision Science Society
2007- Ad Hoc Reviewer, Neurocase
2007-2009 Ad Hoc Reviewer, Journal of Clinical and Experimental Neuropsychology
2008- Ad Hoc Reviewer, Journal of Experimental Psychology: Human Perception & Performance
2010- Member, Cognitive Neuroscience Society
2010- Member, Society for Neuroscience
2010- Ad Hoc Reviewer, PM&R
2011- Ad Hoc Reviewer, Yale Journal of Biology and Medicine
2012- Ad Hoc Reviewer, Journal of Cognitive Neuroscience
2012- Ad Hoc Reviewer, Psychonomic Bulletin & Review
2012- Ad Hoc Reviewer, Journal of Experiment Child Psychology
2012- Ad Hoc Reviewer, Frontiers in Perception Science
2012- Ad Hoc Reviewer, International Journal of Clinical Practice
2013- Ad Hoc Reviewer, PLoS ONE
2013- Ad Hoc Reviewer, Experimental Gerontology
2013- Ad Hoc Reviewer, Rehabilitation Psychology
2013- Ad Hoc Reviewer, Journal of Experimental Psychology: Learning, Memory, and Cognition

Academic and Professional Honors

2006-2009 National Science Foundation (NSF) Graduate Research Fellowship
2008 Research Enhancement Fund grant award for advanced dissertation research, GWU
2009-2010 Graduate Research Fellowship, GWU

2009-2010	Thelma Hunt Research Fellowship in Psychology, GWU
2010-2013	Post-Doctoral Fellowship, Intellectual and Developmental Disabilities Research Center, Children's Hospital of Philadelphia
2013-present	CAM-CTRP Scholar, Cognitive Aging and Memory Clinical Translational Research Program, University of Florida, Gainesville, FL
2013	Nominated as a Junior Fellow to the World Academy of Arts and Sciences

C. Selected Peer-Reviewed Publications

Most relevant to the current application

1. **Woods, A.J.**, Cohen, R.A., Pahor, M. (2013). Cognitive frailty: frontiers and challenges. *Journal of Nutrition, Health, and Aging*, 17, 741-743.
2. **Woods, A.J.**, Philbeck, J.W., & Wirtz, P. (2013). *Hyper-arousal decreases human visual thresholds.* PLoS ONE, 8(4), e61415. doi: 10.1371/journal.pone.0061415
3. **Woods, A.J.**, Goksun, T., Chatterjee, A., Zelonis, S., Mehet, A., Smith, S. (2013). The development of organized visual search. *Acta Psychologica*, 143(2), 191-199. doi: 10.1016/j.actpsy.2013.03.008
4. **Woods, A.J.**, Mark, V.W., Pitts, A., & Mennemeier, M. (2011). Pervasive cognitive impairment in acute rehabilitation patients "without" brain injury. *PM&R*, 3(5), 426-432.
5. **Woods, A. J.**, Philbeck, J. W., Chelette, K., Skinner, R. D., Garcia-Rill, E., & Mennemeier, M. (2011). Cold pressor stimulation diminishes P50 amplitude in normal subjects. *Acta Neurobiologiae Experimentalis*. 71, 348-358.

Additional recent publications of importance to the field

1. Mark, V.W., **Woods, A.J.**, Ball, K.K., Roth, D.L., Mennemeier, M. (2004). Disorganized search is not a consequence of neglect. *Neurology*. 63(1):78-84.
2. Mennemeier, M., Pierce, C., Dowler, R., Chatterjee, A., Anderson, B., Jewell, G., **Woods, A.J.**, Mark, V.W. (2005). Biases in attentional orientation and magnitude estimation explain crossover: neglect is a disorder of both. *Journal of Cognitive Neuroscience*, 17, 1194-1211.
3. Taylor-Cooke, P.A., Ricci, R.; Baños, J.H., Zhou, X., **Woods, A.J.**, Mennemeier, M.S. (2006). Perception of motor strength and stimulus magnitude are correlated in stroke patients. *Neurology*, 66, 1444-1446.
4. Mark, V.W., **Woods, A.J.**, Mennemeier, M., Abbas, S., Taub, E. (2006). Cognitive screening for CI therapy in the outpatient clinic. *Neurorehabilitation*, 21, 139-46.
5. **Woods, A.J.**, Mennemeier, M., Garcia-Rill, E., Meythaler, J., Mark, V.W., Jewell, G.R., Murphy, H. (2006). Bias in magnitude estimation following left hemisphere injury. *Neuropsychologia*, 44, 1406-12.
6. **Woods, A.J.**, Mark, V.W. (2007). Convergent validity of executive organization measures on cancellation. *Journal of Clinical and Experimental Neuropsychology*, 29(7), 719-723.
7. **Woods, A. J.**, Mennemeier, M., Garcia-Rill, E., Huitt, T., Chelette, K. C., McCullough, G., Munn, T., Brown, G., Kiser, T. S. (2012). Improvement in arousal, visual neglect, and perception of stimulus intensity following cold pressor stimulation. *Neurocase*, 18, 115-122.
8. **Woods, A.J.**, Lehet, M., Chatterjee, A. (2012). Context modulates the contribution of time and space in causal inference. *Frontiers in Psychology*, 3, 371. doi: 10.3389/fpsyg.2012.00371
9. Amorapanth, P., Kranjec, A., Bromberger, B., Lehet, M., Widick, P., **Woods, A. J.**, Kimberg, D. Y. & Chatterjee, A. (2012). Language, perception, and the schematic representation of spatial relations. *Brain & Language*, 120, 226-236.
10. Minhas, P., Bikson, M., **Woods, A.J.**, Rosen, A., Kessler, S. (2012). Transcranial direct current stimulation in the pediatric versus adult brain: A computational modeling study. *IEEE Xplore: EMBC*, 63, 859-862. doi: 10.1109/EMBC.2012.6346067.

D. Research Support

Ongoing Research Support

2 P30 AG028740-06 Pahor (PI) 04/15/12-03/31/17

Claude D. Pepper Older Americans Independence Center (OAIC) Pilot Project:

A pilot study to evaluate the role of brain integrity on post-hospital sarcopenia (Pilot PI: Manini)

The goal of this funding is to provide pilot data on the role of brain white matter integrity in post-hospital physical decline.

Role: Co-PI

2 P30 AG028740-06 Pahor (PI) 04/15/12-03/31/17

Claude D. Pepper Older Americans Independence Center (OAIC) RC1 Development Project:

Development of Clinical Methods to Evaluate Neural Function in Aging (Project PI: Buford)

The goal of this development project is to provide support for the enhancement of the methodological skills of Pepper Center investigators to include modern methods of diffusion tensor imaging analysis.

Role: Co-I

McKnight Brain Foundation Cohen (PI) 10/15/13-10/15/16
Cognitive Aging and Memory Clinical Translational Research Program Pilot Study: The ACTIVE Brain Study
The goal of this funding is to provide neuroimaging biomarkers of successful aging.
Role: Co-I

McKnight Brain Foundation **Woods (PI)** 11/1/13-11/1/15
CAM-CTRP Pilot Study: Brain Arousal Mechanisms in Aging
The goal of this funding is to investigate the role of brain arousal mechanisms in cognitive and physical decline associated with advanced age.
Role: PI

McKnight Brain Foundation **Woods (PI)** 12/1/13-12/1/15
CAM-CTRP Pilot Study: Electrophysiological markers of aging
The goal of this funding is to identify biomarkers of aging using event-related electrophysiology in the human brain.
Role: PI

McKnight Brain Foundation Cohen (PI) 1/1/14-1/1/16
CAM-CTRP Pilot Study: Visual assessment of aging processes in the human brain.
The goal of this funding is to investigate aging related changes in visual processing and assessment in the human brain.
Role: Co-I

McKnight Brain Foundation **Woods (PI)** 1/1/14-1/1/16
CAM-CTRP Pilot Study: Neuromodulation using transcranial direct current stimulation improves working memory decline in healthy aging
The goal of this funding is to use transcranial direct current stimulation to improve functional neuroimaging biomarkers of cognitive and metabolic decline in healthy aging.
Role: PI

McKnight Brain Foundation Porges (PI) 1/1/14-1/1/16
CAM-CTRP Pilot Study: Differential declination in attentional processes in advanced age
The goal of this funding is to identify differential change in the four major components of attentional processing using functional magnetic resonance imaging.
Role: Co-PI

Completed Research Support

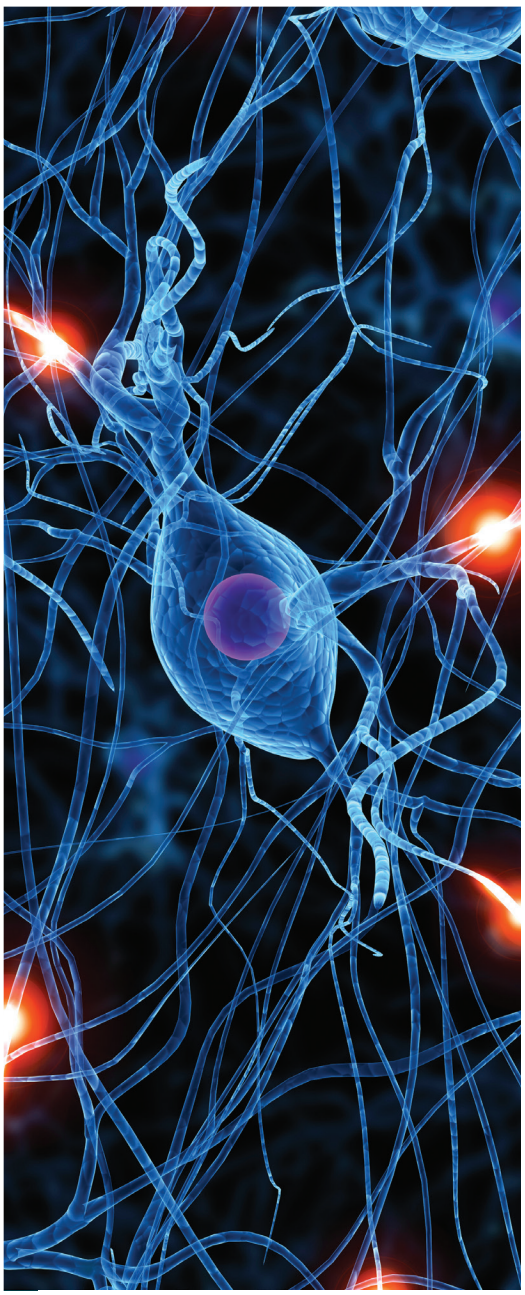
McKnight Brain Institute **Woods (PI)** 11/19/13
Acquisition of a whole brain 31P-1H magnetic resonance spectroscopy coil in the University of Florida AMRIS 3T MRI Scanner.
This fund provided for the acquisition of new equipment in the McKnight Brain Institute.
Role: PI

T32NS007413 Robinson (PI) 09/01/08-08/31/13
Training Grant in Intellectual and Neurodevelopmental Disabilities
The goal of this study is to provide support for neuroscience research training in neurodevelopmental disorders.
Role: Post-Doctoral Trainee

NSF GRFP **Woods (PI)** 09/01/06-09/01/09
National Science Foundation Graduate Research Fellowship: to develop an independent line of research investigating brain arousal systems in human behavior.
Role: PI

RC1NS068910 Mark (PI) 10/01/09-10/01/2011
Validating the NIH Toolbox in the Neurorehabilitation Setting
The goal of this study was to provide validation of the NIH Toolbox screening in rehabilitation inpatients.
Role: Statistical Consultant

Selected Publications



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Distinct manifestations of executive dysfunction in aged rats

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ABSTRACT

Different components of executive function such as working memory, attention, and cognitive flexibility can be dissociated behaviorally and mechanistically; however, the within-subject influences of normal aging on different aspects of executive function remain ill-defined. To better define these relationships, young adult and aged male F344 rats were cross-characterized on an attentional set-shifting task that assesses cognitive flexibility and a delayed response task that assesses working memory. Across tasks, aged rats were impaired relative to young; however, there was significant variability in individual performance within the aged cohort. Notably, performance on the set-shifting task and performance at long delays on the delayed response task were inversely related among aged rats. Additional experiments showed no relationship between aged rats' performance on the set-shifting task and performance on a hippocampal-dependent spatial reference memory task. These data indicate that normal aging can produce distinct manifestations of executive dysfunction, and support the need to better understand the unique mechanisms contributing to different forms of prefrontal cortical-supported executive decline across the lifespan.

1. Introduction

Across species, aging is accompanied by a decline in neurocognitive functions, including learning and memory mediated by medial temporal lobe structures and executive functions mediated by prefrontal cortex (PFC; Alexander et al., 2012; Bizon et al., 2012; Buckner, 2004). Research in animal models has made considerable strides in understanding the neural basis of age-related decline in learning and memory (Burke et al., 2012; Engle and Barnes, 2012; Foster et al., 2012); however, there has been less progress in understanding the neural mechanisms that contribute to impaired executive functioning across the lifespan. This relative paucity of data stems in part from the complexity in defining the distinct cognitive processes that are subserved by the PFC and our still limited understanding of how these processes integrate to effectively organize and guide behavior. Executive functions have been operationalized in a variety of ways but can include attention, planning, cognitive flexibility, working memory, inhibitory control, and decision-making (Fuster, 2000; Glisky, 2007; Kesner and Churchwell, 2011; Miller and Cohen, 2001; Robbins, 1996). Among these processes, age-related decline in working memory and cognitive flexibility are particularly well described. Though many definitions for working memory exist, this term is most often used in reference to the maintenance of a representation "in mind" of a stimulus that is no longer present in the environment (e.g., Goldman-Rakic, 1996). In contrast, cognitive or behavioral flexibility refers to the ability to effectively update internal representations and shift behavioral responses to accommodate changes in environmental contingencies (e.g., Dias et al., 1996).

Cognitive flexibility can be assessed in primates and rodents using "set-shifting" tasks. The prototypical set-shifting task, designed for human subjects, is the Wisconsin Card Sorting task (Berg, 1948), in which subjects are required to sort a deck of cards that contain multiple stimulus features (e.g., shape and color). Subjects must initially learn through trial and error which stimulus feature governs the correct choice (e.g., red indicates correct choice, ignore shape). After acquisition of this rule, an unsignaled 'shift' occurs such that the external contingencies are altered and the subjects must now inhibit the initial rule and shift their response strategies to accommodate the new contingencies (e.g., ignore color, square signals correct choice). Analogues of the Wisconsin Card Sorting task have been developed for use in nonhuman primates and rodents, and across species, damage to the dorsolateral PFC or its rodent homologue, medial PFC (mPFC), does not affect acquisition of the initial rule but selectively impairs the ability to set-shift (Birrell and Brown, 2000; Bissonette et al., 2008; Darrah et al., 2008; Demakis, 2003; Dias et al., 1996;

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Floresco et al., 2008; Owen et al., 1991; Ragozzino, 2007; Ragozzino et al., 1999; Uylings et al., 2003). Working memory tasks are generally designed such that to-be-remembered information varies across trials, requiring active resistance to proactive interference and distraction. Working memory is commonly assessed using delayed response tasks in which subjects are required to remember information about a spatial location over some delay interval, and then to accurately recall that information in a choice setting. As with set-shifting tasks, performance on working memory tasks is impaired after damage to primate dorsolateral or rodent medial PFC, and such lesions tend to disproportionately affect performance at long delays (Floresco et al., 1997; Freedman and Oscar-Berman, 1986; Goldman and Rosvold, 1970; Mishkin, 1957; Ragozzino et al., 1998).

Previous work in humans, nonhuman primates, and rodents has shown that cognitive flexibility and working memory decline across the lifespan. Notably, however, there is considerable variability among aged subjects, such that some perform on par with young whereas others demonstrate varying degrees of impairment (Barense et al., 2002; Bizon et al., 2009; Gallagher et al., 1993; Glisky, 2007; Morrison and Baxter, 2012; Park, 2000; Robbins et al., 1998). Despite such well-documented individual differences, the relationship between the presence and severity of impairment on tasks that assay these different components of executive function is not well defined. The fact that PFC damage impairs working memory and set-shifting performance, and that both functions are compromised in disease states such as schizophrenia, suggest that age-related impairments in working memory and cognitive flexibility are mediated by common neural mechanisms and might be expected to covary (Chudasama and Robbins, 2006). However, these processes can also be dissociated using a variety of PFC manipulations that include modulation of dopaminergic and GABAergic signaling, both of which can be compromised at advanced ages (Cools and D'Esposito, 2011; Durstewitz and Seamans, 2008; Enomoto et al., 2011; Floresco and Magyar, 2006; Li et al., 2010; McQuail et al., 2012). A primary goal of the current study was to determine the relationship between age-related impairments in cognitive flexibility (assessed using a set-shifting task) and working memory (assessed using a delayed response task) in aged Fischer 344 rats. In addition, performance on the set-shifting task was compared with performance on the Morris water maze, an assay that is sensitive to medial temporal lobe-mediated mnemonic dysfunction in aged rats (Bizon et al., 2009; Frick et al., 1995; Gallagher et al., 1993).

2. Methods

2.1. Subjects

Young (5 months old; $n = 20$) and aged (22 months old; $n = 25$) male Fischer 344 rats were obtained from the National Institute on Aging colony (Taconic Farms, Hudson, NY, USA) and housed in the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC)-accredited vivarium facility in the McKnight Brain Institute Building at University of Florida in accordance with the rules and regulations of the University of Florida Institutional Animal Care and Use Committee and National Institutes of Health guidelines. The facility was maintained at a consistent temperature of 25 °C with a 12-hour light/dark cycle (lights on at 8:00 AM) with free access to food and water except as otherwise noted. Rats were tested in 3 cohorts, each including young and aged subjects. After completing the set-shifting protocol, subsets of these rats were subsequently trained on the working memory ($n = 9$ young and $n = 11$ aged) or water maze ($n = 10$ young, $n = 13$ aged) tasks. Note that not all rats tested in experiment 1 were tested in experiments 2 and 3.

2.2. Experimental procedures

2.2.1. Experiment 1: effects of aging on set-shifting

2.2.1.1. Apparatus. Testing in the set-shifting and working memory tasks was conducted in 8 identical standard rat behavioral test chambers (30.5 × 25.4 × 30.5 cm; Coulbourn Instruments, Whitehall, PA, USA) with metal front and back walls, transparent Plexiglas side walls, and a floor composed of steel rods (0.4 cm in diameter) spaced 1.1 cm apart. Each test chamber was housed in a sound-attenuating cubicle, and was equipped with a recessed food pellet delivery trough located 2 cm above the floor in the center of the front wall. The trough was fitted with a photobeam to detect head entries and a 1.12 W lamp for illumination. Food rewards consisted of one 45-mg grain-based food pellet for each correct response (PJAI; Test Diet, Richmond, IN, USA). Two retractable levers were located to the left and right of the food trough (11 cm above the floor), and a 1.12 W cue lamp was located 3.8 cm above each lever. An additional 1.12 W house light was mounted near the top of the rear wall of the sound-attenuating cubicle. A computer interfaced with the behavioral test chambers and equipped with Graphic State 3.01 software (Coulbourn Instruments) was used to control experiments and collect data.

2.2.1.2. Shaping. The design of the set-shifting task was based on that used by Floresco et al. (2008). Before the start of behavioral testing, rats were reduced to 85% of their free feeding weights over the course of 5 days and maintained at this weight for the duration of the experiments involving food restriction. Rats progressed through 4 stages of shaping before the onset of the set-shifting task, with new stages beginning on the day immediately after completion of the previous stage. On the day before shaping stage 1, each rat was given five 45-mg food pellets in its home cage to reduce neophobia to the food reward used in the task. Shaping stage 1 consisted of a 64-minute session of magazine training, involving 38 deliveries of a single food pellet with an intertrial interval of 100 ± 40 seconds. Shaping stage 2 consisted of lever press training, in which a single lever (left or right, counterbalanced across groups) was extended and a press resulted in delivery of a single food pellet. After reaching a criterion of 50 lever presses in 30 minutes, rats were then trained on the opposite lever using the same procedures.

Shaping stage 3 consisted of 90 trials that were designed to train rats to press the levers after their insertion into the test chamber. Each 20-second trial began with illumination of the house light and insertion of a single lever (either left or right, randomly selected within each pair of trials) into the test chamber where it remained for a maximum of 10 seconds. A response on the lever within this time window resulted in retraction of the lever, delivery of a single food pellet, and continued illumination of the house light for an additional 4 seconds. If a rat failed to respond on the lever within 10 seconds, the lever was retracted and the house light turned off, and the trial was scored as an omission. Rats received at least 4 daily sessions in this stage, and were trained until reaching criterion performance of fewer than 10 omissions out of the 90 trials.

Shaping stage 4 was designed to determine each rat's side bias (i.e., preference for one lever over the other). Each trial consisted of multiple phases. In the first phase of a trial, the house light was illuminated and both levers were inserted into the test chamber. A response on either lever resulted in retraction of both levers and delivery of a single food pellet. In the second phase of a trial, both levers were again inserted, but only a response on the lever opposite to the one chosen in the first phase resulted in food delivery. A response on the same lever chosen in the first phase (i.e., "incorrect") resulted in the levers being retracted and in the houselight being extinguished. After a "correct" response on this second phase of a trial, a new trial was initiated, whereas after an

"incorrect" response, the second phase of the trial was repeated. The second phase was repeated until rats made a "correct" response. In cases in which 5 or more of the initial 7 first phase choices were confined to a single side, that side was considered the rat's biased side. However, in cases in which neither side was initially chosen a disproportionate number of times (<5), the side associated with the greatest number of total responses across this stage of testing was considered the rat's biased side.

2.2.1.3. Visual cue discrimination. After the side bias determination session, rats were trained to press the lever associated with a visual cue (light). In this discrimination (Fig. 1A), the illumination of a cue light over a lever signaled the correct response, irrespective of the spatial location (left or right) of the cue. Each 20-second trial began with illumination of 1 of the cue lights (left or right, randomly selected in each pair of trials). After 3 seconds, the house light was illuminated and both levers were inserted into the chamber (the cue light remained illuminated while the levers were extended). A response on the lever corresponding to the cue light (a correct response) resulted in the house light remaining on for 4 seconds, during which time the levers were retracted, the cue light was extinguished, and a single food pellet was delivered. A response on the opposite lever (an incorrect response) or failure to respond within 10 seconds (omission) resulted in retraction of both levers and all lights being extinguished. Rats were considered to have acquired the task on reaching criterion performance of 8 consecutive correct trials (and at least 30 total trials, excluding omissions), with the maximum number of trials per session set at 120. If rats failed to acquire the task within a single session, they received additional sessions on subsequent days.

2.2.1.4. (Set-shift) left/right discrimination. After reaching criterion performance on the visual discrimination task, rats were tested the next day in the set-shift condition, in which the task contingencies were altered. In this new condition, rats were required to ignore the light cue and instead to consistently choose the left or right lever (whichever was not their biased side as determined in shaping stage 4). Hence, accurate performance required rats to "shift" their attention away from the visual cue and toward the left/right position of the lever. Beyond the shift in reward contingencies, trials were identical in presentation to those in the visual cue discrimination (i.e., on each trial, both levers were presented, with the cue light illuminated over one lever). As in the visual cue discrimination, the location of the illuminated cue light was randomized (left or right) in each pair of trials. Rats were considered to have acquired the task on reaching criterion performance of 8 consecutive correct trials, excluding omissions. The maximum number of trials per session was set at 120 and if rats failed to acquire the task within a single session, they received additional sessions on subsequent days.

2.2.1.5. Set-shifting statistical analysis. Raw data files were exported from Graphic State software and compiled using a custom macro written for Microsoft Excel (Dr Jonathan Lifshitz, University of Kentucky). Statistical analyses were conducted using SPSS 19.0. The total numbers of trials and errors required to achieve criterion on the visual discrimination and on the set-shift were used as the indices of performance. Considering that the task design involved explicit presentation of the same set of stimuli during the initial discrimination learning and the set-shift, the nature of the errors was also examined. Specifically, age comparisons were performed separately for errors that involved responses corresponding to previously-reinforced choices (the cue light was incongruent with the correct lever location and the rat chose based on the previous visual discrimination rule) and for errors that had never been reinforced (the cue light and spatial location were congruent and the rat's choice was not correct according to the rule in either type of discrimination; Floresco et al., 2008; Ragozzino et al., 2002).

Comparisons between age groups in the set-shifting task (trials to criterion and errors to criterion) were conducted using *t* tests. A Levene's test was conducted to test for differences in variance in individual performance between age groups. For analyses in experiments 2 and 3, in which performance was compared across cognitive tasks, aged rats were subgrouped into "cognitive groups" on the basis on their set-shifting performance using the trials-to-criterion measure. Aged rats were subdivided into "aged shifting-impaired" (rats in which trials to criterion on the set-shift was greater than 1 standard deviation from the mean of young rat performance) and "aged shifting-unimpaired" (all other rats). A one-factor analysis of variance (ANOVA) was used to compare set-shifting performance among these cognitive groups with Tukey post hoc tests performed when warranted. For this and all subsequent analyses, *p* values less than 0.05 were considered significant.

2.2.2. Experiment 2: effects of age on working memory and relationship to set-shifting performance

Both set-shifting and working memory task performance depend on the integrity of PFC systems and decline with age, but the nature of the relationship between age-related decline across these two distinct components of executive function is unknown. To investigate this relationship, subsets of young and aged rats characterized on the set-shifting task in experiment 1 were subsequently tested on a delayed response working memory task.

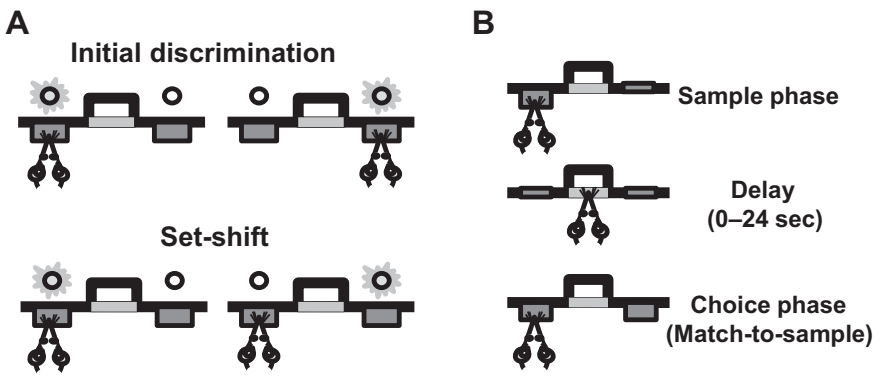

Fig. 1. Schematic diagrams of the set-shifting and working memory tasks. (A) The set-shifting task. Rats were initially trained in a visual discrimination in which they had to press the response lever illuminated by a small lamp, irrespective of its left/right location. On reaching criterion performance, they were shifted to a left/right discrimination in which they had to press the response lever in a particular location, irrespective of whether that lever was illuminated by the lamp. (B) The delayed response working memory task. Rats had to press a lever when extended during the sample phase, then, after a variable delay, press that same lever during the choice phase to earn a food reward.

2.2.2.1. Delayed response working memory task procedures. The delayed response working memory task was conducted in the same testing chambers used for the set-shifting task. Because the rats were already familiar with pressing the retractable levers to earn food rewards, they did not require additional shaping procedures. The design of the task was based on Sloan et al. (2006). Each session was 40 minutes in duration, and the house light was illuminated throughout the entire session except during timeout periods. A trial began with insertion of a single lever (the "sample" lever) into the chamber (Fig. 1B). The left/right position of this lever was randomly selected within each pair of trials, and a lever press caused it to retract and started the delay period timer. During the delay, rats were required to nosepoke into the food trough to initiate the "choice" phase, and the first such nosepoke emitted after the delay timer expired caused both levers to extend. During this choice phase, a response on the same lever pressed during the sample phase (a correct response) resulted in both levers being retracted and the delivery of a single food pellet. Entry into the food trough to collect the food pellet initiated a 5-second intertrial interval, after which the next trial was initiated. A response on the opposite lever from that chosen during the sample phase (an incorrect response) resulted in both levers being retracted and initiation of a 5-second "timeout" period during which the house light was extinguished, followed immediately by the start of the next trial.

During initial sessions in this task, there were no delays between the sample and choice phases, and a correction procedure was employed such that the sample lever was repeated on the same side after an incorrect response to prevent development of side biases. When rats reached a criterion of 80% correct choices across a session for 2 consecutive sessions, this correction procedure was discontinued and a set of 7 delays was introduced. The presentation of delay durations was randomized within each block of 7 trials, such that each delay was presented once. On establishing greater than 80% correct performance across 2 consecutive sessions, delays were systematically increased (set 1: 0, 1, 2, 3, 4, 5, and 6 seconds; set 2: 0, 2, 4, 8, 12, and 16 seconds; set 3: 0, 2, 4, 8, 12, 18, and 24 seconds). Rats were tested for 10 consecutive sessions on the delays in set 3.

2.2.2.2. Delayed response statistical analyses. Performance (percent correct at each delay) was averaged across 10 test sessions to provide a measure of mean accuracy at each delay. Group comparisons in the working memory task were conducted using 2-factor (age or cognitive group by delay) repeated measures ANOVAs. Comparisons of individual performance across the set-shifting (trials and errors to criterion) and working memory tasks (mean percent accuracy at each delay) were conducted using bivariate correlations performed separately for young and aged rats.

2.2.3. Experiment 3: relationship between set-shifting and spatial learning performance in aging

A decline in spatial memory is well-described in normal aging, and our laboratory and others have reported individual differences among aged rats with respect to the presence and degree of impairment on the Morris water maze task (Bizon et al., 2009; Gallagher et al., 1993; LaSarge et al., 2007). To determine the relationship between age-related decline in the PFC-dependent set-shifting task and in hippocampal-dependent spatial abilities, subsets of young and aged rats from experiment 1 were subsequently assessed on the water maze task.

2.2.3.1. Apparatus. The water maze consisted of a circular tank (diameter 183 cm, wall height 58 cm) painted white and filled with water (27 °C) made opaque with the addition of nontoxic white tempera paint. The maze was surrounded by black curtains to which were affixed large white geometric designs which provided extramaze visual cues. For the spatial reference memory (hidden platform) task, a retractable escape platform (12 cm diameter; HVS Image) was submerged 2 cm below the surface of the water in the center of the southwest quadrant of the maze. For the cued (visible platform) task, the platform was painted black and protruded 2 cm above the surface of the water, and was located in a different quadrant of the maze on each trial. A video camera mounted above the center of the maze was connected to a DVD recorder and computer, which were used for data storage and analysis using a video tracking system (Water 2020; HVS Image).

2.2.3.2. Spatial reference memory (hidden platform) task procedure. Spatial reference memory was assessed as described previously (Bizon et al., 2009). Briefly, on 8 consecutive days, rats received 3 trials per day with a 30-second intertrial interval. On each trial, rats were placed into the water facing the wall of the maze at 1 of 4 equally-spaced start positions (north, south, east, or west). The start positions were varied in a pseudo-random fashion, such that all rats started from each of the locations approximately the same number of times. On placement in the water, rats were allowed to swim until they found the hidden platform or until 90 seconds elapsed, at which time they were guided to the escape platform by the experimenter. Rats remained on the platform for 30 seconds and then were placed in a holding chamber for 30 seconds before the next trial. Every sixth trial (i.e., the third trial on days 2, 4, 6, and 8) was a probe trial in which the platform was lowered to the bottom of the maze for the first 30 seconds of the trial, after which it was raised to allow the rats to escape.

2.2.3.3. Cued (visible platform) task. After spatial reference memory training, rats were given a single session with 6 trials of cue training to assess sensorimotor abilities and motivation to escape the water. For this task, rats were trained to swim to a visible platform (painted black and protruding 2 cm above the water's surface). The start position and platform location were varied on each trial, making the extramaze cues explicitly irrelevant to the platform location. On each trial, rats were allowed to search for the platform for a maximum of 90 seconds and then were allowed to remain there for 30 seconds before a 30-second intertrial interval.

2.2.3.4. Water maze statistical analyses. For each task, data files were created using the Water 2020 software and were exported to Microsoft Excel and SPSS (version 19.0) for analysis. Training trial data in the spatial reference memory task were averaged into 4 blocks consisting of the 5 trials preceding each probe trial, and performance on these trials was analyzed using a "cumulative search error" measure. To calculate search error, a rat's distance from the platform was sampled 10 times per second and these distances were averaged into 1-second bins. Cumulative search error is the sum of these 1-second bins over the course of a training trial, minus the optimal path from the start location to the platform (Bizon et al., 2009; Gallagher et al., 1993). On probe trials, a "mean search error" measure was used. Mean search error is the sum of the 1-second bins (minus the optimal path from the start location to the platform), divided by the 30-second duration of the probe trials. Mean search error data from each probe trial were weighted and summed to provide a "spatial learning index" measure, which provides a single value reflecting overall spatial learning ability for each rat (Bizon et al., 2009; Gallagher et al., 1993). Comparisons between groups on training trials (in the hidden and visible platform tasks) were conducted using 2-factor ANOVA (age or cognitive group by training trial), with Tukey post hoc tests performed when warranted. Comparisons of individual performance across the set-shifting (trials and errors to criterion) and water maze (spatial

learning index) tasks were conducted using bivariate correlations performed separately for young and aged rats.

3. Results

3.1. Experiment 1: effects of aging on set-shifting

Young and aged rats required comparable numbers of sessions in the two stages of shaping which included a performance criterion (stage 2: mean [standard error of the mean (SEM)], young = 2.90 [0.22], aged = 2.64 [0.18], $t(43) = 0.93$, $p = 0.36$; stage 3: young = 5.40 [0.57], aged = 5.32 [0.46], $t(43) = 0.11$, $p = 0.93$). Likewise, there were no differences between young and aged rats in the number of trials required to reach criterion performance on the initial (visual) discrimination ($t(43) = 0.01$; $p = 0.99$; Fig. 2A). In contrast, aged rats were impaired relative to young adults on the set-shift task, requiring significantly more trials to reach criterion performance ($t(43) = 2.93$; $p < 0.05$; Fig. 2B). Similarly, aged rats also made significantly more errors before reaching criterion performance ($t(43) = 2.01$; $p < 0.05$; Fig. 2C) and, as expected, total trials and errors to criterion were strongly correlated in both young ($r = 0.71$; $p < 0.05$) and aged ($r = 0.86$; $p < 0.05$) rats.

A number of studies have suggested that age-related deficits in shifting tasks (e.g., Wisconsin Card Sorting task) are preferentially attributable to an inability to inhibit responding based on the previously reinforced rule, which manifests as a greater number of perseverative errors (Gamboz et al., 2009; Moore et al., 2006; Ridderinkhof et al., 2002). Because the current task design involved explicit presentation of the same set of stimuli during the initial discrimination learning and the set-shift, the nature of the age-related impairment could be further investigated using an error analysis. For each rat, errors to reach criterion on the set-shift were divided into those that involved responses that corresponded to previously reinforced choices (i.e., perseverative) and errors that had never been reinforced. As shown in Fig. 2C, aged rats made significantly more previously reinforced errors than young rats ($t(43) = 2.11$; $p < 0.05$). In contrast, there was no significant difference between age groups in the number of never-reinforced errors ($t(43) = 1.57$; not significant).

Significantly more heterogeneity in set-shifting performance was observed among aged in comparison with young adult rats (Levene's test, trials to criterion: $F = 22.98$, $p < 0.05$; errors to criterion: $F = 12.81$, $p < 0.05$). As shown in Fig. 3A, some aged rats performed as well as young adults and performance of others was well outside the range of young adult performance, demonstrating impairment. Subsequent experiments were designed to determine the extent to which this age-related set-shifting impairment predicted impairment in other components of executive function (experiment 2) and in other cognitive domains (experiment 3). For such comparisons, aged rats were subdivided into "aged shifting-impaired" (rats in which the number of trials to criterion on the set-shift was greater than 1 standard deviation from mean young rat performance) and "aged shifting-unimpaired" (all other rats). Using these criteria, $n = 12$ aged rats were classified as aged shifting-impaired and $n = 13$ aged rats were classified as aged shifting-unimpaired. Performance of these subgroups did not differ on the initial visual discrimination ($F(2,42) = 0.38$; $p = 0.68$) but differed significantly on the set-shift ($F(2,42) = 51.01$; $p < 0.05$). Post hoc analyses indicated that, as expected, aged shifting-impaired rats performed significantly worse than young and aged shifting-unimpaired rats on the set-shift ($p < 0.05$), and young and aged shifting-unimpaired subgroups did not differ from each other ($p = 0.80$). Fig. 3B and C show group set-shifting performance of the subsets of young and aged rats used in experiments 2 (young, $n = 9$; aged, $n = 11$) and 3 (young, $n = 10$; aged $n = 13$). Across both subsets of rats, performance reflected that of the overall age groups in that a main effect of age on set-shifting performance was evident, with aged rats requiring significantly more trials to reach criterion performance after the set-shift relative to young adults ($t(21) = 2.29$; $p < 0.05$). Moreover, aged shifting-impaired rats took significantly more trials to reach criterion on the set-shifting task relative to young and aged shifting-unimpaired rats (experiment 2: $F(2,19) = 17.06$, $p < 0.05$; Fig. 3B; and experiment 3: $F(2,22) = 20.78$, $p < 0.05$; Fig. 3C). In both experiments, post hoc analyses indicated that aged shifting-impaired rats were impaired relative to young and aged shifting-unimpaired rats ($ps < 0.05$) but that young rat performance did not differ significantly from aged shifting- unimpaired rats ($ps > 0.67$).

3.2. Experiment 2: effects of age on working memory and relationship to set-shifting performance

A subset of the rats tested in the set-shifting task in experiment 1 ($n = 9$ young, $n = 5$ aged shifting-unimpaired, and $n = 6$ aged shifting-impaired) was subsequently tested in the delayed response working memory task. There was no age difference in the number

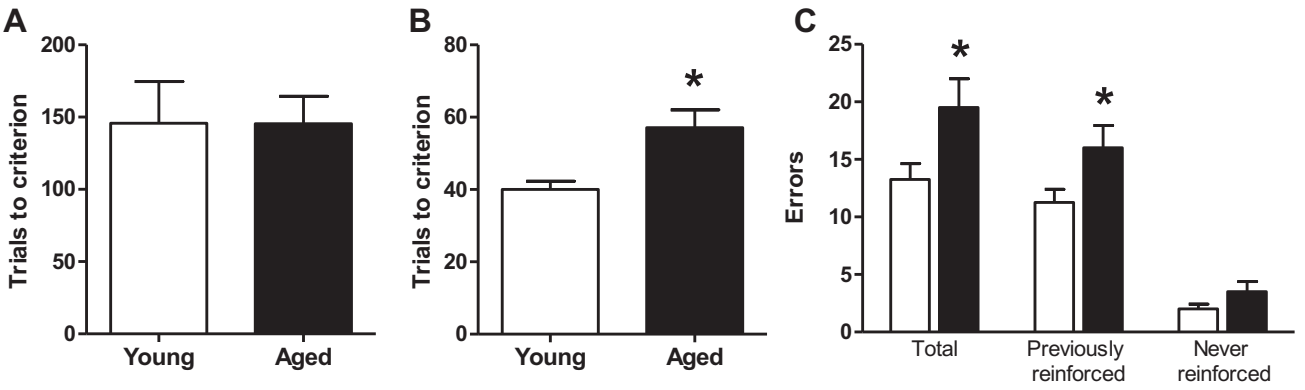

Fig. 2. Performance of young and aged rats on the set-shifting task. (A) Aged rats were no different from young in the number of trials required to reach criterion performance on the initial visual discrimination. (B) In contrast, after the set-shift, aged rats took significantly more trials to reach criterion performance on the left/right discrimination. (C) Aged rats made significantly more total errors than young rats in reaching criterion performance on the set-shift. Most of these errors involved responding according to the previously-reinforced (visual discrimination) response rule (e.g., if the left lever was correct during the left/right discrimination, a "previously-reinforced" error would involve responding on the right lever on trials in which the right lever was illuminated), and aged rats made significantly more previously-reinforced errors than young rats. In contrast, there were much fewer errors of the "never reinforced" type (e.g., in the previous example, responding on the right lever on trials in which the left lever was illuminated), and these did not differ between young and aged rats. * $p < 0.05$.

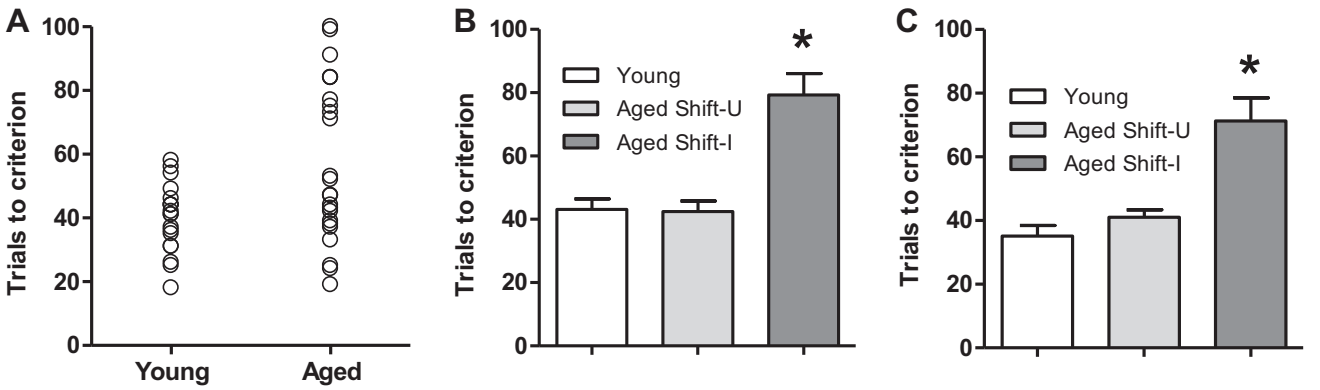

Fig. 3. Variability among aged rats on the set-shifting task. (A) There was significantly greater variability in the number of trials to criterion on the set-shift among aged compared with young rats (each point represents data from a single rat), such that performance of some rats fell within the range of young whereas performance of others fell outside this range, demonstrating impairment. Dividing the aged rats according to a criterion of greater or less than 1 standard deviation from the mean of the young group yielded 2 equally-sized subgroups of aged rats: an "aged shifting-unimpaired" (Aged Shift-U) subgroup that performed identically to young, and an "aged shifting-impaired" (Aged Shift-I) subgroup that performed significantly worse (greater number of trials to criterion) than the young and aged shift-unimpaired subgroups. (B) and (C) show data from the subsets of rats subsequently tested in the delayed response and water maze tasks, respectively. * $p < 0.05$.

of shaping sessions required to reach the longest set of delays in the working memory task (mean [SEM]: young = 13.56 [1.26], aged = 15.91 [0.81], $t(18) = 1.62$, not significant). In contrast, a 2-factor repeated measures ANOVA (age by delay) performed on data averaged across 10 sessions at the longest set of delays, revealed a significant main effect of age on the working memory task, such that across delays, aged rats performed significantly worse than young ($F(1,18) = 5.99$; $p < 0.05$; Fig. 4A). A main effect of delay ($F(6,108) = 140.99$; $p < 0.05$) was also evident such that performance declined as a function of delay duration, but there was no age by delay interaction ($F(6,108) = 0.40$; $p = 0.88$).

A considerably different pattern of results was evident when working memory performance was analyzed as a function of set-shifting performance. As shown in Fig. 4B, a 2-factor repeated measures ANOVA (cognitive group by delay) revealed a main effect of delay ($F(6,102) = 158.84$; $p < 0.05$) and a main effect of cognitive group ($F(2,17) = 9.65$; $p < 0.05$), and an interaction between delay and cognitive group ($F(12,102) = 1.90$; $p < 0.05$). Surprisingly, the main effect of cognitive group was carried by the fact that aged shifting-unimpaired rats were significantly impaired on the working memory task relative to young and aged shifting-impaired rats ($ps < 0.05$), whereas aged shifting-impaired rats performed comparably with young on the working memory task ($p = 0.65$). Hence, these data indicate an inverse relationship between age-related impairments on set-shifting and working memory tasks.

The nature of this inverse relationship was further tested using bivariate correlations conducted on individual performance measures of set-shifting (trials and errors to criterion) and working memory. Note that, for these analyses, performance at each delay used in the working memory task was expressed as "100 − mean percent correct at each delay" such that inverse relationships between performance on the 2 tasks would result in negative correlations. As shown in Table 1 and Fig. 4C, among aged rats, significant negative correlations were present between set-shifting and working memory performance at the 12-second ($r = -0.61$; $p < 0.05$) and 24-second ($r = -0.77$; $p < 0.05$) delays with a similar trend also evident at the 18-second delay ($r = -0.54$; $p = 0.09$). These correlations indicate that better set-shifting performance in aged rats was associated with worse working memory performance at long delays. Notably, in contrast to this inverse relationship at long delays, set-shifting performance (errors to criterion) in aged rats was positively associated with performance on the delayed response task at the 0-second delay ($r = 0.65$; $p < 0.05$). No significant relationships between performance on these tasks were observed among young rats at any delay, although trends toward positive correlations between set-shifting (trials and errors to criterion) and working memory performance were observed at 0- and 2-second delays ($rs > 0.6$; $ps < 0.1$; see Table 1).

3.3. Experiment 3: relationships between set-shifting and spatial learning performance in aging

A subset of the rats tested in the set-shifting task ($n = 10$ young, $n = 7$ aged shifting-unimpaired, and $n = 6$ aged shifting-impaired rats) was also tested in the Morris water maze task. As shown in Fig. 5A, aged rats were significantly impaired relative to young rats in their ability to locate a hidden platform in the water maze. A repeated measures ANOVA (age by trial block) revealed that all rats improved over the course of training (main effect of trial block, $F(3,63) = 9.66$; $p < 0.05$) but that aged rats had significantly greater search error associated with locating the hidden platform than did young adults, demonstrating impaired performance (main effect of age, $F(1,21) = 6.66$; $p < 0.05$). Similar to previous findings in this study population (Bizon et al., 2009; Murchison et al., 2009), these group age differences were not present on the first training trial ($t(21) = 0.004$; not significant), nor were there differences between young and aged rats in their ability to locate the visible platform during cue training (mean [SEM] path length: young = 242.38 [37.73], aged = 274.08 [27.62]; $t(21) = 0.70$; $p = 0.50$). Together, these data demonstrate that deficits associated with locating the hidden platform in aged rats were not because of impairments in sensorimotor function, motivation, or ability to learn the procedural aspects of the task.

Fig. 5B shows water maze performance plotted as a function of set-shifting ability among aged rats. A repeated measures ANOVA (cognitive group by trial block) revealed that all rats improved over the course of training (main effect of trial block, $F(3,60) = 9.68$; $p < 0.05$) but there was neither a significant main effect of cognitive group ($F(1,20) = 3.21$; $p = 0.06$) nor an interaction between cognitive group and trial block ($F(6,60) = 0.38$; $p = 0.89$). Nevertheless, because the main effect of cognitive group in this analysis was near statistical significance, post hoc tests were conducted to determine the relationships among the 3 cognitive groups. These tests revealed that although, in agreement with the main effect of age on performance previously described, there was a trend toward aged shifting-unimpaired and aged shifting-impaired groups differing from young ($ps = 0.13$ and 0.10, respectively), the 2 aged groups clearly did not differ from each other ($p = 0.97$).

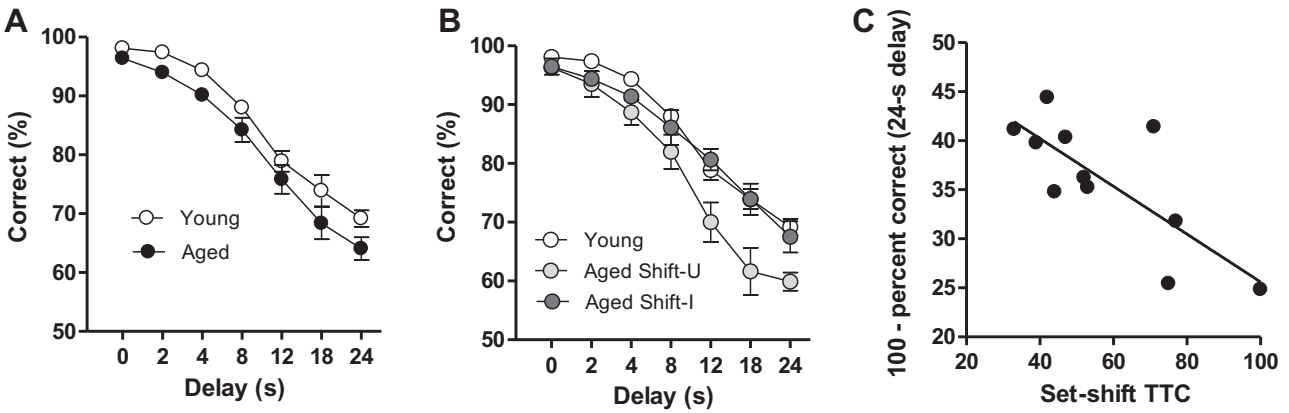

Fig. 4. Performance on the delayed response working memory task in young and aged rats, and relationships with set-shifting performance. (A) All rats showed delay-dependent decrements in performance on the delayed response task, but aged rats were impaired relative to young. (B) Aged shifting-impaired (Aged Shift-I) rats performed comparably with young on the delayed response task, whereas aged shifting-unimpaired (Aged Shift-U) rats performed worse than shifting-impaired and young cohorts. (C) Among aged rats, performance on the set-shifting task was significantly correlated with performance on the delayed response task at the 24-second delay, such that worse set-shifting predicted better working memory (TTC = trials to criterion).

To further compare performance across set-shifting and water maze tasks, an overall measure of spatial learning ability was derived for each rat using performance on the 4 interpolated probe trials. The spatial learning index was calculated as previously described (Bizon et al., 2009; Gallagher et al., 1993). These learning index scores have been associated with age-related changes in neurobiological substrates of spatial memory, and other aspects of cognition (Banuelos et al., 2013; Bizon et al., 2001; LaSarge et al., 2007; McQuail et al., 2012; Smith et al., 2000). As expected, an unpaired *t* test performed on the mean spatial learning indices in young and aged rats indicated that aged rats were significantly impaired (higher learning index scores) relative to young (young = 239.28 [9.73], aged = 277.47 [10.88]; $t(21) = 2.53$; $p < 0.05$). However, in agreement with the group comparisons in Fig. 5B, bivariate correlations performed separately on young (not shown) and aged (Fig. 5C) rats revealed no significant relationships between set-shifting and spatial memory performance among either young ($r = 0.33$, $p = 0.35$) or aged ($r = 0.06$, $p = 0.85$) rats. Hence, in agreement with previous work, these data indicate a lack of relationship between age-related impairments in measures of cognitive flexibility and spatial learning (Barense et al., 2002; Schoenbaum et al., 2002).

4. Discussion

The overarching goal of these experiments was to determine the relationship between age-associated performance deficits in 2 aspects of PFC-dependent executive functions: set-shifting and working memory. In agreement with previous population-based studies in humans, nonhuman primates, and rodents (Barense et al., 2002; Bizon et al., 2009, 2012; Glisky, 2007; Mizoguchi et al., 2009; Morrison and Baxter, 2012; Park, 2000; Ramos et al., 2003; Robbins et al., 1998; Segovia et al., 2008), aged rats in the current study were impaired relative to young in the set-shifting and working memory tasks. Among aged rats, however, there was a striking inverse relationship between individual performance measures across the 2 tasks such that aged rats impaired on the set-shifting task performed comparably with young on the working memory task, and aged rats impaired on the working memory task performed comparably with young on the set-shifting task. These data suggest that normal brain aging can result in distinct manifestations of executive dysfunction among individual subjects and support the need to better understand the mechanisms that might contribute to different forms of executive impairment that emerge at advanced ages.

Notably, this inverse relationship between set-shifting and delayed response performance was evident only in aged rats and was specific to long (>12 seconds) delays. It is possible that the absence of such a relationship in young rats reflects a statistical limitation rather than the influence of factors specific to advanced age. Indeed, there was significantly less variability in individual performance measures on both tasks within the young cohort, reducing the power to detect reliable cross-task correlations. However, contrary to this interpretation, it is notable that among young and aged rats, there was evidence of a positive relationship between performance at the 0-second delay on the delayed response task and performance on the set-shifting task. These different relationships that were evident at short and long delays argue against several other alterative explanations for the inverse relationship between set-shifting and long delay performance in the working memory task. First, they indicate that the inverse relationship is not carried by chance performance among aged rats (i.e., a "regression to the mean" across multiple behavioral measures). Second, they indicate that the inverse relationship at long delays is not attributable to performance strategies learned in the set-shifting task (e.g., "always press the left lever") carrying forward to influence delayed response performance, because such performance strategies would be expected to influence delayed response performance similarly at all delays. Indeed, performance measures in the delayed response task (Fig. 4) were obtained after several weeks of shaping in this task, and analyses of lever selection showed no evidence of side biases (not shown) as would be expected if set-shifting strategies directly influenced delayed response performance. Finally, it is important to note that the absence of

Table 1
Correlations between set-shifting and working memory performance

Set-shifting measure	Working memory (100 − percent correct at each delay)						
	0 s	2 s	4 s	8 s	12 s	18 s	24 s
Young							
Trials to criterion	0.63^{+}	0.63^{+}	0.53	−0.23	−0.52	−0.27	−0.29
Errors to criterion	0.52	0.63^{+}	0.68*	−0.36	−0.60^{+}	−0.28	−0.35
Aged							
Trials to criterion	0.36	0.08	0.01	−0.12	−0.61*	−0.54^{+}	−0.77*
Errors to criterion	0.65*	0.40	0.02	0.34	−0.42	−0.35	−0.55^{+}

$^{+}$ $p < 0.1$.
* $p < 0.05$.

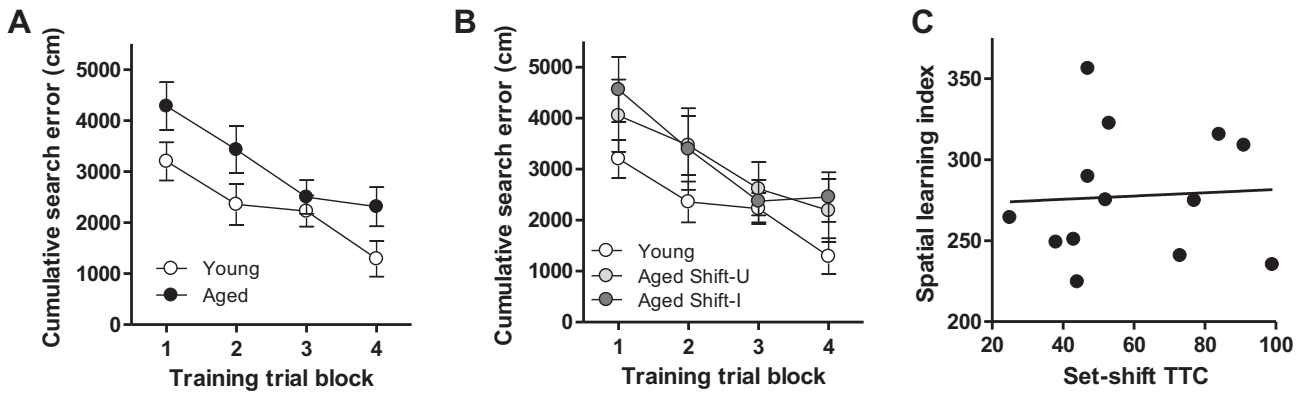

Fig. 5. Relationships between performance in the set-shifting and water maze tasks. (A) Aged rats performed significantly worse than young (greater cumulative search error) across the 4 blocks of training trials in the water maze. (B) Both the aged shifting-unimpaired (Aged Shift-U) and shifting-impaired (Aged Shift-I) subgroups were impaired relative to young rats (greater cumulative search error), but the 2 aged subgroups did not differ from each other. (C) Among aged rats, there was no correlation between performance on set-shifting measured by trials to criteria (TTC) and performance on the interpolated probe trials in the water maze (as assesed by the learning index measure; see text for details) (TTC = trials to criterion).

age-related deficits on the visual discrimination in the set-shifting task and at any stage of shaping strongly supports that age-related impairments in either task are not attributable to differences in motivation to press the levers for food or other nonspecific effects of age on appetitive operant behavior (see also Simon et al., 2010).

The opposing relationships between set-shifting and working memory across different delays suggest that somewhat different neurocognitive mechanisms mediate performance at short and long delays in the delayed response task. Notably, performance at the 0-second delay in the delayed response task would be expected to strongly tax the "updating" component of working memory and the ability to minimize proactive interference from immediately previous trials. Updating of the contingencies that signal the correct (rewarded) choice on the delayed response task involves focusing attention to new stimuli and inhibition of previously rewarded responses, both of which would also enable effective set-shifting. In contrast, performance at long delays might be mediated to a greater degree by the "maintenance" component of working memory or the ability to hold trial-specific information across the duration of the trial and minimize distraction during these extended delays. Indeed, because cognitive demands critical for maintenance likely involve minimizing attention to external stimuli, such maintenance processes might be viewed as functionally oppositional to those that enable effective updating and set-shifting. The current data suggest the intriguing possibility that aging disrupts the normal coordination of these updating and maintenance functions, such that some subjects show an impaired ability to hold information or representations stable across time (hereon referred to as impaired "representational stability") whereas others show an impaired ability to flexibly modify those representations as dictated by alterations in environmental contingencies (hereon referred to as impaired "cognitive flexibility").

It is possible that a single mnemonic deficit could mediate the inverse relationship between performance on working memory and set shifting tasks observed in the current study. Specifically, set-shifting might be expected to be facilitated in subjects unable to effectively recall the previously-learned rule (i.e., the visual discrimination). In this case, however, a strong relationship between learning of the initial (visual discrimination) and shifted (left/right discrimination) rules would be expected. Notably, no such relationships were observed in the current study among young or aged rats. Indeed, despite the fact that all rats required multiple sessions to acquire the visual discrimination rule, there were no age differences in trials-to-criterion to learn this rule as would be expected if between-session intervals were associated with age-related mnemonic deficits.

Across species, advanced age is associated with impairments in set-shifting and other tests of cognitive flexibility. In humans, aged individuals show impaired performance relative to young cohorts on the Wisconsin Card Sorting task (Ashendorf and McCaffrey, 2008; Robbins et al., 1998; Terry and Sliwinski, 2012; Volkow et al., 1998a) and similar set-shifting impairments have been observed in aged monkeys (Moore et al., 2005, 2006; although see Zeamer et al. 2011). The present findings in aged rats are consistent with these data, as well as with previous studies reporting set-shifting performance deficits in aged rats using a "digging task" in which rats are trained to shift between olfactory and tactile stimulus discriminations to obtain a food reward buried in a small pot (Barense et al., 2002; Nieves-Martinez et al., 2012). It could be argued that aged rats' impaired performance after the set-shift in the current study was attributable to the spatial nature of the post-shift discrimination problem, rather than an impairment in set-shifting per se. Despite well-documented spatial learning deficits in aged rats (Bizon et al., 2009; Foster et al., 2012; Gallagher et al., 1993), we believe this explanation to be unlikely for two reasons. First, although water maze navigation and spatial (i.e., left/right) discrimination might represent somewhat different cognitive operations, it is notable that no correlations were observed between individual measures of aged rat performance across set-shifting and spatial learning tasks (Fig. 5B and C). Second, and more importantly, considering that the task design involved explicit presentation of the same set of stimuli during the initial discrimination learning (visual discrimination) and during the set-shift (left/right discrimination), it was possible to determine whether errors committed during the left/right discrimination were consistent with perseveration on the initial visual cue response rule or instead reflected never-reinforced responses. If the increase in errors observed in aged rats after the set-shift were primarily because of an inability to perform the left/right discrimination, it would be expected that errors would be similarly distributed across previously- and never-reinforced categories (Enomoto et al., 2011; Floresco et al., 2008). Instead, in young and aged rats, most of the errors were of the previously-reinforced type. This pattern is consistent with the interpretation that errors across both ages largely reflected persistent responding to the initial rule and that the reliable increase in the number of perseverative errors in aged rats reflected an impaired ability of aged rats to shift their behavior in accordance with the new response rule.

Despite substantial evidence that domain-specific cognitive processes can be dissociated behaviorally and mechanistically, relationships between different aspects of age-related cognitive decline remain poorly delineated. Consistent with previous work in aged rats and as previously described herein, individual measures of aged rat performance on the set-shifting task in the current study were not related to performance measures on the water maze task (Barense et al., 2002). These data are consistent with the idea that age-related deficits in PFC-mediated executive functions emerge somewhat independently from deficits in medial temporal lobe-dependent mnemonic functions and suggest that unique mechanisms contribute to domain-specific cognitive dysfunction in aging (Bizon et al., 2012; Gallagher and Rapp, 1997; Glisky, 2007; Ramos et al., 2003; Schoenbaum et al., 2002). Compared with the spatial reference memory water maze task, working memory assessed by the delayed response task more heavily engages the same PFC circuitry that supports set-shifting. Indeed, many working memory tasks engage the PFC and the hippocampus, making it difficult to precisely define the neural substrates underlying impaired performance (Floresco et al., 1997; Shaw and Aggleton, 1993). An advantage of the task design used here is that performance is reportedly unaffected by lesions of the hippocampus (Sloan et al., 2006). In contrast, lesions of the mPFC produce pronounced performance deficits on this task, mimicking those observed in aged rats in the current study (Sloan et al., 2006). These data suggest that the age-related deficits observed in the working memory task are attributable to decline in PFC function, an interpretation which agrees with other findings linking age-related working memory impairments to alterations in PFC anatomy, physiology, and neurochemistry (Arnsten et al., 2012; Hara et al., 2012; Mizoguchi et al., 2009; Rapp and Amaral, 1989). It is important to note that the design of the delayed response task, wherein rats must nosepoke in the centrally-located food trough during the delay phase to initiate the choice phase, specifically discourages the use of nonmnemonic "mediating" strategies to solve the task (e.g., remaining stationary in front of the sample lever during the delay period). However, this design does result in some variation in the actual duration of the delays. Analysis of actual delay durations showed that they were on average several seconds longer than the programmed delays, although they were comparable in young and aged rats (e.g., the actual durations of the 24-second delays were: young = 27.3 seconds, aged = 28.7 seconds). Most importantly, the actual delays did not correlate with choice accuracy in either age group (not shown), indicating that the actual delay duration was not a significant mediator of individual differences in delayed response task performance.

A growing body of literature has shown that dopamine signaling in PFC-striatal circuits is important for the integration of representational stability and cognitive flexibility in normal behavior. Representational stability and cognitive flexibility are dependent on intact dopamine signaling, but perturbations in dopamine availability in frontostriatal circuits can differentially influence these two components of executive function (Brozoski et al., 1979; Crofts et al., 2001; Floresco and Magyar, 2006; Robbins and Arnsten, 2009). Specifically, dopamine signaling in the PFC has been heavily implicated in representational stability, possibly by maximizing signal-to-noise ratio and distracter resistance during delays (Arnsten et al., 2009; Sawaguchi and Goldman-Rakic, 1991; Vijayraghavan et al., 2007). This is evident in individuals with gene polymorphisms (Val^{158}Met) that regulate activity of the dopamine catabolic enzyme catechol-O-methyltransferase and presumptive dopamine availability in PFC. The Met allele is associated with the highest PFC dopamine levels and carriers consistently exhibit superior working memory performance relative to individuals carrying the Val allele (putatively low PFC dopamine). Interestingly, however, this enhanced working memory performance might occur at the expense of less cognitive flexibility. Met allele carriers perform worse than Val carriers on task-switching and reversal learning, both of which require flexible adaptation of established response rules (Colzato et al., 2010; Krugel et al., 2009).

Opposing roles for dopamine in representational stability and cognitive flexibility have also been suggested by the dual-state theory of PFC dopamine receptor signaling (Durstewitz and Seamans, 2008). This theory, which is based on empirical evidence from in vitro pharmacological and electrophysiological studies, suggests that a predominance of D1 receptor signaling promotes stable PFC network states which should facilitate information maintenance. In contrast, a predominance of D2 receptor signaling promotes switching between different PFC network states, which should favor cognitive flexibility. Notably, aging is accompanied by a range of alterations in dopamine signaling, including reductions in dopamine synthesis, release, and receptor availability (Backman et al., 2010; Segovia et al., 2008; Volkow et al., 1998b). Such alterations could result in a failure to rapidly adjust between "stable" and "flexible" modes of PFC operation, leading to dominance of one mode and impairment in the other. Beyond dopamine, there is evidence that PFC GABAergic signaling might differentially influence representational stability and cognitive flexibility. Specifically, in a recent study examining a battery of mPFC-dependent aspects of behavior in young adult rats, intra-mPFC administration of a GABA (A) receptor antagonist impaired set-shifting but not working memory (Enomoto et al., 2011), indicating that the two functions are neurochemically dissociable at least under some conditions (Floresco and Magyar, 2006). Determining how alterations in dopaminergic, GABAergic, and other neurochemical systems contribute to distinct manifestations of executive dysfunction in aging, and how such alterations develop in relation to changes in executive function over the lifespan, will be important avenues for future research.

Disclosure statement

The authors have no actual or potential conflicts of interest to disclose. All work was conducted in accordance with the rules and regulations of the University of Florida Institutional Animal Care and Use Committee and National Institutes of Health guidelines.

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Atlas-derived perfusion correlates of white matter hyperintensities in patients with reduced cardiac output

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Abstract

Reduced cardiac output is associated with increased white matter hyperintensities (WMH) and executive dysfunction in older adults, which may be secondary to relations between systemic and cerebral perfusion. This study preliminarily describes the regional distribution of cerebral WMH in the context of a normal cerebral perfusion atlas and aims to determine if these variables are associated with reduced cardiac output. Thirty-two participants (72 ± 8 years old, 38% female) with cardiovascular risk factors or disease underwent structural MRI acquisition at 1.5 T using a standard imaging protocol that included FLAIR sequences. WMH distribution was examined in common anatomical space using voxel-based morphometry and as a function of normal cerebral perfusion patterns by overlaying a single photon emission computed tomography (SPECT) atlas. Doppler echocardiogram data was used to dichotomize the participants on the basis of low ($n = 9$) and normal ($n = 23$) cardiac output. Global WMH count and volume did not differ between the low and normal cardiac output groups; however, atlas-derived SPECT perfusion values in regions of hyperintensities were reduced in the low versus normal cardiac output group ($p < 0.001$). Our preliminary data suggest that participants with low cardiac output have WMH in regions of relatively reduced perfusion, while normal cardiac output participants have WMH in regions with relatively higher regional perfusion. This spatial perfusion distribution difference for areas of WMH may occur in the context of reduced systemic perfusion, which subsequently impacts cerebral perfusion and contributes to subclinical or clinical microvascular damage.

Keywords

Cardiovascular disease; SPECT; MRI; Perfusion; Cardiac output; White matter hyperintensities

Many vascular risk factors, such as hypertension, diabetes mellitus, and atherosclerosis, are associated with central nervous system (CNS) injury, including abnormal age-associated

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neuroanatomic (Carmelli et al., 1999; DeCarli et al., 1999) and cognitive changes (Muller et al., 2007) as well as clinical dementia (Borenstein et al., 2005; Hofman et al., 1997; Kivipelto et al., 2005). A related but poorly understood aspect of vascular aging is the association between cardiac function and CNS injury. Though cardiac dysfunction has been related to neuropsychological impairments among patients with severe cardiomyopathies (Zuccala et al., 1997), less is known about how subtle cardiac dysfunction impacts brain aging through reductions in systemic blood flow in the absence of end-stage heart failure.

Recent studies from our laboratory suggest that subtle reductions in cardiac output are related to abnormal brain aging in the absence of end-stage heart failure. In particular, reduced cardiac output is associated with specific elements of executive dysfunction (Jefferson et al., 2007a,b) and increased white matter hyperintensities (WMH) (Jefferson et al., 2007a,b) adjacent to the subcortical nuclei in older patients with cardiovascular disease. The mechanism accounting for these associations remains unknown, but reduced systemic perfusion may impact cerebral perfusion homeostasis. The cerebral vasculature plays an essential role in maintaining cerebral perfusion. Microvasculature and perfusion disruptions can cause CNS damage and neuronal death, contributing to clinical or subclinical brain injury through the development and progression of microvascular changes. For instance, mouse models suggest that chronic cerebral hypoperfusion induces the development and progression of WMH (Shibata et al., 2004). In humans, reduced cerebral blood flow is associated with hyperintensities but not areas of normal appearing white matter as evidenced by structural MRI (Hatazawa et al., 1997) and perfusion weighted MRI (Marstrand et al., 2002).

Convention suggests that auto-regulatory mechanisms augment blood flow to the brain and other critical organs during periods of acute reduced systemic perfusion (Saxena and Schoemaker, 1993); however, these mechanisms are less effective with subtle or chronic reductions in systemic blood flow. For example, research in macaque monkeys has demonstrated that lowering systemic blood flow, specifically cardiac output, directly reduces cerebral blood flow (Tranmer et al., 1992). In humans, cerebral blood flow is significantly reduced among end-stage heart failure patients, but values are restored to healthy levels following heart transplantation (Gruhn et al., 2001). These studies suggest that auto-regulatory mechanisms for maintaining cerebral perfusion may be disrupted during conditions of reduced cardiac function, such that blood flow from the heart to the brain is not consistently maintained. Such disruptions in systemic blood flow (which impact cerebral blood flow homeostasis) may contribute to clinical or subclinical brain injury. Thus, reduced cardiac output may exacerbate the vulnerability of neuroanatomical regions that are uniquely susceptible to changes in perfusion and thereby contribute to white matter damage and related cognitive impairment (Gunning-Dixon and Raz, 2000).

The purpose of the present study is to preliminarily explore the cross-sectional associations between normal patterns of cerebral perfusion as defined by an existing single photon emission computed tomography (SPECT) atlas (Holland et al., 2008) in relation to WMH spatial distribution in the context of reduced cardiac output. Among a referral sample of patients with prevalent but stable cardiovascular disease, we hypothesize that WMH will be present among areas of reduced cerebral perfusion, as defined by the perfusion atlas, for patients with low cardiac output as compared to patients with normal cardiac output values.

1. Methods

1.1. Participants

Participants were 32 community-dwelling individuals recruited from local hospitals, rehabilitation programs, private practices, and general advertisements. Inclusion criteria

required a documented history of cardiovascular disease (i.e., prior myocardial infarction, heart failure, coronary artery disease, cardiac surgery) or risk factor (i.e., hypertension). Exclusion criteria included end-stage heart failure; history of traumatic brain injury with loss of consciousness greater than 10 min, neurological disease (e.g., Parkinson's disease, multiple sclerosis, dementia), major psychiatric illness (e.g., schizophrenia); current depressed mood as assessed by the Beck Depression Inventory (Beck et al., 1961); previous drug or alcohol abuse requiring hospitalization; or MRI contraindication, including ferrous metal implants or pacemakers. Participants consisted of 20 males and 12 females, ranging 57–85 years of age with 10–18 years of education. The sample's mean global cognitive functioning was in the normal range based on the Mini-Mental State Examination (Folstein et al., 1975) and Dementia Rating Scale (Mattis, 1973). Each participant provided written informed consent prior to testing, and the study was approved by the local IRB.

1.2. Echocardiogram

A complete, transthoracic echocardiogram was obtained from each participant according to standards put forth by the American Society of Echocardiography. From these data, cardiac output was derived. Cardiac output is the amount of blood in liters per minute (L/min) that is pumped from the heart into systemic circulation and is a function of stroke volume and heart rate. Forward stroke volume can be calculated as the flow of blood leaving the left ventricle recorded with Doppler echocardiography multiplied by the area of left ventricular outflow tract measured from the 2D echo image (Jefferson et al., 2007a,b). This noninvasive method is strongly correlated with invasive measures of cardiac output (Moulinier et al., 1991).

1.3. Brain MRI acquisition and WMH quantification

Our neuroimaging protocol has been described in detail elsewhere (Gunstad et al., 2005; Jefferson et al., 2007b). Briefly, brain MRI was acquired using a Siemens Symphony 1.5 T magnet and a standard imaging protocol was obtained consisting of axial T1-, T2-, and fluid attenuated inversion recovery (FLAIR; TR/TE = 6000/105, slice thickness = 5 mm/2 mm gap, inplane resolution = 1 mm × 1 mm) images. For this particular study, we utilized the FLAIR sequence because its suppression of CSF signal increases the sensitivity to detecting WMH. Post-processing was conducted using the commercially available Mayo Clinic software program ANALYZE® (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). The skull, brain stem, and cerebellum were removed manually to leave only the cerebral brain parenchyma. A semi-automated thresholding method was applied to FLAIR images to segment and quantify WMH. Intra- and inter-rater reliability for WMH quantification were consistently >0.90 (Jefferson et al., 2007b).

Participant MR images and WMH segmentations were registered into the ICBM452 coordinate space for analysis with the FMRIB linear image registration tool (FLIRT, Analysis Group, FMRIB Oxford, UK) (Jenkinson and Smith, 2001), using 12 degrees of freedom (affine) transformation. Quantitative WMH counts and volume were calculated for each participant in standard (atlas) space to control for inter-subject variation in head size and total brain volume.

WMH distribution was then examined in the context of normal cerebral perfusion patterns by superimposing WMH segmentations with an atlas of normal cerebral perfusion derived from whole brain SPECT images of 47 healthy individuals aged 22–49 (34.3 ± 7.6 years). These images are publicly available for research via an archive maintained by The Society of Nuclear Medicine Brain Imaging Council (http://brainscans.indd.org/brncncl4.htm). Briefly, the SPECT scans were acquired using the tracer Tc-99m ethylene cysteinate dimer (Neurolite, DuPont Pharma, Billerica, MA), 1000 MBq of which was injected intravenously. Images were acquired with a triple-headed Picker camera (Prism 3000, Picker International,

Cleveland, OH) with a 2.2 mm^3 × 2.2 mm^3 × 3.6 mm^3 nominal voxel size. The images were reconstructed using a standardized low pass filter (order = 4.0/cutoff = 0.26) and spatially normalized to Talairach space.

We generated a SPECT atlas based on these healthy adult images, which we restricted to archive participants under age 50 years. Contemporaneous MR images are not available for comparison with the normal SPECT data for each healthy subject, so the condition of the white matter of these healthy individuals is unknown. Therefore, the age restriction (i.e., adults under age 50 years) was determined a priori to minimize the likelihood of incidental WMH in the archive SPECT sample, because the incidence of subclinical WMH is known to increase substantially in individuals age 60 years and older (Meyer et al., 1992). Our goal for this study was to generate a normative SPECT perfusion atlas based on data from healthy adults that would provide an estimate of normal perfusion patterns as a context for analyzing the distribution of white matter damage in patients with cardiovascular risk factors and disease. Because perfusion is dynamic and fluctuates in response to many factors, including regional brain activity, an atlas based on the average of many healthy adults removes some of the temporal and functional variability present in individual scans. The atlas then yields mean perfusion values for all brain regions in arbitrary units with a range of 1–1000.

We related the SPECT atlas perfusion values to each voxel of WMH for our cardiovascular patients in native participant space. Our utilization of SPECT allowed for the comparison of relative but not absolute differences in perfusion within the white matter (De Cristofaro et al., 1990; Lycke et al., 1993).

1.4. Statistical Analysis

Group dichotomization was based on cardiac output status: low (<4.0 L/min) and normal (≥4.0 L/min). The rationale for this dichotomy was based on two factors. First, we did not anticipate any meaningful variations in normal cardiac output that would correspond to white matter changes. Second, and most clinically relevant, the dichotomization of cardiac output was based on widely accepted cut-offs utilized by cardiologists to identify impaired vs. normal cardiac function (Grossman and Baim, 1995). This dichotomization allows our data to be applied in a clinical context.

Descriptive statistics and between-group comparisons were conducted to summarize the sample's clinical characteristics (age, education, sex, Mini-Mental State Examination, Dementia Rating Scale, vascular risk factors, and prevalent cardiovascular disease). Between-group comparisons for quantitative WMH counts, WMH volume, and perfusion values co-localized with WMH were calculated using the Student's *t*-test. For all analyses, statistical significance was defined a priori as $p < 0.05$.

2. Results

2.1. Clinical characteristics

There were no between-group differences for the low ($n = 9$) and normal ($n = 23$) cardiac output patients for age ($t_{(31)} = 0.15, p = 0.88$), education level ($t_{(30)} = -0.41, p = 0.69$), sex ($x^2 = 1.74, p = 0.19$), global cognitive status as assessed by the Mini-Mental State Exam (Folstein et al., 1975) ($t_{(31)} = 1.01, p = 0.32$) or Dementia Rating Scale (Mattis, 1973) ($t_{(31)} = -0.28, p = 0.78$). Chi-square analyses yielded no significant between-group differences for vascular risk factors or prevalent cardiovascular disease (all *p*-values > 0.39). Descriptive statistics for demographic, cognitive, and cardiovascular variables are displayed in Table 1.

2.2. Quantitative comparison of WMH & perfusion correlates

A total of 975 unique hyperintensities were identified for the sample. In Table 2, we present the quantitative WMH statistics and WMH perfusion values for the entire cohort and for each cardiac output group. There were no between-group differences for the average number of hyperintensities ($t_{(30)} = -0.08, p = 0.93$) or mean volume of WMH per participant ($t_{(30)} = -0.97, p = 0.34$); however, the distribution of hyperintensities across levels of cerebral perfusion differed between the two groups. Specifically, WMH were present in regions of significantly lower cerebral perfusion in the low, as compared to the normal, cardiac output group according to the normative perfusion atlas ($t_{(30)} = -30.1, p < 0.0001$). Qualitative illustration of the WMHs unique to the low cardiac output group and the corresponding arbitrary perfusion values is provided in Fig. 1.

2.3. Qualitative illustration of WMH & perfusion correlates

Examining WMH distribution in relation to normal perfusion patterns, as defined by the healthy adult SPECT perfusion atlas, yielded the histogram of WMH volume per participant (mL/participant) presented in Fig. 2. Shaded regions correspond to 95% confidence intervals. The illustration suggests increased WMH prevalence in regions of lower relative normal perfusion, which is supported by the quantitative findings above. A peak is present at approximately 500–550 (arbitrary perfusion units) for both groups, representing a similar distribution that may reflect a common mechanism of white matter damage in regions of white matter in this perfusion range. However, the strong peak in regions of white matter with the relative perfusion (i.e., 350–400 arbitrary perfusion units) qualitatively appears to be unique to the low cardiac output group.

3. Discussion

Our preliminary cross-sectional findings suggest that, despite having comparable total WMH burden (i.e., WMH count and volume), the cardiac output groups differed with respect to normative cerebral perfusion patterns in areas of hyperintensities based on an atlas generated from healthy adults. Among participants with low cardiac output, hyperintensities were present in regions with lower normative perfusion values. Though there are auto-regulatory mechanisms that augment cerebral blood flow at the expense of other organs during critical and sudden reductions in systemic blood flow (Saxena and Schoemaker, 1993), these mechanisms are less effective when systemic blood flow reductions are chronic or subtle and result in reduced cerebral perfusion (Gruhn et al., 2001; Tranmer et al., 1992). Therefore, chronic reductions in cardiac output may impact cerebral perfusion and exacerbate the susceptibility of these regions to hypoperfusion or ischemia, thereby leading to white matter damage (Shibata et al., 2004; Tranmer et al., 1992).

The between-group differential distribution of perfusion values in regions of hyperintensities is qualitatively supported by the histogram curves observed for each group (Fig. 2). The cross-sectional nature of the present study precludes inferences about causality; however, systemic perfusion may be the distinguishing feature for the unique peak observed at lower perfusion levels for the low cardiac output group. Reduced cardiac output may act as a unique mechanism of injury, or it may lead to white matter damage in normally spared regions (Jefferson et al., 2007b). These interpretations are purely speculative, and additional investigation comparing vascular risk factors and systolic function among larger samples will extend these preliminary data and provide insight regarding perfusion differences relative to WMH lesion burden.

It is worthwhile to note that the subgroups share a peak around 500–550 arbitrary perfusion units in Fig. 2 and have comparable mean WMH burden, which is likely due to a common or

shared mechanism of white matter injury for the two groups. One probable shared mechanism is advanced age, which is a well-known risk factor for hyperintensities (Meyer et al., 1992). Alternatively, the comparable vascular risk factor burden and prevalent cardiovascular disease seen in the low and normal cardiac output groups may be a common mechanism of injury. Specifically, microvascular disease can occur in the absence of reduced cardiac output, and vascular risk factors known to be associated with white matter damage, including blood pressure (Murray et al., 2005) and diabetes (Carmelli et al., 1999), are prevalent in our sample regardless of subgroup status. Future studies with larger samples are needed to determine the distribution and cerebral perfusion correlates of hyperintensities and relations between white matter injury and systemic blood flow to confirm whether subtle systolic dysfunction is a risk factor for abnormal brain aging.

There are limitations to the current study that restrict the generalizability of our preliminary findings. First, the demographics and referral source of our sample may limit generalizability, because the sample was predominantly college educated, White of European descent, with a history of cardiovascular disease or vascular risk factor. As acknowledged above, our sample size was small, which precludes more rigorous statistical comparisons due to insufficient power. Low spatial resolution is a well-known limitation of perfusion imaging techniques, including SPECT, and can lead to partial voluming effects. Finally, the SPECT atlas was based on an archival dataset of healthy adults, so detailed clinical characteristics are unavailable for this normative dataset. As a solution, we restricted inclusion of SPECT scans to those adults under age 50 years to minimize confounding clinical characteristics (Holland et al., 2008). However, limiting the sample to a younger cohort (age 22–49 years) may have introduced another limitation of excessive homogeneity in perfusion characteristics versus the heterogeneity that might be seen in an older cohort.

With these limitations in mind, the present preliminary findings support previous research that links reductions in cerebral perfusion to the presence and progression of WMH in animal (Shibata et al., 2004) and human models (Marstrand et al., 2002). The present results also extend our prior work, which found that reduced cardiac output is related to very specific elements of executive dysfunction, including sequencing and planning difficulties (Jefferson et al., 2007a), and regional WMH adjacent to the subcortical nuclei (Jefferson et al., 2007b). In light of the association between cardiac output and abnormal brain aging, chronic alterations in systemic perfusion may have important implications for the development and progression of cognitive impairment secondary to cerebral perfusion changes and microvascular disease. Additional investigation is warranted to further assess the mechanism(s) accounting for cardiac function and brain aging relations, to assess the longitudinal implications of reduced cardiac output for cognitive aging and white matter integrity, and to better understand relations between cerebral perfusion and white matter disease with age.

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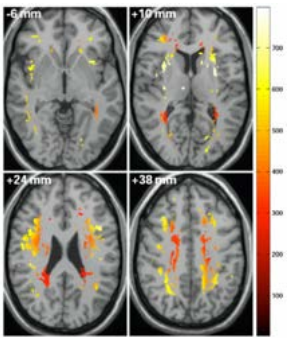

Fig. 1.
Illustration of perfusion values in regions of WMH unique to the low cardiac output subgroup.

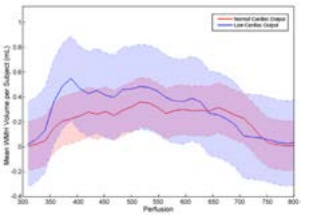

Fig. 2.

WMH frequency histogram in relation to normal atlas-derived perfusion values for normal cardiac output and low cardiac output subgroups. Data reflects mean WMH volume per subject measured in mL in relation to arbitrary perfusion units. Shaded error regions indicate 95% confidence intervals for each group, with the purple area illustrating subgroup overlap.

Table 1

Clinical characteristics.

	Normal cardiac output	Low cardiac output
Age, years	72.4 ± 6.8	72.8 ± 7.9
Education level, years	13.9 ± 2.1	13.4 ± 2.2
Sex, % female	30	46
Mini-mental state exam	28.8 ± 1.1	29.2 ± 1.3
Dementia rating scale	138.6 ± 4.5	137.6 ± 4.4
Cardiac output, L/min*	5.2 ± 1.5	3.4 ± 0.5
Family history of heart disease, %	64	50
Hypertension, %	83	78
Hypercholesterolemia, %	50	63
Diabetes mellitus, %	18	0
Atrial fibrillation, %	17	11
Prior coronary artery bypass, %	48	33
Heart failure, %	11	11
Prior myocardial infarction, %	48	22

Note: Data presented as mean ± standard deviation or as percentage; vascular risk factors and prevalent vascular disease data are based on self report and confirmed via medical records when possible;

*Significant between-group difference, $p < 0.05$.

Table 2

Quantitative WMH and atlas-derived perfusion data.

	Normal cardiac output	Low cardiac output	*t*-test (normal vs. low output)
WMH count mean (range)	30.2 (2–75)	31.1 (4–124)	$p = 0.93$
WMH volume (mL) per participant median (25th, 75th)	4.6 (2.9, 7.7)	4.2 (2.3, 16.4)	$p = 0.34$
WMH perfusion median (25th, 75th)	542 (457, 635)	507 (422, 593)	$p < 0.0001$

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Oxytocin and socioemotional aging: Current knowledge and future trends

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The oxytocin (OT) system is involved in various aspects of social cognition and prosocial behavior. Specifically, OT has been examined in the context of social memory, emotion recognition, cooperation, trust, empathy, and bonding, and—though evidence is somewhat mixed-intranasal OT appears to benefit aspects of socioemotional functioning. However, most of the extant data on aging and OT is from animal research and human OT research has focused largely on young adults. As such, though we know that various socioemotional capacities change with age, we know little about whether age-related changes in the OT system may underlie age-related differences in socioemotional functioning. In this review, we take a genetic-neuro-behavioral approach and evaluate current evidence on age-related changes in the OT system as well as the putative effects of these alterations on age-related socioemotional functioning. Looking forward, we identify informational gaps and propose an *Age-Related Genetic, Neurobiological, Sociobehavioral Model of Oxytocin* (*AGeNeS-OT model*) which may structure and inform investigations into aging-related genetic, neural, and sociocognitive processes related to OT. As an exemplar of the use of the model, we report exploratory data suggesting differences in socioemotional processing associated with genetic variation in the oxytocin receptor gene (*OXTR*) in samples of young and older adults. Information gained from this arena has translational potential in depression, social stress, and anxiety-all of which have high relevance in aging—and may contribute to reducing social isolation and improving well-being of individuals across the lifespan.

Keywords: oxytocin, aging, socioemotional functioning, amygdala, anterior cingulate

Social and emotional processes and their associated genetic and neurobiological mechanisms in aging are still incompletely understood (Nielsen and Mather, 2011). In this paper we propose to combine neuroendocrine, genetic, and sociobehavioral approaches to examine the role of the oxytocin (OT) system in the context of socioemotional aging. Aspects of the OT system warranting investigation include: (1) changes in endogenous and dynamic OT levels; (2) changes in systems which directly impact OT function (i.e., gonadal hormones); (3) genetic variation in aspects of the OT system, including the gene for oxytocin (*OXT*), its receptor (*OXTR*), and the related CD38 system; (4) changes in OT-rich neural regions; (5) the effect of exogenous OT. There is increasing evidence that OT plays a significant role in many of the socioemotional capacities that undergo age-related changes. However, to date, very little is known about the role of OT in human aging (Huffmeijer et al., 2012). Thus, it will be crucial for future research to clarify links between age-related changes in the aforementioned aspects of the OT system and changes in neural processing and subsequent alterations in experience as well as behavior in socioemotional domains in older compared to young adults.

To foreshadow, this focused review conceptually integrates two lines of research. First, we summarize evidence for age-associated changes in socioemotional capacities (Isaacowitz et al., 2007; Ruffman et al., 2008; Scheibe and Carstensen, 2010). Second, we review evidence for the involvement of OT in socioemotional functioning (Bartz et al., 2011; Meyer-Lindenberg et al., 2011; Van IJzendoorn and Bakermans-Kranenburg, 2012). Synthesizing these two lines of work, we present an *Age-Related Genetic, Neurobiological, Sociobehavioral Model of Oxytocin* (*AGeNeS-OT model*) which may stimulate questions and organize investigations into the role of OT in socioemotional aging. As an example of the use of the *AGeNeS–OT* model, we report preliminary data suggesting neural and behavioral differences in socioemotional processing associated with genetic variations in *OXTR* in samples of young and older adults. We conclude by suggesting future directions for research implied by the model. Ultimately, these investigations will increase our understanding of the role of OT in aging and will have the

potential for generating new interventions to improve health and well-being.

SOCIOEMOTIONAL FUNCTIONING AND AGING

From life's beginning, humans are confronted with critical, survival-enhancing socioemotional stimuli related to self and others. To maintain successful social interactions and avoid the negative consequences of social isolation (Baumeister and Leary, 1995; Norman et al., 2011), we learn to quickly and accurately process, respond to, and remember social cues (Baron-Cohen et al., 2000; Grady and Keightley, 2002; Adolphs, 2003). Socioemotional functioning may become particularly relevant in old age when-due to the experience of increasing physical ailment, dependency, and age-related social losses-the experience of social isolation often increases with negative effects on physical and mental health (Cornwell and Waite, 2009).

The extant literature suggests a mixed picture of age-related changes in socioemotional capabilities: Some capacities (e.g., emotion regulation, emotional problem solving) improve with age, whereas other skills (e.g., recognition of emotions in others) decline (cf. Scheibe and Carstensen, 2010). In particular, across various studies, older compared to young adults show increased emotion regulation capacity (Carstensen, 2006; Blanchard-Fields et al., 2007; Riediger et al., 2009; Scheibe and Blanchard-Fields, 2009; Voelkle et al., 2013) and greater confidence in this ability (Lawton et al., 1992; Gross and Levenson, 1997; Kessler and Staudinger, 2009). The majority of older adults are well-adjusted emotionally and report relatively high levels of affective well-being and emotional stability as documented in cross-sectional (Carstensen et al., 2000) as well as longitudinal (Carstensen et al., 2011) studies (see also Charles et al., 2001; Teachman, 2006). In addition, older compared to young adults are at least equally (and often more) effective in their ability to regulate their emotional experiences, autonomic arousal, and outward display of negative emotions in language and faces when instructed to do so (Kunzmann et al., 2005; Magai et al., 2006; Phillips et al., 2008), and show improved socioemotional problem solving capacity (Blanchard-Fields et al., 2007).

At the same time, older adults often show increased difficulties in accurate recognition of social and emotional cues (for reviews see Isaacowitz et al., 2007; Ruffman et al., 2008; see also Ebner and Johnson, 2010; see **Figure 1A**). Recent functional magnetic resonance imaging (fMRI) data suggests that these difficulties are associated with greater activity in dorsomedial prefrontal cortex (dmPFC) in older compared to young adults during facial emotion reading, particularly for angry expressions (Williams et al., 2006; Keightley et al., 2007; Ebner et al., 2012; see **Figure 1C**). This association comports with previous evidence that dmPFC is involved in complex processing and cognitive and emotional control (Amodio and Frith, 2006). Another age-related change in socioemotional functioning is that older compared to young adults demonstrate more interpersonal trust (List, 2004; Castle et al., 2012). This change may be due to the difficulty older adults often have in "reading" the emotions of others, as suggested by recent findings that older compared to young adults are less proficient at detecting lies, mediated by deficits in emotion recognition (Ruffman et al., 2012). With respect to changes in memory, there is evidence that the majority of older adults experience declines in remembering critical socioemotional cues, including names (Crook et al., 1993; Verhaeghen and Salthouse, 1997) and faces (Bartlett et al., 1989; Grady et al., 1995; Ebner and Johnson, 2009; see **Figure 1B**). Finally, in terms of social motivation, there is robust evidence that older adults are more avoidance-oriented and less approach-oriented than young adults (Ebner et al., 2006; Freund, 2006; Nikitin et al. in revision).

Importantly, the mechanisms underlying these age-related changes in socioemotional functioning are not well-understood yet. One potential explanation is differences in visual processing (Isaacowitz et al., 2006; Ebner et al., 2011), perhaps as a function of age-related changes in motivation (Mather and Carstensen, 2005; Carstensen, 2006; Samanez-Larkin and Carstensen, 2011). In particular, there is evidence that older compared to young adults spend more time looking at positive than negative information (Isaacowitz et al., 2006) and, when processing faces, spend less time viewing the eye region and more time viewing the mouth

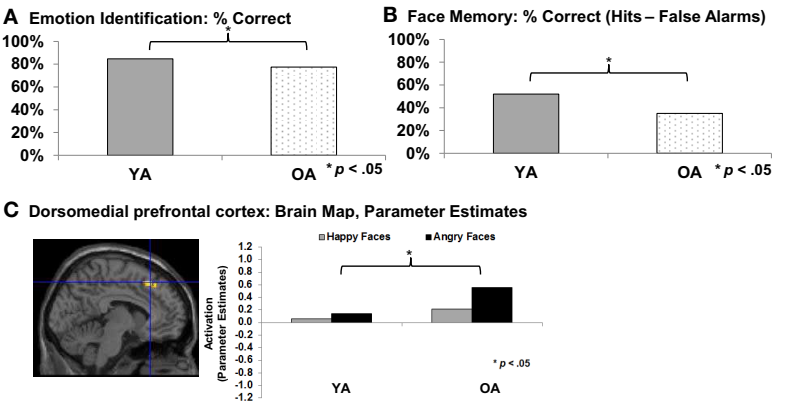

FIGURE 1 | (A) Emotion identification (Ebner et al., 2010); **(B)** Face memory (Ebner and Johnson, 2009); **(C)** Emotion identification: dorsomedial prefrontal cortex (Ebner et al., 2012). YA, Young adults; OA, Older adults.

(Firestone et al., 2007). This age-differential visual processing pattern may be important given that the eye vs. mouth regions of a face carry different socioemotional information (Calder et al., 2000; Ebner et al., 2011).

A complementary, mechanistic explanation for age-related changes in socioemotional function may be changes in brain structure or function in regions associated with socioemotional processing such as amygdala, PFC, insula, or fusiform gyrus (Keightley et al., 2007; Grady, 2008; Cacioppo et al., 2009; Ebner et al., 2012; see Ruffman et al., 2008; Samanez-Larkin and Carstensen, 2011; St. Jaques et al., 2013, for overviews). For instance, there is well-documented, age-related structural decline in regions such as the lateral PFC (lPFC), insula, and striatum (Raz, 2005; Raz et al., 2005). Regarding functional changes, one common finding is an age-related decrease in amygdala activation during the perception of emotional stimuli (especially negative stimuli) accompanied by an age-related increase in activity in a number of lPFC and mPFC regions (Iidaka et al., 2002; Gunning-Dixon et al., 2003; Fischer et al., 2005, 2010; Tessitore et al., 2005; but see Mather and Carstensen, 2005; Wright et al., 2006; Ebner et al., 2013).

Crucially, however, extant literature suggests that age-related differences in socioemotional processing cannot be explained solely by age-related visuoperceptual and/or neurocognitive changes (Samanez-Larkin and Carstensen, 2011). In addition, it may be that changes in socioemotional function are also linked with age-related alterations in neuroendocrine function. In particular, the neuropeptide OT appears as a particularly promising candidate, given increasing evidence of its role in socioemotional domains (Insel and Fernald, 2004; Donaldson and Young, 2008; Bartz et al., 2011; Meyer-Lindenberg et al., 2011; Norman et al., 2011). However, to date, we know very little about age-related changes in the OT system, particularly in the context of socioemotional aging (Huffmeijer et al., 2012).

OXYTOCIN AND SOCIOEMOTIONAL FUNCTIONING

OT is a nine amino acid peptide, with peripheral and central functions (Gimpl and Fahrenholz, 2001). It is synthesized in magnocellular neurosecretory cells of paraventricular nuclei (PVN) and supraoptic nuclei (SON) of the hypothalamus and released through the posterior pituitary gland into the periphery (Insel, 2010). OT is also released into the brain by magnocellular dendrites (Leng and Ludwig, 2006) and by OT-releasing neurons projecting to specific brain regions such as the amygdala, hippocampus, and striatum (Kimura et al., 1992; Landgraf and Neumann, 2004; Knobloch et al., 2012). Human and animal studies combined suggest that the function of the OT system is reflected at a variety of physiological and anatomical levels, including: (1) peripheral hormone levels (i.e., plasma and saliva); (2) central hormone levels [i.e., in cerebrospinal fluid (CSF)]; (3) histological levels (i.e., presence and size of OT cells); (4) receptor levels (in OT receptor binding in defined brain regions); (5) genetic levels, or the level of "neuropeptidergic individuality" (MacDonald, 2012); i.e., polymorphisms related to *OXT* or *OXTR*, or genes related to OT release (i.e., *CD38*; Sauer et al., 2012, 2013).

In particular, accumulating evidence suggests that OT may serve as a key effector in socioemotional functioning such as emotion recognition, memory for faces, interpersonal trust, and bonding as briefly summarized next (see Bartz et al., 2011; Meyer-Lindenberg et al., 2011; Norman et al., 2011; Zink and Meyer-Lindenberg, 2012, for comprehensive overviews).

After the discovery that certain neuropeptides could be delivered intranasally to the human brain (Born et al., 2002), a number of experimental studies using intranasal OT revealed intriguing effects on diverse aspects of socioemotional functioning. For example, research in healthy adults suggests that OT impairs performance in verbal memory tasks (Ferrier et al., 1980; Heinrichs et al., 2004; but see Feifel et al., 2012), while enhancing recognition of social (i.e., faces) but not non-social stimuli (Rimmele et al., 2009; see also Heinrichs et al., 2004), especially for neutral and angry compared to happy faces (Savaskan et al., 2008). Furthermore, intranasal administration of OT increases overall gaze time toward faces (Guastella et al., 2008; Andari et al., 2010; Averbeck, 2010; Gamer et al., 2010) and increases emotion recognition, specifically of happy and fearful faces (and under certain conditions angry faces; see Shahrestani et al., 2013, for a recent review).

In addition, recent studies have shown that intranasal OT increases facial trustworthiness and attractiveness ratings (Theodoridou et al., 2009) as well as interpersonal trust and the willingness to take social risks (Kosfeld et al., 2005; Baumgartner et al., 2008; Phan et al., 2010). These effects of OT on trust seem to be particularly pronounced in positive social interactions (Zak et al., 2005; Mikolajczak et al., 2010) and with respect to in-group vs. out-group members (Van IJzendoorn and Bakermans-Kranenburg, 2012). Moreover, these effects seem moderated by interindividual differences (Rockliff et al., 2011; but see Guastella et al., 2013), including genetic polymorphisms associated with OT function (Riedl and Javor, 2011; see also Rodrigues et al., 2009; MacDonald, 2012, for reviews).

Besides these effects on facial processing and trust, intranasal OT has been shown to influence social approach behavior, attachment, bonding, and social rejection with associated health benefits (Ditzen et al., 2009; Gouin et al., 2010; Scheele et al., 2012; Schneiderman et al., 2012; Fekete et al., 2013). For example, intranasal OT increased positive relative to negative behaviors during a laboratory couple conflict and reduced post-conflict cortisol levels (Ditzen et al., 2009). This potential stress reducing-effect of OT has been further documented by evidence that participants with increased plasma OT healed faster and had a greater number of positive interactions with partners during a 24-h hospital stay (Gouin et al., 2010; see also Kéri and Kiss, 2011; Kiss et al., 2011; see Taylor et al., 2006, for a discussion of OT's role during relaxation vs. stress; see also Feldman et al., 2011).

An ever-expanding body of neuroimaging data suggests that OT's effects on socioemotional functioning are due to its attenuation of the neural circuitry for anxiety and aversion and its activation of social reward neural networks (cf. Yoshida et al., 2009; Zink and Meyer-Lindenberg, 2012). In particular, a number of studies have provided evidence that the amygdala might be a key structure for the mediation of the social-cognitive effects of OT (Kirsch et al., 2005; Domes et al., 2007a; Petrovic et al.,

2008; Singer et al., 2008; Labuschagne et al., 2010; Riem et al., 2011; Zink and Meyer-Lindenberg, 2012; cf. Huffmeijer et al., 2012; but see Domes et al., 2010). For example, OT attenuates amygdala response to fear-inducing stimuli (Kirsch et al., 2005). Baumgartner et al. (2008; see also Kosfeld et al., 2005; Mikolajczak et al., 2010) provide evidence that OT reduced betrayal aversion to breaches of trust via a reduction in bilateral amygdala activation and midbrain regions and greater ventral striatum and orbitofrontal cortex (OFC) activity. Furthermore, there are suggestions of specific modulatory influences of OT on subregions within the amygdala during processing of socioemotional information (Gamer et al., 2010; see also Huber et al., 2005; Viviani et al., 2011; Knobloch et al., 2012). These central effects, importantly, occur in interaction with a network of other neurochemicals including estrogen, dopamine, and serotonin (Riedl and Javor, 2011).

Thus there are suggestions in the literature that OT increases approach-related behaviors, while decreasing withdrawal-related behaviors (Kemp and Guastella, 2010). At the same time, however, there is evidence suggesting that OT may play a somewhat more complex role in social behavior than simply directing approach vs. avoidance behavior and/or attentional biases to positive and negative information, respectively. Rather, OT may increase social engagement, salience of social agents, and social value of processed information, largely independent of valence (Shamay-Tsoory et al., 2009; Tops, 2009; Shamay-Tsoory, 2010; Bartz et al., 2011). In line with this suggestion, brain regions such as the ventral tegmentum, PFC, nucleus accumbens, and insula associated with the social-reward neural network have shown sensitive to OT (Balleine et al., 2007; Riem et al., 2011; Wittfoth-Schardt et al., 2012; Groppe et al., 2013; Scheele et al., 2013).

The central effects of OT are mediated by its G-protein-coupled receptor, located on a variety of tissues including the brain, heart, kidney, and uterus (Loup et al., 1991; Gimpl and Fahrenholz, 2001). Polymorphisms of the gene encoding the OT receptor, *OXTR*, have been shown to contribute to individual differences in various social phenotypes (cf. Gimpl and Fahrenholz, 2001; Meyer-Lindenberg et al., 2011; Ebstein et al., 2012; Zink and Meyer-Lindenberg, 2012; Kumsta et al., 2013; Westberg and Walum, 2013). For example, *OXTR* single nucleotide polymorphisms (SNPs) have been associated with lower positive affect (Lucht et al., 2009), lower levels of responsiveness of mothers to their toddlers (Bakermans-Kranenburg and van IJzendoorn, 2008), lower empathy scores and increased stress reactivity (Rodrigues et al., 2009), non-verbal displays of prosociality (Kogan et al., 2011), and pair-bonding (Walum et al., 2012). *OXTR* SNPs have also been studied in relation with autism spectrum disorder (ASD; see Ebstein et al., 2012, for a review), with evidence that they contribute to risk for some phenotypes observed in ASD (Egawa et al., 2012; but see Tansey et al., 2010).

Taken together, this review highlights the importance of simultaneously considering behavioral, neural, and genetic perspectives when examining OT's role in socioemotional functioning, as will be discussed in more detail below (see **Figure 2**). In addition, it raises five important caveats and informational gaps.

First, some of the effects associated with OT are inconsistent and come from small, homogeneous samples, creating a need for replication of key findings in larger, more representative samples.

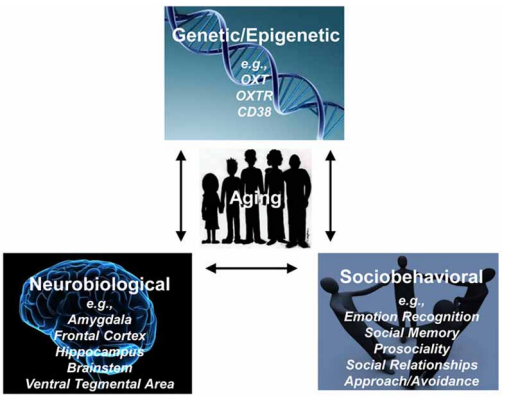

FIGURE 2 | Age-related Genetic, Neurobiological, Sociobehavioral Model of Oxytocin (AGeNeS-OT model).

Second, many of OT's effects seem to vary by individual difference variables such as the level of social proficiency (Bartz et al., 2011; but Guastella et al., 2013).

Third, there is increasing evidence suggesting that the effects of OT are dependent on context (Domes et al., 2007b) and influenced by early life experiences (see MacDonald, 2012, for a review). For example, women (Heim et al., 2008) and men (Meinlschmidt and Heim, 2007) who were abused or neglected as children showed altered OT system sensitivity as adults (e.g., decreased CSF level of OT; see also Winslow et al., 2003; Fries et al., 2005; but see Anderson, 2006; cf. MacDonald, 2012, for a review).

Fourth, due to both theoretical safety concerns using OT in women as well as the complexity introduced by OT's sex-specific effects, a large majority of studies conducted so far refer to men exclusively, even though there are growing indications that some of OT's effects may differ by sex (Savaskan et al., 2008; Guastella et al., 2009; Domes et al., 2010; Marsh et al., 2010; cf. MacDonald, 2012). This sex-specific pattern raises the possibility that the effects of OT on social cognition may be differentially regulated by gonadal steroids (estrogen and testosterone) or other sex-specific biological factors (Choleris et al., 2009; Gabor et al., 2012; see also Van Anders et al., 2011; see also Weisman and Feldman, 2013).

A fifth shortcoming in the current human literature on oxytocin—critical in the present context—is that current studies have almost exclusively been conducted with young adults. Given the aforementioned evidence of age-group differences in socioemotional functioning (Scheibe and Carstensen, 2010; Samanez-Larkin and Carstensen, 2011), a comprehensive examination of aging-related aspects of the OT system (including genetic, neurobiological, and behavioral aspects) is warranted (Huffmeijer et al., 2012).

OXYTOCIN AND AGING

Despite a significant need for research addressing the growing older segment of the population, research on OT and aging is scarce and inconclusive. To date, the few studies that have

addressed age-related differences in the OT system almost exclusively refer to non-human species with limited applicability to humans (Quinn, 2005). Also, studies conducted to date are characterized by large methodological differences in terms of species examined, OT parameters measured, brain regions targeted, etc., which makes a direct comparison difficult and a meta-analytic approach not feasible. Most importantly, a theoretical framework for generating hypotheses regarding age-related differences in the OT system (including changes in endogenous OT physiology, function, and differential response to exogenous OT) is entirely lacking (cf. Huffmeijer et al., 2012).

Table 1 provides a summary of the current studies on OT and aging. Whereas some studies suggest no noticeable effects of aging on the OT system (Fliers et al., 1985; Zbuzek et al., 1988; Wierda et al., 1991; Arletti et al., 1995), other studies report age-related change (Fliers and Swaab, 1983; Melis et al., 1992, 1995; Arsenijevic et al., 1995; Parker et al., 2010). Notably, some of the studies reporting comparability of the OT system across older and

Table 1 | Literature Review on Oxytocin and Aging.

Authors	Species	Age group	Measurement	Difference	Main findings
EVIDENCE OF STABILITY IN THE OT SYSTEM IN AGING					
Arletti et al. (1995)	Rats (M)	O	Intraperitoneal OT injection	O = Y	Comparable improved social memory and anti-depressant effect of OT injection
Fliers et al. (1985)	Rats (M)	Y/O	OT fiber density	O = Y	Comparable OT fiber density in the brain
Wierda et al. (1991)	Human (M, F)	Y/O	Number of OT cells in PVN (post-mortem)	O = Y	Comparable numbers of OT-expressing cells in PVN (normal aging and Alzheimer's Disease)
Yu et al. (2006)	Rats (M)	Y/O	OT cell size and numbers in SON	O = Y	Comparable cell numbers, cell size, or reactive density of NOS-expressing neurons
EVIDENCE OF CHANGE IN THE OT SYSTEM WITH AGE					
Arsenijevic et al. (1995)	Rats (M)	Y/O	OT receptor binding	O < Y	Age-related decrease in binding to OT receptors in caudate putamen, olfactory tubercle, and ventromedial hypothalamic nucleus
Fliers and Swaab (1983)	Rats (M)	Y/MA/O	Plasma OT levels	O > Y (neurosecretory activity) O = Y (plasma levels)	Age-related increase in OT secretion in PVN (but not SON); Comparable plasma OT levels
Keck et al. (2000)	Rats (M)	O	Intracerebral and peripheral OT release patterns	O > Y (peripheral) O < Y (intracerebral)	Age-related increase in basal peripheral OT secretion and decrease in stress-induced intra-PVN OT secretion
Melis et al. (1992)	Rats (M)	Y/MA/O	OT levels	O < Y (CNS) O = Y (HNS and plasma)	Age-related decrease in OT levels in septum and hippocampus; comparable OT levels in hypothalamus and hypophysis, and no change for plasma OT levels
Melis et al. (1995)	Rats (M)	Y/MA/O	OT-like immunoreactive peptides in thymic extract	O > Y	Age-related increase in content of OT-like immunoreactive peptides in thymic extract
Parker et al. (2010)	Rhesus monkeys (F)	Y/O	CSF OT levels	O > Y	CSF OT levels positively correlated with adult female age (but negatively correlated with infant age)
Zbuzek et al. (1988)	Rats (M)	O	Plasma and hypothalamic OT concentration	O = Y (plasma, hypothalamic concentration) O > Y (secretory release)	Comparable OT concentration in plasma and hypothalamus; age-related increase in secretory release of OT

Y, Young subjects; MA, Middle-aged subjects; O, Older subjects; M, Male; F, Female; OT, Oxytocin; PVN, Paraventricular nuclei of hypothalamus; SON, Supraoptic nuclei (SON) of hypothalamus; AVP, Arginine vasopressin; NOS, Nitric oxide synthase; CSF, Cerebrospinal fluid.

young subjects refer to peripheral OT levels (Fliers and Swaab, 1983; Zbuzek et al., 1988; Melis et al., 1992), whereas several of the studies documenting age-related change relate to central OT levels (Fliers and Swaab, 1983; Melis et al., 1992; Arsenijevic et al., 1995; Parker et al., 2010). Thus, it is possible that aging may change OT transmission in the CNS but not in the neurohypophyseal (peripheral) system (Melis et al., 1999). A summary of the evidence reported in **Table 1** would be that current evidence does not allow yet a firm conclusion of the existence or direction of age-related changes in the OT system, leaving the question open to empirical examination.

To our knowledge, only one very recent study explicitly examined the effects of intranasal OT in a group of older men (mean age of 80 years) focusing on OT's effects on social engagement and physical health (Barraza et al., 2013). Results from this double-blind, placebo-controlled 10-day clinical trial suggested improvement in dispositional gratitude in older adults in the OT compared to the placebo group. In addition, the OT group had a slower decline in physical functioning and decreased self-reported fatigue than the placebo group. No changes in mood, cardiovascular states, or social activity and engagement patterns were observed across the study interval. Importantly, this study did not include a comparison group of young adults and did not extensively explore OT's effects on other aspects of socioemotional functioning. Thus, it is critical to follow up on these first promising findings regarding OT and aging and to conduct systematic examinations of age differences in baseline levels of OT. In addition, a comprehensive evaluation of both single-dose as well as longer-term administration of intranasal OT and its effect on socioemotional functioning in young and older men and women is warranted. Finally, these studies should take into account genetic variations related to OT.

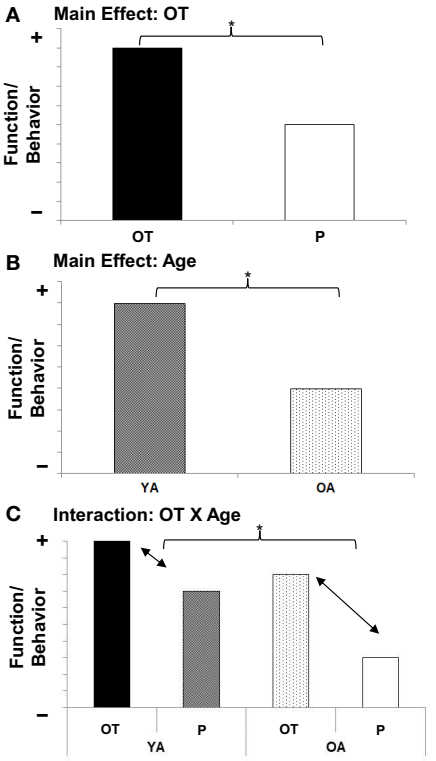

FIGURE 3 | (A) Main effect for Age; **(B)** Main effect for Oxytocin; **(C)** Oxytocin X Age interaction effect. Schematic representation of guiding working hypotheses. YA, Young adults, OA, Older adults; OT, Oxytocin, P, Placebo.

OXYTOCIN AND SOCIOEMOTIONAL AGING: AGE-RELATED GENETIC, NEUROBIOLOGICAL, SOCIOBEHAVIORAL MODEL OF OXYTOCIN

Based on the following rationale, we propose an *OT X Age* interaction (see **Figure 3C**) as the guiding working hypothesis for future research on the role of OT in socioemotional aging: As mentioned above, there is early evidence that the beneficial effects of OT in socioemotional domains (see **Figure 3A**) vary by individual factors (Bartz et al., 2011). Notably, "preexisting social impairment" seems to play a role, in that more socially impaired individuals benefit more from OT than less socially impaired individuals (Bartz et al., 2010; Guastella et al., 2010; but see Bakermans-Kranenburg and van IJzendoorn, 2013). Also there may be a "ceiling effect," a point beyond which OT cannot further improve social abilities (Bartz et al., 2011). As laid out above, older adults experience deficits in various socioemotional capacities (Scheibe and Carstensen, 2010; see **Figure 3B**), rendering them more socially impaired than young adults in some regards. Therefore, it may well be that OT is particularly beneficial in older compared to young adults (see **Figure 3C**).

However, an alternative hypothesis exists: As reported above, even though some aspects of socioemotional functioning (i.e., emotion recognition and memory for emotional information) decline with age, other aspects increase or remain stable. That is, given broad evidence for a positivity effect and for healthy socioemotional functioning in old age (Carstensen, 2006; Carstensen et al., 2011), as well as some evidence for increased trustworthiness in old age (Castle et al., 2012), on average, older adults can be described as highly positive, trustworthy, and prosocial. These characteristics may be adaptive in some contexts (e.g., social interactions within close relationships) but maladaptive in others (e.g., putting aging adults at greater susceptibility to fraud). This reasoning, combined with the current lack of proof that aging is associated with declines in the OT system and mixed evidence regarding OT's effect on cognitive performance (Heinrichs et al., 2004; Feifel et al., 2012), suggest the possibility that under certain circumstances OT may have harmful effects in older adults. Given that OT is currently being investigated in clinical populations such as schizophrenia (cf. MacDonald and Feifel, 2012, 2013), comprising samples of people who are late middle-aged, a thorough investigation of age-related aspects of the OT system-including beneficial or detrimental effects on outcome measures in socioemotional as well as cognitive domains-will be crucial.

As summarized above, the OT system is represented at genetic, neural, and behavioral levels (Meyer-Lindenberg et al., 2011). Furthermore, each of these levels and their functional interactions are influenced by the aging process. We therefore propose for future research in the domain of OT and socioemotional aging to adopt an *Age-Related Genetic, Neurobiological, Sociobehavioral Model of Oxytocin* (*AGeNeS-OT model*; **Figure 2**). In particular,

this model suggests that a comprehensive examination of the central OT system should consider interactions between OT-related genes (*OXT, OXTR, CD38;* Meyer-Lindenberg et al., 2011; Sauer et al., 2013), the brain (e.g., amygdala, frontal cortex, brainstem, ventral tegmental area; Pedersen et al., 1994; Kirsch et al., 2005; Balleine et al., 2007; Baumgartner et al., 2008; Gamer et al., 2010), and behavior (e.g., social memory, emotion identification, approach/avoidance biases; Rimmele et al., 2009; Domes et al., 2010; Lischke et al., 2011), by combining genetics, functional and structural brain imaging, and sociobehavioral measures. Crucially, the model proposes that interactions between neuroendocrine and sociobehavioral factors need to be considered from a developmental perspective, taking age variations into account. Along these lines, the model offers a theoretical framework to address vital research questions: (1) Are OT-related genotypes associated with composition and quality of social networks in the elderly? How do brain structures involved in social processing such as mPFC and OFC, temporoparietal junction, or amygdala mediate these relationships? (2) Is older adults' increased social avoidance compared to approach motivation represented in neural processing differences in brain networks involving PFC and amygdala? To what extent do these associations interact with OT-related genotypes? (3) Are detrimental effects that early abuse has on morbidity and mortality in the elderly moderated by OT-related genotypes or OT levels? How is this relationship structurally and functionally represented in the brain? (4) Are effects of social relationships on cognitive functioning in the elderly mediated by the OT system (either OT-levels or OT-related genotypes)? Do structural changes in brain regions such as the hippocampus underlie this relationship?

In the attempt to provide a concrete empirical application of the *AGeNeS-OT Model*, we here present a preliminary report of an experiment in which we examined associations between *OXTR* polymorphisms, brain activity and behavioral response during reading of facial emotions in young and older adults. This exploratory, secondary data analysis was based on our group's previous finding of increased activation in ventromedial PFC (vmPFC) during emotion identification of happy compared to angry faces and increased dorsomedial PFC (dmPFC) activity to angry compared to happy faces (Ebner et al., 2012; see also Keightley et al., 2007) in both young and older adults. In the present set of analyses, we examined the extent to which these processing differences in mPFC would be further qualified when considering *OXTR* polymorphisms in both of the age groups. In particular, we examined (1) the extent to which *OXTR* polymorphisms were associated with differences in young and older adults' brain activity in bilateral mPFC (Haxby et al., 2000, 2002; Pessoa and Adolphs, 2010; Ebner et al., 2012) during a facial emotion reading task; and (2) the extent to which *OXTR* polymorphisms were associated with young and older adults' ability to read facial emotions.

Young [$n = 25$, 12 females, $M = 25.1$ years ($SD = 3.6$, range = 20–31)] and older [$n = 29$, 17 females, $M = 68.3$ years ($SD = 2.8$, range = 65–74)] healthy participants underwent fMRI on a 3T Siemens Magnetom TrioTim scanner, while identifying happy, neutral, and angry facial emotions (see Ebner et al., 2012, for details on participants, study design, and image acquisition). Participants were subsequently genotyped by KBioscience (http://www.kbioscience.co.uk) using KASPar methodology for 14 *OXTR* single nucleotide polymorphisms (SNPs in order from the 3′ to the 5′ end: rs7632287, rs6770632, rs1042778, rs237887, rs2268493, rs2254298, rs53576, rs237897, rs4686302, rs4564970, rs2301261, rs2268498, rs2270465, rs75775), previously shown to be associated with social behavior (Apicella et al., 2010; Meyer-Lindenberg et al., 2011; Ebstein et al., 2012; Walum et al., 2012; Westberg and Walum, 2013).

Data from this event-related fMRI study was analyzed using Statistical Parametric Mapping (SPM5; Wellcome Department of Imaging Neuroscience) and pre-processing and data analysis was conducted as reported in Ebner et al. (2012). The following *T*-contrasts were specified across young and older adults, based on our previous findings (Ebner et al., 2012): (1) *Happy Faces* > *Angry Faces*, (2) *Angry Faces* > *Happy Faces*. We focused on select regions of interest (ROIs: bilateral medial frontal gyrus and anterior cingulate gyrus) in which we had previously seen processing differences for happy vs. angry faces, at a threshold of $p < 0.05$, FDR corrected. For each region of activation identified by these two contrasts, peak voxel beta values were extracted for each participant to produce a single value for each condition of interest. These values are depicted in the bar graphs of **Figure 4**. In the fashion of follow-up *F*- and *t*-tests ($p < 0.05$), for each of the 14 *OXTR* SNPs that were genotyped, we examined differences in brain activation between polymorphisms across the total sample as well as separately for young and older adults. The most consistent associations found in these analyses were in relation to *OXTR* rs237887 (cf. Lerer et al., 2008; Israel et al., 2009; Liu et al., 2010; Lori et al., 2012; but see Apicella et al., 2010).

OXTR rs237887 AA carriers ($n = 10$ young participants; $n = 10$ older participants) and GA/GG carriers ($n = 15$ young participants; $n = 19$ older participants) were comparable in terms of chronological age, level of education, cognitive status (e.g., Mini Mental State Examination; Folstein et al., 1975; 2-Back Digits Task; Kirchner, 1958; Verbal Fluency Task; Lezak, 1995), and affective variables (Geriatric Depression Scale; Brink et al., 1982; Gottfries, 1997; State-Trait Anxiety Inventory; Spielberger et al., 1970).

For the contrast *Happy Faces* > *Angry Faces*, we found greater BOLD response to happy compared to angry faces in bilateral anterior cingulate cortex (ACC; MNI: $x = 3$, $y = 45$, $z = 0$ and $x = -3$, $y = 51$, $z = 0$) and bilateral mPFC (MNI: $x = 3$, $y = 60$, $z = -3$ and $x = -3$, $y = 57$, $z = -3$). **Figure 4A** shows brain activity in left ACC (MNI: $x = -3$, $y = 51$, $z = 0$) for this contrast. To then examine associations between *OXTR* rs237887 polymorphisms and brain activity during facial emotion identification of happy vs. angry faces in young and older adults, we conducted follow-up univariate ANOVA collapsed across young and older participants on extracted beta values at the peak voxel of activation. Left ACC activity was greater for AA carriers than GA/GG carriers [$F_{(1,\ 51)} = 6.51$, $p = 0.014$, $\eta_p^2 = 0.11$; see **Figure 4B**]. More interestingly, however, this effect was more pronounced in older than young adults, as tested in univariate ANOVAs conducted separately within young and older participants [Young participants: $F_{(1,\ 23)} = 2.38$, $p = 0.136$, $\eta_p^2 =$

0.09; Older participants: $F_{(1,\ 26)} = 3.09$, $p = 0.035$, $\eta_p^2 = 0.16$; see **Figure 4C**]. A comparable pattern of results was found for right ACC [$F_{(1,\ 51)} = 6.34$, $p = 0.015$, $\eta_p^2 = 0.11$]. In addition, the results for left [$F_{(1,\ 51)} = 3.24$, $p = 0.078$, $\eta_p^2 = 0.06$] and right [$F_{(1,\ 51)} = 1.29, p = 0.261, \eta_p^2 = 0.03$] mPFC pointed in the same direction but were not significant.

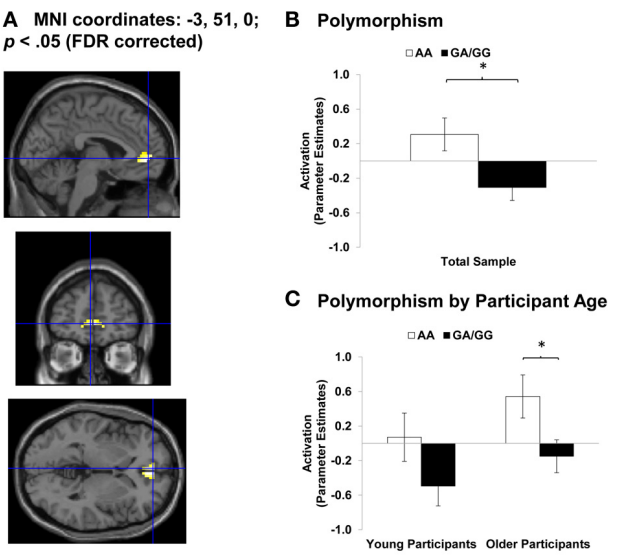

FIGURE 4 | Area of Anterior Cingulate Cortex (ACC) showing Happy Faces > Angry Faces (T-contrast). (A) Left ACC (BA 32, 10; MNI: $x = -3$, $y = 51$, $z = 0$; cluster size: 26 voxels; maximum *T*-value for cluster: 4.19). The region of activation represents the T-map of the contrast; it is displayed on the standard reference brain in SPM. The crosshair indicates the peak voxel (local maximum) within the region of activation. **(B)** Bar graphs show the mean left ACC parameter estimates (beta values) separately for *OXTR* rs237887 AA and GA/GG carriers. **(C)** Bar graphs show the mean left ACC parameter estimates (beta values) separately for *OXTR* rs237887 AA and GA/GG carriers and young and older participants, respectively; betas depicted were extracted for each individual from a 5-mm sphere around the local maximum within the region of activation and averaged to produce a single value for each condition of interest, respectively. Note. $^*p < 0.05$. Error bars represent standard errors of the between-group differences.

ACC is a brain region associated with affective processing (Bush et al., 2000; Amodio and Frith, 2006; Ebner et al., 2012), suggesting that AA compared to GA/GG carriers may process happy compared to angry faces more affectively. This interpretation was further supported by the finding that AA-genotype carriers of *OXTR* rs237887 ($M = 1111$ ms, $SD = 171$ ms) were faster at labeling happy expressions than individuals carrying a G-allele [$M = 1212$ ms, $SD = 173$ ms; $F_{(1,\ 50)} = 4.26$, $p = 0.044$, $\eta_p^2 = 0.08$], with comparable effects in young and older participants. No comparable effect was found for accuracy in emotion expression identification. However, interestingly, greater recruitment of right ACC in individuals carrying a G-allele was positively correlated ($r = 0.35$; $p = 0.049$) with accuracy in reading happy faces but uncorrelated in AA-genotype carriers ($r = 0.05$; $p = 0.838$). This suggests that GA/GG carriers, as the group who needed more time on the task, benefitted from recruiting ACC during the facial emotion reading task. This positive brain-behavior correlation in GA/GG carriers was comparable in young and older participants (Fisher's $z = -0.42$; $p = 0.337$).

For the contrast *Angry Faces > Happy Faces*, we found greater BOLD response to angry compared to happy faces in left mPFC (MNI: $x = -6$, $y = 15$, $z = 51$). In a follow-up univariate ANOVA collapsed across young and older participants on extracted beta values at the peak voxel of activation, activity in left mPFC did not vary by *OXTR* rs237887 polymorphism ($p > 0.05$).

To our knowledge this is the first study that considers young and older participants in a genetic-neuro-behavioral examination of facial emotion processing, as suggested in the *AGeNeS-OT model*. Though this secondary data analysis was largely exploratory and replication in a larger independent sample of young and older adults is warranted, our study provides some first indication of a role of *OXTR* rs237887 in reading positive compared to negative facial expressions, with some variation as a function of the age of the participant. Intriguingly, *OXTR* rs237887 has previously been associated with susceptibility for

Box 1 | Questions for future research.

1. Is aging accompanied by increases or decreases in central and peripheral release of OT?
2. Does the dynamic activity of the OT system change with age and, if so, how and why?
3. Do age-related differences in OT system dynamics underlie age-related differences in socioemotional functioning? If so, how do these changes frame our understanding of the age-associated changes in important social skills (i.e., reading facial emotions, face memory, approach, and avoidance behavior)?
4. How do OT-related individual genetic (and epigenetic) differences interact with neural and behavior age-related changes in socioemotional domains?
5. Does the OT system mediate some of the effects of adverse early experience on health and well-being? How does this play out in old age?
6. Does the OT system mediate some of the salutary psychological and health effects of ongoing social relationships (both intimate and larger social networks)? To what extent do age-related changes in social relationships influence these effects?
7. How do sex differences in OT system dynamics play out in the context of aging? For example, what is the role of age-related changes in estrogen and testosterone?
8. Does the OT system have a role in age-related changes in cognition and memory?
9. Might OT be an effective treatment for conditions like social anxiety or depression in the elderly? Would such treatment improve quality of life?
10. Might older adults be at increased risk of OT-related side effects (i.e., hyponatremia) with chronic dosing?

ASD (Liu et al., 2010), prosocial behavior (Israel et al., 2009, but see Apicella et al., 2010), and face recognition (Lori et al., 2012). We found improved processing of happy compared to angry faces for AA carriers compared to GA/GG carriers, as reflected in their faster response time in reading happy faces and their increased recruitment of ACC during emotion reading of happy compared to angry faces. Examining young and older participants separately, this increased activation of ACC in AA compared to GA/GG carriers was more pronounced in older than young participants. This is very interesting given broad evidence of preferential processing of positive over negative information in older compared to young adults (Mather and Carstensen, 2005). In addition, our findings suggest that GA/GG carriers' ability to correctly identify happy faces improved when recruiting ACC during the task.

FUTURE TRENDS IN RESEARCH ON OXYTOCIN AND SOCIOEMOTIONAL AGING

Taken together, this research review indicates that a targeted investigation of age-related changes in the OT system—especially one that considers genetic, neural, and behavioral processes—has the potential to substantively increase our understanding of socioemotional change in aging. We believe that our *AGeNeS-OT model* will be a fruitful conceptual basis in that it raises a set of vital research questions necessary to refine our understanding of OT-related dynamics in aging in socioemotional contexts (see **Box 1**). In addition, future research along those lines has great potential to inform both pharmacological and psychosocial interventions targeting social and emotional dysfunction in the elderly. In particular, there is an increasing body of research suggesting a significant role of OT in the context of various disorders characterized by socioemotional dysfunction such as social-bonding deficits or related to social anxiety and stress (Zetzsche et al., 1996; Heinrichs et al., 2003; Taylor et al., 2006; see MacDonald and Feifel, 2012, for an overview), deficits with great relevance in an aging context. Thus, future research toward implementation of pharmacological neuropeptide treatments with the potential to decrease emotional and social stress, anxiety, and depression (Arletti and Bertolini, 1987; Carter and Altemus, 1997) will be important. These interventions may consequently promote positive social interaction and willingness to engage in more frequently rewarding social risks (Heinrichs et al., 2003; Kosfeld et al., 2005), improving health and life quality up until late in life.

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Environmental enrichment restores neurogenesis and rapid acquisition in aged rats

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Abstract

Strategies combatting cognitive decline among the growing aging population are vital. We tested whether environmental enrichment could reverse age-impaired rapid spatial search strategy acquisition concomitantly with hippocampal neurogenesis in rats. Young (5–8 months) and aged (20–22 months) male Fischer 344 rats were pair-housed and exposed to environmental enrichment ($n = 7$ young, 9 aged) or housed individually ($n = 7$ young, 7 aged) for 10 weeks. After 5 weeks, hidden platform trials (5 blocks of 3 trials; 15 m inter-block interval), a probe trial, and then visible platform trials (5 blocks of 3 trials; 15 m inter-block interval) commenced in the water maze. One week after testing, rats were given 5 daily intraperitoneal bromodeoxyuridine (50 mg/kg) injections and perfused 4 weeks later to quantify neurogenesis. Although young rats outperformed aged rats, aged enriched rats outperformed aged individually housed rats on all behavioral measures. Neurogenesis decreased with age but enrichment enhanced new cell survival, regardless of age. The novel correlation between new neuron number and behavioral measures obtained in a rapid water maze task among aged rats, suggests that environmental enrichment increases their ability to rapidly acquire and flexibly use spatial information along with neurogenesis.

Keywords: Adult neurogenesis; Learning; Memory; Enrichment; Water maze; Age-related; Fisher 344; Neural progenitor cell; Hippocampus

1. Introduction

Altered hippocampal function likely contributes to age-related changes in cognitive ability because hippocampus-dependent tasks are sensitive to age-related cognitive decline (Foster, 1999). Decades ago, the standard Morris water maze task revealed impaired performances among some senescent rats (Gage et al., 1984; Rapp et al., 1987). More recent behavioral assessments have sought to increase task sensitivity to age-related cognitive decline (Kennard and Woodruff-Pak, 2011), so that the deficits and their underlying mechanisms can be better characterized and potentially manipulated. Here we employ a rapid water maze task sensitive to age-related cognitive decline to test whether daily exposure to an enriched environment can reverse the effects of age on hippocampal function concomitantly with hippocampal neurogenesis.

Neurogenesis is a striking form of neural plasticity that persists throughout life in the hippocampus and olfactory bulbs of all mammals investigated, including humans (Altman and Das, 1965; Cameron et al., 1993; Eriksson et al., 1998). Although the precise role that new neurons play in hippocampal integrity is debated, new neuron number in young animals generally correlates with their performance measures in hippocampus-dependent tasks (Deng et al., 2010; but see Epp and Galea, 2009). Manipulations that attenuate neurogenesis chronically associate with impaired performance (Madsen et al., 2003; Raber et al., 2004; Saxe

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et al., 2006; Shors et al., 2002; Snyder et al., 2005; Winocur et al., 2006) while those that potentiate neurogenesis associate with better performance (Ormerod et al., 2004; van Praag et al., 2005; Dalla et al., 2009). Postmortem signs of hippocampal neurogenesis in human patients who exhibited profound memory impairments are scarce (Coras et al., 2010; Correa et al., 2004; Crossen et al., 1994; Monje et al., 2007; Roman and Sperduto, 1995; Siffert and Allen, 2000).

Hippocampal neurogenesis declines with age in rodents primarily because neural progenitor cells (NPCs) become increasingly quiescent and NPCs that do divide may be less likely to produce surviving neuronal progeny (Cameron and McKay, 1999; Hattiangady and Shetty, 2008; Kempermann et al., 1997; Kuhn et al., 1996; Lichtenwalner et al., 2001; Nacher et al., 2003). While several studies have related new neuron number and cognitive measures in aged rats (Drapeau et al., 2003, 2007; Driscoll et al., 2006; Lemaire et al., 2000), dogs (Siwak-Tapp et al., 2007), and nonhuman primates (Aizawa et al., 2009), the strength of this relationship among aged rats tested in the water maze varies. For example, new neuron number appears unrelated to the performance of aged rats in water maze tasks that distribute training across 8–10 days (Bizon and Gallagher, 2003; Bizon et al., 2004; Merrill et al., 2003) but related in protocols that mass training across 2–3 days (Drapeau et al., 2003; Driscoll et al., 2006). Moreover, new neuron survival in the hippocampi of aged rats is enhanced by their participation in early but not later trials of the distributed water maze protocol (Drapeau et al., 2007). These results suggest that the strength of the relationship between neurogenesis and water maze performance in aged rats may depend upon the speed of learning demanded by the task.

In aged rodents, daily exposure to environmental enrichment primarily stimulates neurogenesis by increasing the probability that new neurons survive to maturity (Kempermann et al., 1997, 1998, 2002; Leal-Galicia et al., 2008; Segovia et al., 2006) and improves the rapid acquisition of spatial information in a condensed water maze task (Kumar et al., 2012). Here we tested the hypothesis that daily exposure to environmental enrichment would reverse age-related impairments in rats' abilities to rapidly acquire a spatial search strategy concomitantly with ongoing rates of neurogenesis.

2. Methods

2.1. Subjects

Young (5–8 months old) and aged (20–22 months old) sexually naive male F344 rats obtained from the National Institute of Aging colony at Harlan Sprague Dawley (Indianapolis, IN, USA) were treated in accordance with University of Florida and federal policies regarding the ethical use of animals for experimentation. Rats exhibiting signs of aggression (bites and scratches) or age-related health problems (poor grooming, hunching, excessive porphyrin secretion, weight loss, and tumors) were euthanized humanely.

2.2. Differential experience: environmental enrichment and individual housing

For the 10-week experiment, the rats were housed in a 12:12 hour light cycle with access to food and water *ad libitum* either individually ($n = 7$ young [YI] and $n = 7$ aged [AI]) or pair housed with 2–3 hours of access daily to an enriched environment ($n = 7$ young [YE] and $n = 9$ aged [AE]). The goal of the differential experience protocol was to provide opportunities for the enriched group to engage in a variety of hippocampus-dependent behaviors while limiting them for the individually housed group. The enriched environment consisted of a large wooden box, empty water maze tank, or large wire cage containing assorted 3-dimensional toys (e.g., plastic tubes, balls, and various objects), food, and water. The environment and toys were randomly rotated daily to maintain novelty. Daily exposure to this environment modifies hippocampal electrophysiology and facilitates the rapid acquisition of a spatial search strategy in aged rats (Foster and Dumas, 2001; Kumar et al., 2007, 2012). Behavioral testing commenced in the 4th week of differential experience and bromodeoxyuridine (BrdU) injections commenced 1 week after behavioral testing was completed. The rats were perfused 4 weeks after the final BrdU injection to quantify neurogenesis (Fig. 1).

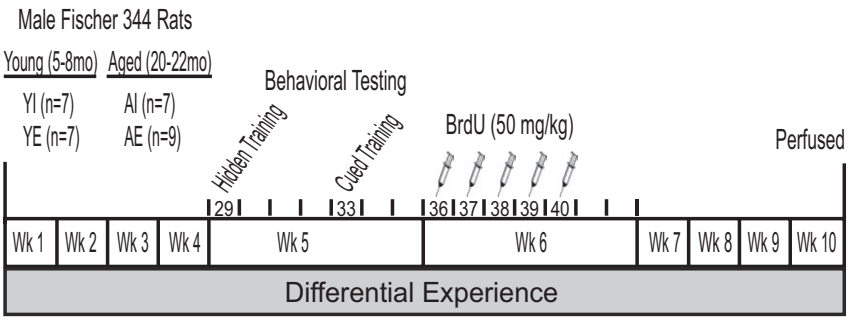

Fig. 1. Experiment timeline. Rats were housed individually ($n = 7$ young, $n = 7$ aged) or in pairs and exposed to an enriched environment daily ($n = 7$ young, $n = 9$ aged) for 10 weeks. In the 5th week, rats were trained and tested on hidden platform trials and then visible platform trials 3 days later. Beginning 1 week after testing, rats were injected daily with bromodeoxyuridine (BrdU; 50 mg/kg) over 5 days and then perfused 4 weeks later to quantify neurogenesis.

2.3. Water maze training and testing

A black water maze tank (1.7 m diameter) filled with water (27 ± 2 °C) to a depth of 8 cm below its rim was housed in a well-lit room. A Columbus Instruments (Columbus, OH, USA) tracking system recorded escape latencies (seconds) and path lengths (cm; see Fig. 2). Hidden and cued platform training consisted of 5 blocks (15 minute inter-block interval) of 3 60-second trials (20 second inter-trial interval) administered in a single session. This massed protocol is sensitive to both age-related cognitive decline (Carter et al., 2009; Foster and Kumar, 2007; Foster et al., 2003) and the effects of differential experience on cognition in aged rats (Kumar et al., 2012). Rats were dried between blocks.

2.3.1. Hidden platform trials

After 4 weeks of differential experience, rats were trained over a single session to locate a platform (29 cm diameter) hidden approximately 1 cm below the water surface in the north-east quadrant of the pool in the presence of highly visible extramaze cues. Rats were first habituated to the pool by being given 3 opportunities to climb onto the platform from different directions. On the subsequent hidden platform trials, the rats were released randomly from north, south, west, or east start locations and given 60 seconds to locate the hidden platform before being guided.

2.3.2. Probe trial

A 60-second free swim probe trial during which the platform was removed from the pool was conducted 15 minutes after the last hidden platform training block. The rats were released from the quadrant opposite the goal quadrant and discrimination scores $[t(G) - t(O)]/[t(G) + t(O)]$, where t(O) is time spent in the opposite quadrant and t(G) is time spent in the goal quadrant, served as our strength of learning measure.

2.3.3. Cued trials

Three days after the hidden platform training session, rats were trained to locate the now flagged platform that protruded approximately 1.5 cm above the water in water maze tank now surrounded by a black curtain to mask distal cues. The rats were guided to the flagged platform if they failed to escape the maze within 60 seconds. The north, south east, and west release points and the location of the flagged platform were changed on each trial.

2.4. BrdU injections and histology

BrdU was dissolved in fresh 0.9% sterile saline (20 mg/mL wt/vol) and injected intraperitoneally (2.5 mL/kg or 50 mg/kg) once per day over 5 days, starting 1 week after behavioral testing to minimize the well-known effects of learning on neurogenesis (Epp et al., 2010; Gould et al., 1999). This BrdU dose safely and effectively labels dividing NPCs in the hippocampus of young and aged adult rodents (Cameron and McKay, 2001; Drapeau et al., 2003; Kolb et al., 1999).

Approximately 4 weeks after the final BrdU injection, the rats were anesthetized with 90 mg/kg ketamine and 10 mg/kg xylazine (Webster Veterinary, Sterling, MA, USA) and perfused transcardially with ice-cold isotonic saline and 4% paraformaldehyde (Electron Microscopy Sciences, Hatfield, PA, USA). By 4 weeks, many new cells express mature neuronal proteins and are relatively permanent (Cameron and McKay, 2001; van Praag et al., 2002). Extracted brains were stored overnight in perfusate, equilibrated in 30% sucrose (appproximately 4 days) at 4 °C and then sectioned coronally through the rostral caudal extent of the hippocampal dentate gyrus at 40 μm intervals using a freezing stage sledge microtome (American Optical Corp., Buffalo, NY, USA). Sections were stored at −20 °C in 30% ethylene glycol, 25% glycerin, and 45% 0.1 M sodium phosphate buffer (vol/vol/vol) until immunostained.

2.5. Immunohistochemistry

Free-floating sections were stained immunohistochemically to quantify 28-32 day-old $BrdU^+$ cells and confirm their neuronal or glial phenotypes as described previously (Ormerod et al., 2004; Palmer et al., 2000). Sections were washed repeatedly between steps in Tris-buffered saline (TBS; pH 7.4).

2.5.1. Enzyme substrate immunostaining

$BrdU^+$ cells were revealed enzymatically on every 12th section through the dentate gyrus of each rat and counted under light microscopy to estimate total new cell numbers (Fig. 3). Sections were incubated in 0.3% H_2O_2 for 10 minutes to quench endogenous peroxidase, rinsed in 0.9% NaCl and then incubated in 2M HCl for 20 minutes at 37 °C to denature DNA. The sections were then blocked in a solution of 3% normal donkey serum and 0.1% Triton-X in TBS and incubated overnight in blocking solution containing rat anti-BrdU (1:500; AbD Serotec, Raleigh, NC, USA) at 4 °C and then for 4 hours in biotinylated secondary anti-rat IgG (Jackson ImmunoResearch, West Grove, PA, USA; 1:500) at room temperature (RT). Next, the sections were incubated in avidin-biotin horseradish peroxidase (Vector Laboratories, Burlingame, CA, USA) and then reacted in a solution of 0.02% 3,3'-diaminobenzidine tetrahydrochloride (DAB; Sigma Aldrich, St. Louis, MO, USA) and 0.5% H_2O_2. Sections were mounted on glass slides, dried overnight, dehydrated in an alcohol series and then coverslipped under Permount (Fisher Scientific, Pittsburgh, PA, USA).

2.5.2. Fluorescent immunostaining

The percentage of $BrdU^+$ cells expressing neuronal or glial protein was quantified on sections that were immunostained using fluorescent secondary antibodies under confocal microscopy (Fig. 4). The sections were blocked in a

solution of 3% normal donkey serum and 0.1% Triton-X in TBS and then incubated overnight at 4 °C in blocking solution containing the mature neuronal marker mouse anti-Neuronal Nucleii (NeuN, 1:500; Chemicon, Temecula, CA, USA) and the immature neuronal marker goat anti-doublecortin (DCX, 1:500; Santa Cruz Biotechnology, Santa Cruz, CA, USA) or the oligodendrocyte precursor marker rabbit anti-chondroitin sulfate proteoglycan (NG2, 1:500; Chemicon) and the astrocyte marker chicken anti-glial fibrillary acidic protein (GFAP, 1:750; EnCor Biotech, Alachua, FL, USA). The next day, sections were incubated in maximally cross-adsorbed fluorescein isothiocyanate (FITC)-conjugated anti-mouse and cyanine 5 (Cy5)-conjugated anti-goat secondary antibodies to reveal neurons or FITC-conjugated anti-rabbit and Cy5-conjugated anti-chicken secondary antibodies to reveal glia for 4 hours at RT (all secondary antibodies 1:500; Jackson Immunoresearch, Westgrove, PA, USA). Sections were then fixed in 4% paraformaldehyde, rinsed in 0.9% NaCl, incubated in 2 M HCl and then incubated overnight at 4 °C in rat anti-BrdU (1:500; AbD Serotec, Raleigh, NC, USA) and then Cy3-conjugated anti-rat secondary for 4 hours at RT the next day before being incubated in 4',6-diamidino-2-phenylindole (DAPI; 1:10,000; Calbiochem, San Diego, CA, USA) for 10 minutes and then mounted on glass slides under 2.5% diazobicyclooctane (in TBS with 10% polyvinyl alcohol and 20% glycerol).

2.6. Cell quantification

2.6.1. Total new cell number

$BrdU^+$ cells distributed through the subgranular zones and granule cell layers (GCL; Fig. 3A) were counted on sets of every 12th section (9–10 sections per rat) through the rostral-caudal extent of the hippocampal dentate gyrus under a 40× objective on a Zeiss AxioObserver Z1 inverted microscope (Thornwood, NY, USA) and optical fractionator principles (Kempermann et al., 2002; West et al., 1991). The first section of each rat's set was randomly selected from the 1st–11th section of dentate gyrus. Because $BrdU^+$ cells are typically distributed irregularly, we counted all new cells (mean ± standard error of the mean [SEM] total $BrdU^+$ cells: YI = 297 ± 66; YE = 493 ± 75; AI = 183 ± 25; AE = 370 ± 51), excluding obvious cell "caps" that could represent cells in adjacent cell sections and multiplied that number by 12 (the section interval) to generate a stereological estimate of total cell number (see Fig. 3) without fractionating section thickness (Kempermann et al., 2002). Because age- or enrichment-related changes in $BrdU^+$ cell nucleus diameter could affect cell estimates estimated this way, we confirmed that nuclear diameters of approximately 10–20 $BrdU^+$ cells completely contained within 1 of these sections in 3–4 rats per group were consistent (YI = 8.48 ± 0.40 μm, YE = 8.19 ± 0.13 μm, AI = 8.79 ± 0.33 μm and AE = 8.79 ± 0.22 μm; age effect [$F(1,9) = 2.82$], enrichment effect [$F(1,9) = 0.29$], interaction effect [$F(1,9) = 0.28$]). Because exposure to enriched environments can increase hippocampal volumes, we measured GCL and subgranular zone areas (in mm^2) under a 20× objective using AxioVision software (version 4.8, Zeiss, Thornwood, NY, USA) and then calculated volumes using a truncated cone formula that accurately predicts the volume of many biological regions (Galea et al., 2000; Seifert et al., 2010; Uylings et al., 1986): Volume = $\frac{1}{3}I(h_1 + \sqrt{h_1} \times \sqrt{h_2} + h_2)$, where I is the distance between sections (480 μm) and the 2 section areas for which volumes between are calculated are h_1 and h_2. Although neither age nor differential experience affected $BrdU^+$ cell nuclei diameters, $BrdU^+$ cells per mm^2 as well as total cell estimates are reported because of expected effects of enrichment on dentate volumes.

2.6.2. New cell phenotypes

To determine whether new cells differentiated into neurons or glia, we examined at least 100 $BrdU^+$ cells on quadruple fluorescent-stained sections (2–4 in young rats and 4–6 in aged rats) randomly selected from a set of every 12th section through the dentate gyrus for the coexpression of neuronal and glial proteins using a Zeiss meta LSM 710 fully spectral laser scanning confocal microscope with 405, 488, 543 and 633nm laser lines (Thornwood, NY, USA) under a 40× objective (and 2.3× digital zoom). $BrdU^+$ cells were considered colabeled when a full "z-dimension" scan revealed its BrdU/$DAPI^+$ nucleus was unambiguously associated with DCX and/or NeuN, NG2, or GFAP. The percentage of $BrdU^+$ cells expressing each protein was calculated (Fig. 4).

2.7. Statistical analyses

Statistical analyses were performed using Statistica software (Version 10; Statsoft, Tulsa, OK, USA). Analyses of variance (ANOVA) explored the effects age (young, aged) and experience (individually housed, enriched group-housed), on cognitive (latencies, path lengths, and probe trial discrimination index scores), health (body mass, swim speeds), and neurogenesis (new cell numbers, percentage and total new neurons and glia) measures and Newman–Keuls post hoc tests revealed group differences. χ^2 tests revealed the number of animals that performed at or above chance on probe trials and Pearson product moment correlations (r) tested relationships between neurogenesis and behavioral measures. The α level for all statistical tests was set at 0.05.

3. Results

3.1. Daily enrichment partially reverses the effect of age on spatial ability

3.1.1. Enrichment enhances spatial learning in aged rats

Because measures of path length and latency over trials were correlated positively ($r(29) = 0.82$; $p < 0.0001$), we

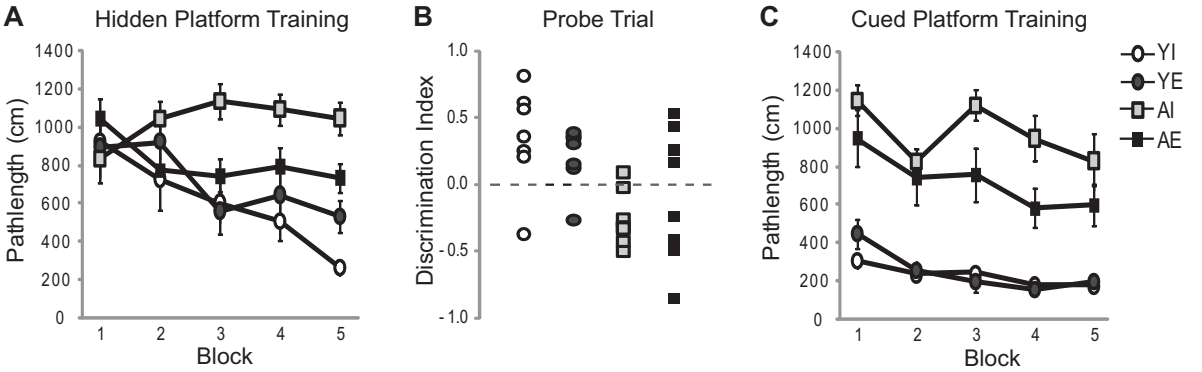

Fig. 2. Exposure to an enriched environment subdues age-dependent impairments on hidden and visible platform trials. The rats were trained on hidden platform trials (A), tested on a probe trial administered 15 minutes after the last hidden platform trial (B) and cued platform trials 3 days later (C). Line graphs depict group means (± standard error of the mean) of measures obtained from the young rats housed individually (YI; white circles), young rats housed in an enriched environment (YE; dark gray circles), aged rats housed individually (AI; light gray squares) and aged rats housed in an enriched environment (AE; black squares) groups. (A) Enrichment enhanced the ability of aged rats to rapidly acquire a spatial search strategy. On all training blocks combined, young rats swam more directly to the hidden platform than aged rats. AI rats swam more circuitous routes to the hidden platform than either AE rats or young rats in either group. (B) Probe trial discrimination index (DI) scores varied by age and experience. χ^2 tests confirmed that the percentage of rats that performed above or below chance (discrimination index (DI) score = 0, dashed line) decreased with age but increased with exposure to enrichment. Specifically, 69% of enriched rats performed above chance whereas only 50% of individually housed rats performed above chance. (C) Previous experience influences performance on visible platform trials. Young rats outperformed aged rats on all training blocks, including the initial training block, likely because they retained procedural information from the spatial task and AE rats outperformed AI rats.

report only path lengths to avoid redundancy. An ANOVA exploring the effects of age (young vs. aged), training block (blocks 1–5), and differential experience (individually housed vs. enriched) on path length (Fig. 2A) revealed significant effects of age ($F(1,26) = 15.65$; $p < 0.001$) and training block ($F(4,104) = 5.85$; $p < 0.001$) and significant age × environment ($F(1,26) = 5.57$; $p < 0.05$), age × training block ($F(4,104) = 4.94$; $p < 0.001$) and age × environment × training block ($F(4,104) = 3.24$; $p < 0.05$) interaction effects. All rats improved their performance across blocks (block 1 > 3–5 and 3 > 5; p values < 0.005) but, as expected, young rats outperformed aged rats. Across all blocks, AI rats performed more poorly than AE rats ($p < 0.05$) and young rats in either group (p values < 0.001) while YI and YE rats' performance improved equally rapidly across training blocks (p values > 0.1). Specifically, AI rats performed significantly more poorly on training blocks 3, 4, and 5 (p values < 0.01) and AE rats performed significantly more poorly only on training block 5 relative to YI and YE rats (p values < 0.01).

An ANOVA on swim speeds (mean ± [SEM] cm/second = 26.06 ±1.07 [YI], 29.92 ± 2.07 [YE], 19.45 ± 0.94 [AI], and 18.68 ± 1.64 [AE]) revealed a significant effect of age ($F(1,26) = 33.49$; $p < 0.001$) and a significant environment × training block interaction ($F(4,104) = 2.68$; $p < 0.05$). Young rats swam significantly faster than aged rats across all training blocks and enriched rats swam significantly faster during the first training block relative to all other training blocks (p values < 0.05). The effects of age on swim speed are unsurprising because aged rats were heavier than young rats (mean [± SEM] g = 336.83 ± 6.38 [YI], 347.37 ± 4.44 [YE], 419.21 ± 10.78 [AI], and 406.74 ± 8.21 [AE]; $F(1,26) = 78.87$; $p < 0.001$). The effect of enrichment on the performance of aged rats on hidden trials is likely related to cognition because enrichment neither affected swim speeds nor body mass in aged rats.

An ANOVA exploring the effects of age, training block, and environment on the percent of time spent in the outer annulus during hidden platform trials (mean [± SEM] % = 56.07 ± 4.47 [YI], 43.00 ± 4.15 [YE], 81.98 ± 0.92 [AI], and 64.32 ± 3.13 [AE]) revealed significant effects of age ($F(1,26) = 46.63$; $p < 0.0001$), environment ($F(1,26) = 19.76$; $p < 0.0001$), training block ($F(4,104) = 3.32$; $p < 0.05$), and a significant age × training block interaction effect ($F(4,104) = 3.95$; $p < 0.01$). Overall, the percentage of time spent in the outer annulus significantly decreased in young versus aged rats, in enriched versus individually housed rats and on later versus earlier training blocks block 1 and 2 > 5; p values < 0.05). While all young rats decreased their time spent in the outer annulus across blocks (block 1 and 2 > 3–5; p values < 0.01), aged rats maintained their time across blocks (p values > 0.78).

An ANOVA revealed a significant effect of age on probe trial discrimination index scores ($F(1,26) = 8.40$, p values < 0.01) but no effect of environment (Fig. 2B). Because 1 YI and 1 YE rat performed at chance (i.e., discrimination index = 0) and only 1 AI rat performed above chance, χ^2 tests on the percentage of rats performing above or below chance were employed to confirm effects of age ($\chi^2 = 78.55$, $p < 0.0001$) and differential experience ($\chi^2 = 14.44$, $p < 0.0005$), with 69% of enriched rats performing above chance and only 50% of individually housed rats performing above chance. The effect of differential experience was mainly due to an effect of environmental enrichment ob-

served in aged rats ($\chi^2 = 71.59$, $p < 0.0005$). Taken together, these data confirm that although young rats outperformed aged rats, enrichment enhanced the ability of aged rats to rapidly acquire a spatial search strategy.

3.1.2. Enrichment enhances cue discrimination learning in aged rats

An ANOVA exploring the effects of age, training block, and environment on path length for the cued discrimination task revealed significant effects of age ($F(1,26) = 62.37$; $p < 0.001$) and training block ($F(4,104) = 9.92$; $p < 0.001$) but not enrichment. Post hoc tests confirmed that young rats swam more directly to the visible platform than aged rats but that all groups exhibited improved performance across training blocks (block 1 > 2 > 3, 4, and 5; p values ≤ 0.05). An ANOVA across blocks within each age and treatment group indicated a significant effect of training in 3 groups (YE: $F(4,24) = 5.68$; $p < 0.005$; AE: $F(4,32) = 3.66$; $p < 0.05$; AI: $F(4,24) = 3.28$; $p < 0.05$), with a tendency ($p = 0.07$) for a training effect in YI animals. This tendency was due, in part, to near asymptotic performance on the first training block. Indeed, young rats exhibited shorter path lengths on the first block of cue training relative to the first block of spatial training (Fig. 2A and C) indicating a carryover effect of prior training on the spatial task. Finally, age tended to interact with environment ($p < 0.10$) and post hoc tests indicated that AE rats swam shorter path lengths than AI rats ($p = 0.05$; Fig. 2C).

An ANOVA exploring the effects of age, training block, and environment on average swim speed across visible platform trials (YI = 27.88 ± 1.04 cm/second, YE = 26.28 ± 1.33 cm/second, AI = 20.69 ± 1.10 cm/second, and AE = 22.74 ± 1.31 cm/second) confirmed that young rats swam significantly faster than aged rats ($F(1,26) = 18.82$; $p < 0.001$), but there was no effect of differential experience. Age tended to interact with training block ($F(4,104) = 2.32$; $p = 0.062$) such that young rats increased their swim speeds (block 1 < 4–5; p values < 0.05, while aged rats maintained their slower swim speeds ($p > 0.74$) across all blocks.

An ANOVA exploring the effects of age, training block, and environment on the percentage of time spent in the outer annulus during cued platform training (YI = 36.00 ± 2.94%, YE = 28.90 ± 2.94%, AI = 75.14 ± 4.08%, and AE = 64.15 ± 4.69%) revealed significant effects of age ($F(1,26) = 88.64$; $p < 0.0001$) and differential experience ($F(1,26) = 5.24$; $p < 0.05$). Less time was spent in the outer annulus by young versus aged rats and by enriched versus individually housed rats. While all rats decreased the time they spent in the outer annulus across blocks ($F(4,104) = 12.57$; $p < 0.0001$; training blocks 1 and 2 > 3–5; $p < 0.05$), young rats ventured from the maze wall in early trials (block 1 > 2 > 3–5; p values < 0.001) whereas aged rats ventured from the wall only in later training blocks (block 3 > 4 and 5; p values < 0.05; age × block interaction effect: $F(4,104) = 8.18$; $p < 0.001$).

3.2. The effect of enrichment overcomes the effect of age on neurogenesis

3.2.1. Enriched environment reverses the effect of age on total new cell number

An ANOVA revealed significant effects of age ($F(1,26) = 4.26$; $p < 0.05$) and environment ($F(1,26) = 11.14$; $p < 0.01$) on the total number of new ($BrdU^+$) cells produced and/or surviving 4 weeks in young and aged rats (Fig. 3). More new cells were found in the dentate gyri of young versus aged rats and in enriched versus individually housed rats (Fig. 3C). Enrichment similarly increased the number of new cells in the dentate gyri of both young and aged rats. This effect of enrichment appears robust because we found

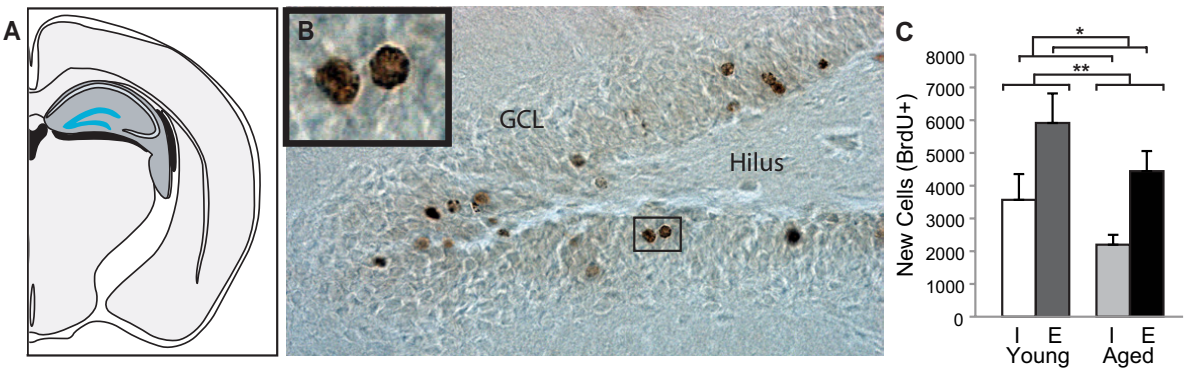

Fig. 3. Exposure to an enriched environment reversed the effects of age on neurogenesis. Rats were given 5 daily injections of bromodeoxyuridine (BrdU) beginning 1 week after behavioral testing and perfused 4 weeks later. The total number of new cells surviving 4 weeks was estimated stereologically using $BrdU^+$ cell counts obtained under light microscopy from every 12th section through the dentate gyrus (DG). The bar graph depicts group means (± standard error of the mean) of total new cell number in the dentate gyri of young rats housed individually (YI; white bars), young rats housed in an enriched environment (YE; dark gray bars), aged rats housed individually (AI; light gray bars) and aged rats housed in an enriched environment (AE; black bars). (A) Coronal view of the rat brain. The dentate granule cell layer (GCL) is highlighted in turquoise. (B) Photomicrograph of new ($BrdU^+$) cells in the DG of an aged rat. Representative examples of 4-5 week-old cells labeled with BrdU (in brown) revealed enzymatically with 3,3'-diaminobenzidine tetrahydrochloride (DAB). (C) Total new cell numbers declined with age but were potentiated by enrichment, regardless of age. More new cells survived approximately 4 weeks in the dentate gyri of young vehrsus aged and enriched versus individually housed rats. * $p \leq 0.05$ and ** $p \leq 0.01$.

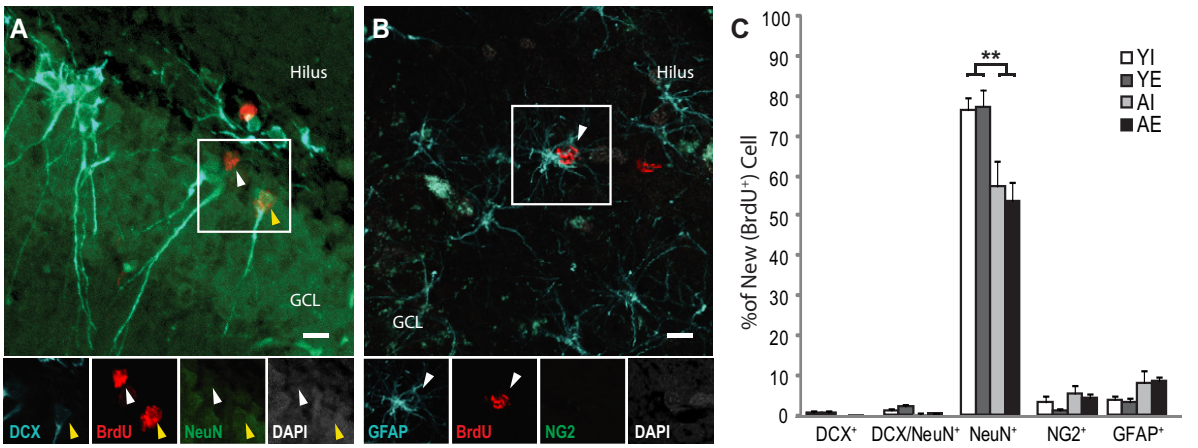

Fig. 4. Fewer new cells expressed mature neuronal phenotypes in the dentate gyri of aged rats. At least 100 bromodeoxyuridine $(BrdU)^+$ cells per rat were examined under confocal microscopy (40× objective with 2.3× digital zoom) to calculate proportions expressing markers of immature (doublecortin $[DCX]^+$), transitioning ($DCX/NeuN^+$), or mature (Neuronal Nucleii $[NeuN]^+$) neurons, as well as glial fibrillary acidic protein $(GFAP)^+$ astrocytes or chondroitin sulfate proteoglycan $(NG2)^+$ oligodendrocyte precursors, which were revealed using fluorescent immunohistochemistry. All $BrdU^+$ cells stained with the nuclear marker 4'6-Diamidino-2-Phenylindole Dihydrochloride (DAPI). (A and B) Confocal images of new neurons and astrocytes in the dentate gyrus of an adult rat. Representative images of approximately 4-week-old $BrdU^+$ cells (in red) that express the neuronal markers DCX (in blue) and/or NeuN (in green; A) or the glial markers GFAP (in blue) or NG2 (in green; B). (C) The proportion of new cells expressing neuronal phenotypes decreased with age and was unaffected by enrichment regardless of age. Mean (± standard error of the mean) percentage of new cells in the dentate gyri of young rats housed individually (YI; white bars), young rats housed in enriched environment (YE; dark gray bars), aged rats housed individually (AI; light gray bars), and aged rats housed in an enriched environment (AE; black bars) expressing neuronal and glial phenotypes are shown. In all rats, the majority of approximately 4-week-old cells expressed mature neuronal phenotypes. However, a lower percentage of new cells expressing mature neuronal phenotypes and a higher percentage of new cells expressing glial phenotypes was detected in aged versus young rats. No effect of differential experience on the percentage of new cells expressing either phenotype was detected in young or aged rats. * $p \leq 0.05$ and ** $p \leq 0.01$.

similarly increased (mean ± [SEM] new cell densities enriched: 1345.13 ± 204.12 cells/mm^3 vs. individually housed: 881.10 ± 156.82 cells/mm^3, $F(1,26) = 5.83$; $p < 0.05$) despite increased GCL volumes (enriched: 3.97 ± 0.31 mm^3 vs. individually housed: 3.25 ± 0.17 mm^3; $F(1,26) = 7.81$; $p < 0.01$). Neither cell density nor GCL volume was affected by age or the interaction between age and environment.

3.2.2. Enriched environment does not reverse the effect of age on neuronal differentiation

We calculated the proportion of $BrdU^+$ cells that coexpressed markers for immature (DCX^+), transitioning ($DCX/NeuN^+$), or mature ($NeuN^+$) neurons, or $GFAP^+$ astrocytes, or $NG2^+$ oligodendrocyte precursors (Fig. 4A–C). An ANOVA exploring the effects of age and environment on the percentage of new cells expressing each phenotype revealed significant effects of age ($F(1,26) = 7.99$; $p < 0.01$) and phenotype ($F(1,104) = 532.30$; $p < 0.001$) and a significant age × phenotype interaction effect ($F(1,104) = 17.18$; $p < 0.001$; Fig. 4D). Consistent with the extended survival period of the study, the majority of new cells expressed a mature neuronal phenotype ($p < 0.0001$ vs. all other phenotypes). Of the < 10% of $BrdU^+$ cells expressing glial or immature neuronal phenotypes, astrocyte phenotypes were expressed most frequently ($p < 0.01$ vs. immature and transitioning neurons). Significantly fewer $BrdU^+$ cells expressed a mature neuronal phenotype in aged versus young rats ($p < 0.0001$) and this effect was not reversed by enrichment. In fact, a higher proportion of $BrdU^+$ cells in aged versus young rats did not express the markers of differentiation employed in this study (YI = 13.80 ± 3.79, YE = 15.94 ± 5.07, AI = 27.85 ± 8.10, AE = 33.05 ± 4.39% $BrdU^+$ cells; $F(1,26) = 8.00$; $p < 0.01$).

3.2.3. Enriched environment increases net neurogenesis

We next determined the total number of new neurons (immature, transitioning, and mature neurons combined) and new glia (oligodendrocytes and astrocytes) by multiplying the estimated total number of $BrdU^+$ cells by the proportion of $BrdU^+$ cells coexpressing each phenotype (Fig. 5). An ANOVA exploring the effects of age and environment on total new neuron number revealed statistically significant effects of age ($F(1,26) = 10.32$; $p < 0.01$) and environment ($F(1,26) = 7.18$; $p < 0.05$). More new neurons were found in the dentate gyri of young versus aged rats and in enriched versus individually housed rats (Fig. 5A). Importantly, no age × environment interaction was observed indicating that enrichment increased net neurogenesis similarly in young and aged rats. An ANOVA exploring the effects of age and environment on total new glia revealed a statistically significant effect only for age ($F(1,26) = 4.26$; $p = 0.05$), such that more new glia (primarily astrocytes) were found in the dentate gyri of aged versus young rats (Fig. 5B). However, the reliability of this effect requires replication in future work because of the low frequency in which new glia were observed.

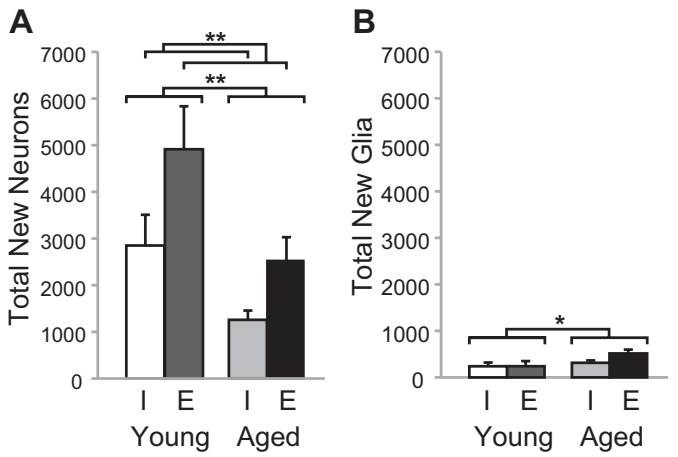

Fig. 5. Net neurogenesis declines with age but is increased by exposure to enrichment whereas age-dependent increases in gliogenesis are unaffected by enrichment. Net neurogenesis and gliogenesis was calculated by multiplying total new cell numbers (Fig. 3) by percentage of new cells expressing neuronal and glial phenotypes (Fig. 4), respectively. The bar graphs depict group mean (± standard error of the mean) numbers of neurons (A) or glia (B) in the dentate gyri of young rats housed individually (YI; white bars), young rats housed in an enriched environment (YE; dark gray bars), aged rats housed individually (AI; light gray bars), and aged rats housed in an enriched environment (AE; black bars) rats. (A) Net neurogenesis declines with age but increases with enrichment, independent of age. Neurogenesis declined with age and was potentiated by exposure to an enriched environment regardless of age. A few weeks of exposure to an enriched environment, therefore, returned levels of hippocampal neurogenesis in aged rats to those observed in young individually housed rats. (B) Age-dependent increases in gliogenesis are unaffected by exposure to enrichment. We detected a small but significant increase in gliogenesis in aged versus young rats that was unaffected by differential experience. * $p \leq 0.05$ and ** $p \leq 0.01$.

3.3. Higher rates of neurogenesis relate to better water maze performance in aged rats

Pearson product-moment correlations were employed to measure the relationships between ongoing neurogenesis and measures of water maze performance (mean path length and discrimination index) in each age group. Note that longer path lengths on hidden platform trials are indicative of more circuitous routes and therefore poorer performance whereas higher discrimination index scores indicate better discrimination between the target and opposite quadrants on probe trials and therefore better performance. New neuron number correlated significantly with average path length across hidden platform trials ($r = -0.56$; $p < 0.05$; Fig. 6B) and probe trial discrimination index scores ($r = 0.59$; $p < 0.05$; Fig. 6D), in aged but not young rats.

4. Discussion

In the current study, we confirmed that hippocampal neurogenesis and spatial learning are compromised by age and that exposure to environmental enrichment potentiates neurogenesis, regardless of age. We found that environmental enrichment improves the performance of aged but not young rats on a water maze task in which the hidden platform location is learned in a single day. We propose that this task requires the ability to rapidly acquire and flexibly use spatial information that appears intact and therefore unaffected by enrichment in young rats but compromised and improved by enrichment in aged rats. We also reveal a novel age-specific relationship between total new neuron number and indexes of ability in a rapid water maze task.

Decreased hippocampal neurogenesis is characteristic of aging (Cameron and McKay, 1999; Kuhn et al., 1996; Nacher et al., 2003). Although our single experiment end point cannot disentangle the effects of age on NPC proliferation versus new cell survival, our effect is consistent with the well-known effects of age on NPC proliferation. Fewer $BrdU^+$ cells expressed neuronal markers and more $BrdU^+$ cells were devoid of differentiation markers in the hippocampi of aged versus young rats, which is consistent with some reports that neuronal differentiation is compromised by age (Kempermann et al., 1998) Our finding that gliogenesis increased with age has been noted by others (Bizon et al., 2004) but because so few new glia were detected in the dentate gyri of either young or aged rats, the reliability of this effect should be tested in future work. Overall, our findings support published work showing age-related decreases in neurogenesis are mediated by increasing NPC quiescence across life and because fewer NPC progeny adopt neuronal fates.

Environmental enrichment increases neurogenesis in aged rodents by potentiating neuronal differentiation and new cell survival (Kempermann et al., 1998, 2002; Leal-Galicia et al., 2008; Segovia et al., 2006). Indeed, we found similar enrichment-induced increases in the number of new cells surviving 4–5 weeks in the dentate gyri of young and aged rats (Fig. 3). However, enrichment neither reversed the effects of age on the proportion of $BrdU^+$ cells that expressed neuronal phenotypes nor increased the proportion in young rats (Fig. 4). Other studies showing that exposure to enriched environments potentiates neuronal differentiation in young and aged have employed running wheels, larger social groups, and earlier more extended exposures to enriched environments, which could each potentiate different components of neurogenesis and probably each require more detailed investigation (Lazarov et al., 2010; Lugert et al., 2010). Overall, we show that just a few weeks of exposure to environmental enrichment can increase net neurogenesis (Fig. 5) in the hippocampus of aged rats by robustly enhancing new cell survival to the extent that it overcomes the effects of age on NPC proliferation (Fig. 3) and neuronal fate choice (Fig. 4).

We expanded upon work showing that exposure to environmental enrichment enhances the ability of aged rats to discriminate the spatial location of a platform hidden in water maze tasks that distribute training across days (Fernández et al., 2004; Frick and Fernandez, 2003; Lores-Arnaiz et al., 2006) by confirming that it also enhances their

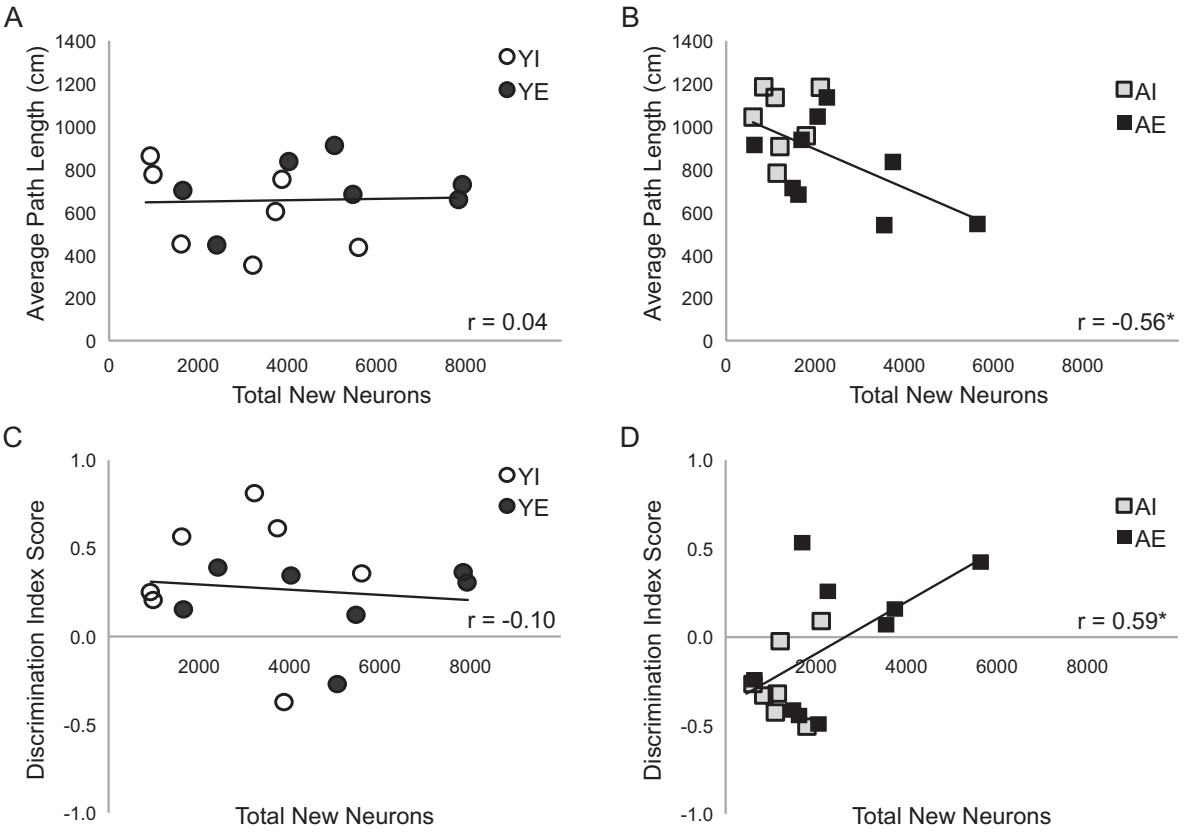

Fig. 6. New neuron number correlates with measures of spatial ability. Graphs depict total neuron number plotted against mean path lengths across hidden platform training blocks (A and C) or against probe trial discrimination index scores (B and D) for young rats housed individually (YI; white circles), young rats housed in an enriched environment (YE; dark gray circles), aged rats housed individually (AI; light gray squares), and aged rats housed in an enriched environment (AE; black squares). Mean path lengths correlated negatively with total new neuron number in aged rats ($r = -0.56$; A). Note that shorter path lengths indicate better performance. (D) The number of new neurons and discrimination index score are correlated positively in aged rats ($r = 0.59$). * $p \leq 0.05$.

ability to discriminate a platform spatially (Fig. 1A and B; Kumar et al., 2012) and visually (Fig. 1C) in a water maze task that masses training sessions into a single day. We did not observe the anticipated beneficial effect of enrichment on water performance in our young rats (Leggio et al., 2005; Schrijver et al., 2002). However, the effects of weeks rather than longer exposures to enrichment on spatial ability may be sex-dependent and only observable in water maze protocols that distribute training across days (for example Frick et al., 2003; Harburger et al., 2007). The rapidly asymptotic performances of YE and YI rats across hidden platform training blocks is consistent with the notion that the rapid water maze task may be sensitive to performance impairments but not enhancements in young rodents and precludes a meaningful evaluation of the relationship between their measures of neurogenesis and spatial ability.

Our data showing that AE and AI rats exhibited similar anxiety levels (percentage of time spent in the outer annulus), fitness (swim speeds and body mass), and perhaps visual acuity (similar performance was exhibited on early visible platform blocks), suggests that enrichment reverses age-related changes in systems mediating spatial and visual discrimination, independent of overt effects on sensorimotor ability. Exposure to enrichment improves cerebellar, in addition to hippocampal function (Camel et al., 1986; Greenough and Volkmar, 1973; Kumar et al., 2012), which could improve both spatial and visual discrimination. In addition, our unpublished data and previous research (Gerlai, 2001; Ormerod and Beninger, 2002) suggests that training on sequential tasks (including spatial vs. visual discrimination) may beneficially or detrimentally affect performance on the second task. Indeed, young rats appeared to readily employ procedural information they acquired on spatial discrimination trials about escaping the water maze on early visual discrimination blocks (Fig. 2A vs. C).

Exposure to an enriched environment produces many effects in the hippocampus that could relate to improved spatial discrimination in aged rats. For example, exposure to an enriched environment increases hippocampal and vascular volumes as well as morphological and electrophysiological measures of plasticity in aged rats (Hattiangady and Shetty, 2008; Kumar et al., 2012; Leventhal et al., 1999; Palmer et al., 2000). In support of other work employing water maze protocols with massed training schedules

(Drapeau et al., 2003; Driscoll et al., 2006), measures of neurogenesis and spatial ability correlated strongly (Fig. 6). This rapid task may be more sensitive to the relationship than distributed training water maze protocols (Bizon and Gallagher, 2003; Bizon et al., 2004; Merrill et al., 2003) because it taxes the hippocampus by requiring faster acquisition and more flexible use of spatial information (Foster, 2012). We also may have simply increased the variability within our measures enough to detect the relationship by exposing aged rats to differential experience.

We cannot conclude that neurogenesis mediates spatial ability from our correlational data. However, our data do suggest that neurogenesis may be a marker of spatial ability and hippocampal integrity in aged rats because aged rats with higher ongoing rates of neurogenesis exhibited better spatial ability than those with lower rates. Indeed, environmental enrichment increases the expression of factors associated with enhanced spatial ability and neurogenesis, such as brain-derived neurotrophic factor (Lee et al., 2002; Obiang et al., 2011) and stimulates the production of factors that are downregulated with age and are known to be neurogenic, such as fibroblast growth factor-2, vascular endothelial growth factor, and insulin growth factor-1 (Shetty et al., 2005). Our data do suggest that future work investigating the relationship between neurogenesis and hippocampal function across age may provide insight into the etiology and potential interventions for age-related cognitive decline.

In summary, we found that several weeks of daily exposure to an enriched environment partially reverses the effects of age on the rapid acquisition of a spatial search strategy in the water maze, potentially through its effects on neurogenesis because we found higher ongoing rates of neurogenesis in aged rats that exhibited better performance in the task. Our data suggest that engaging in mentally and physically stimulating activity could reverse some aspects of age-related cognitive decline perhaps by potentiating neurogenesis.

Disclosure statement

The authors declare no potential conflicts of interest.

All rats used as subjects in this study were treated in accordance with the policies set forth by the University of Florida Institutional Animal Care and Use Committee and the National Institutes of Health and are in accordance with the guidelines established by the U.S. Public Health Service Policy on the Humane Care and Use of Laboratory Animals. Every effort was made to minimize the number of animals used and their suffering.

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Age-related changes in rostral basal forebrain cholinergic and GABAergic projection neurons: relationship with spatial impairment

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Abstract

Both cholinergic and GABAergic projections from the rostral basal forebrain contribute to hippocampal function and mnemonic abilities. While dysfunction of cholinergic neurons has been heavily implicated in age-related memory decline, significantly less is known regarding how age-related changes in codistributed GABAergic projection neurons contribute to a decline in hippocampal-dependent spatial learning. In the current study, confocal stereology was used to quantify cholinergic (choline acetyltransferase [ChAT] immunopositive) neurons, GABAergic projection (glutamic decarboxylase 67 [GAD67] immunopositive) neurons, and total (neuronal nuclei [NeuN] immunopositive) neurons in the rostral basal forebrain of young and aged rats that were first characterized on a spatial learning task. ChAT immunopositive neurons were significantly but modestly reduced in aged rats. Although ChAT immunopositive neuron number was strongly correlated with spatial learning abilities among young rats, the reduction of ChAT immunopositive neurons was not associated with impaired spatial learning in aged rats. In contrast, the number of GAD67 immunopositive neurons was robustly and selectively elevated in aged rats that exhibited impaired spatial learning. Interestingly, the total number of rostral basal forebrain neurons was comparable in young and aged rats, regardless of their cognitive status. These data demonstrate differential effects of age on phenotypically distinct rostral basal forebrain projection neurons, and implicate dysregulated cholinergic and GABAergic septohippocampal circuitry in age-related mnemonic decline.

Keywords: Water maze; Stereology; Acetylcholine; GABA; Inhibitory; Spatial learning; Hippocampus; NeuN; Neuron number; Memory; Aging

1. Introduction

Explicit and spatial memory in humans is dependent upon the hippocampus and medial temporal lobe system, the function of which can decline precipitously with advanced age (Burke and Barnes, 2006; Della-Maggiore et al., 2002; Squire, 2004; Wilson et al., 2004). While aged individuals can exhibit learning and memory dysfunction similar to individuals with direct hippocampal damage (Gallagher and Rapp, 1997), neuron number in medial temporal lobe structures is stable across species during normal aging, even in subjects exhibiting profound mnemonic impairments (Calhoun et al., 1998; Rapp and Gallagher, 1996; Rapp et al., 2002; Rasmussen et al., 1996; Shamy et al., 2006; West et al., 2004). Despite the absence of frank hippocampal neuron loss, there is clear evidence that aging can negatively impact the processing of hippocampal-dependent spatial information (e.g., Barnes et al., 1997; Shen et al., 1997; Tanila et al., 1997) and that altered integrity of

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both cholinergic and GABAergic basal forebrain afferents to hippocampus may contribute to this functional decline (Gage et al., 1984; Gallagher and Nicolle, 1993; Smith and Pang, 2005; Ypsilanti et al., 2008).

Given their vulnerability to degeneration in Alzheimer's disease, basal forebrain cholinergic neurons have been studied extensively within the context of aging. Some studies have reported that cholinergic basal forebrain neurons decline with age, supporting the notion that their degeneration mediates age-related spatial learning impairments (Altavista et al., 1990; Armstrong et al., 1993; Bartus et al., 1982; De Lacalle et al., 1996; Durkin, 1992; Fadda et al., 2000; Fischer et al., 1989, 1992; Fragkouli et al., 2005; Gustilo et al., 1999). Notably, however, others have found no relationship between decline in cholinergic cell number and loss of cognitive abilities, and several recent studies have reported that cholinergic neuron number remains relatively stable at advanced ages (Lee et al., 1994; McQuail et al., 2011; Ypsilanti et al., 2008). The latter findings are consistent with those from studies showing that hippocampal-dependent spatial memory is largely spared following selective neurotoxic ablation of cholinergic neurons in rodents (Baxter et al., 1995).

It is becoming increasingly clear that corticopetal basal forebrain GABAergic neurons influence hippocampal physiology and hippocampal-supported cognition (Freund and Antal, 1988; Kiss et al., 1990a; Pang et al., 2001) and that the combined influence of cholinergic and GABAergic afferents is important for optimal hippocampal function. For example, septohippocampal connectivity is critical for the generation of hippocampal theta rhythms, 3–12-Hz oscillations which are strongly implicated in successful spatial cognition, memory processes, and sensorimotor integration (Bland and Colom, 1993; Bland and Oddie, 2001; Buzsáki, 2002; Colom, 2006; Rawlins et al., 1979; Winson, 1978). Lesion studies have shown that both cholinergic and GABAergic afferents from rostral basal forebrain neurons are critically important for generating these oscillations (Yoder and Pang, 2005). In addition, pronounced spatial learning impairments are produced by disruption of both cholinergic and GABAergic input to the hippocampus but not by disruption of either projection system in isolation (Baxter et al., 1995; Becker et al., 1980; Everitt and Robbins, 1997; McDonald and White, 1994; Pang et al., 2001; Parent and Baxter, 2004).

Alterations in inhibitory circuitry occur in a variety of neurodegenerative and neuropsychiatric diseases such as epilepsy, depression, schizophrenia, and autism, many of which are associated with abnormal cognitive function (Briggs and Galanopoulou, 2011; Gonzalez-Burgos et al., 2011; Lewis et al., 2005; Pizzarelli and Cherubini, 2011). Indeed, gamma aminobutyric acid (GABA)-mediated transmission appears crucial for processing information both within and between brain regions essential for mediating a variety of neurocognitive processes (Bartos et al., 2007; Volk and Lewis, 2002). While inhibitory circuitry is increasingly the focus of mechanistic studies associated with neurodegenerative diseases, considerably less attention has been paid to the anatomical integrity of GABAergic inhibitory circuits in normal aging (McKinney, 2005).

Nevertheless, there is emerging evidence that GABAergic indices change in normal aging. For example, interneurons in both prefrontal cortex and hippocampus of aged rats degenerate or cease to express the GABA-synthesizing enzyme, glutamic decarboxylase (GAD)67 (Shetty and Turner, 1998; Stanley and Shetty, 2004; Stranahan et al., 2012). Moreover, normal aging produces regionally specific changes in $GABA_B$ receptor expression and function (McQuail et al., 2012) and attenuated $GABA_A$ receptor activity and expression (Yu et al., 2006). Evoked GABA release is also reportedly decreased in the CA1 subregion of the aged rat hippocampus (Stanley et al., 2012). Finally, drugs targeting GABAergic signaling can improve cognitive functioning in both young and aged rats (Getova and Bowery, 1998, 2001; Helm et al., 2005; Lasarge et al., 2009; Mondadori et al., 1996a, 1996b).

This study was designed to determine if changes in the integrity of hippocampal-targeting basal forebrain cholinergic and GABAergic neurons are associated with loss of spatial learning abilities in aging. Confocal and stereological methods were employed to determine cholinergic (choline acetyltransferase [ChAT] immunopositive), GABAergic projection (GAD67 immunopositive) and total (NeuN immunopositive) neuron numbers in rostral basal forebrain of young and aged rats which were first characterized on a spatial learning task. The findings indicate that normal biological aging differentially impacts cholinergic and GABAergic projection neurons in rostral basal forebrain and suggest that alterations in inhibitory networks may be important contributors to age-related mnemonic dysfunction.

2. Methods

2.1. Subjects

Young adult (6 months; $n = 8$) and aged (24 months; $n = 16$) male F344 rats were obtained from the National Institute on Aging colony and housed in the vivarium in the Psychology Building at Texas A&M University for 2 weeks prior to the start of behavioral testing. This Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC)-accredited vivarium was maintained at a consistent 25 °C with a 12:12 hour light/dark cycle (lights on at 8:00 AM). Rats had free access to food and water at all times. All rats in the study were screened for health problems including, but not limited to, cataracts, jaundice, food and water intake, and tumors. Sentinel rats, housed alongside the rats in this study, routinely tested negative for a range of pathogens. All animal procedures were conducted in accordance with approved institutional animal care procedures and National Institutes of Health guidelines.

2.2. Spatial learning assessment

2.2.1. Apparatus

Spatial learning abilities were assessed using the Morris water maze task as described previously (Bizon et al., 2009; LaSarge et al., 2007). The water maze apparatus consisted of a white circular tank (183 cm in diameter with a wall height of 58 cm) filled with water (27 °C) made opaque with the addition of nontoxic white tempera paint. A retractable white escape platform (12 cm diameter, HVS Image, Buckingham, UK) was submerged 2 cm below the water's surface near the center of the southwest quadrant of the maze. Black curtains, to which large white geometric shapes (extramaze cues) were affixed, surrounded the maze. Data were acquired via a video camera mounted above the maze which was connected to a DVD recorder and computer with a video tracking system and Water 2020 software (HVS Image).

2.2.2. Spatial reference memory (hidden platform) task

Rats' spatial learning abilities were tested according to methods developed by Gallagher and colleagues (Gallagher et al., 1993), with specific modifications for training F344 rats (Bizon et al., 2009; LaSarge et al., 2007). Briefly, rats received three training trials per day with a 30-second intertrial interval, over eight consecutive days. On each trial, rats were placed into the water facing the wall of the maze at one of four equally spaced start positions (north, south, east, or west). The start positions were varied in a pseudorandom fashion, such that all rats started from each of the locations approximately the same number of times. Rats were allowed to search until they found the hidden platform or until 90 seconds elapsed, at which time rats were guided to the escape platform by the experimenter. Rats remained on the platform for 30 seconds and then were placed in a holding chamber for a 30-second intertrial interval. Every sixth trial was a probe trial in which the platform was lowered to the bottom of the maze for the first 30 seconds of the trial, after which it was raised to allow the rats to escape.

2.2.3. Cued (visible platform) task

Following spatial reference memory training, rats were given a single session with six trials of cue training to assess sensorimotor abilities and motivation to escape. For cue training, rats were trained to escape to a visible platform (painted black and protruding 2 cm above the water's surface). Both the start position and platform location were varied on each trial, making the extramaze cues explicitly irrelevant to the platform location. On each trial, rats were allowed to search for the platform for 90 seconds and then were allowed to remain there for 30 seconds before a 30-second intertrial interval.

2.2.4. Behavioral and statistical analyses

Data files were created by the Water 2020 software (HVS Image) and exported to SPSS (version 16.0; SPSS, Inc., Cary, NC, USA) for analysis. Accuracy of performance on training and probe trials was assessed using a search error measure originally described by Gallagher et al. (1993). To calculate search error, the rat's distance from the platform location was sampled 10 times per second and these distances were averaged into 1-second bins. For training trials, cumulative search error was derived by summing these 1-second averages and then subtracting the optimal path between the start location and the platform location. For probe trials, a mean search error measure was derived by dividing cumulative search error by the 30-second duration of the probe trials. Training trial data were averaged into 4 blocks consisting of the 5 trials preceding each probe trial. Comparisons between groups on training trials were conducted using two-factor repeated measures analysis of variance (ANOVA) (age $\times$ training block) with Tukey's post hoc tests performed when warranted. In all statistical comparisons, p values ≤ 0.05 were considered significant.

To provide an overall measure of spatial learning ability for each rat, a "spatial learning index" (SLI) was calculated using mean search error from the interpolated probe trials as described previously (Bizon et al., 2009; Gallagher et al., 1993). Mean search error on probe trials was weighted and summed to provide the spatial learning index (Bizon et al., 2009). For some comparisons of cell number, aged rats were subgrouped on the basis of their spatial learning index. This classification approach has been successfully used in prior studies to identify and investigate structural and signaling alterations in the hippocampus and related circuitry that are relevant to decline of spatial learning abilities in aged rats (Bizon et al., 2001, 2004; Colombo et al., 1997; Foster and Kumar, 2007; Nicolle et al., 1999; Rapp and Gallagher, 1996). Aged rats that fell more than two times the standard deviation outside of the mean spatial learning index calculated for young adult rats were classified as "aged spatially impaired" (SLI $>$ 275) and all other aged rats (which fell within the range of the young adult cohort) were classified as "aged spatially-unimpaired" (SLI $\leq$ 275).

2.3. Immunofluorescent labeling of cholinergic, GABAergic projection, and total rostral basal forebrain neurons

One week after completion of behavioral testing, rats were rapidly euthanized with an overdose of pentobarbital and perfused transcardially with ice cold 0.9% saline followed by 4% paraformaldehyde. Brains were removed from the skull, postfixed for 24 hours in perfusate, and then cryoprotected in 20% sucrose in 0.1 M phosphate buffer. Systematic uniform random sampling was achieved by exhaustively sectioning brains coronally on a calibrated freezing stage microtome (35 μm) through the full rostrocaudal extent of the medial septum and vertical limb of the diagonal band of Broca (beginning just caudal to the olfactory bulbs and ending caudal to the crossing of the anterior commissure). A registered 1-in-4 series of sections was obtained for each animal and separate series (spaced at 140 μm intervals) were randomly assigned for processing to detect

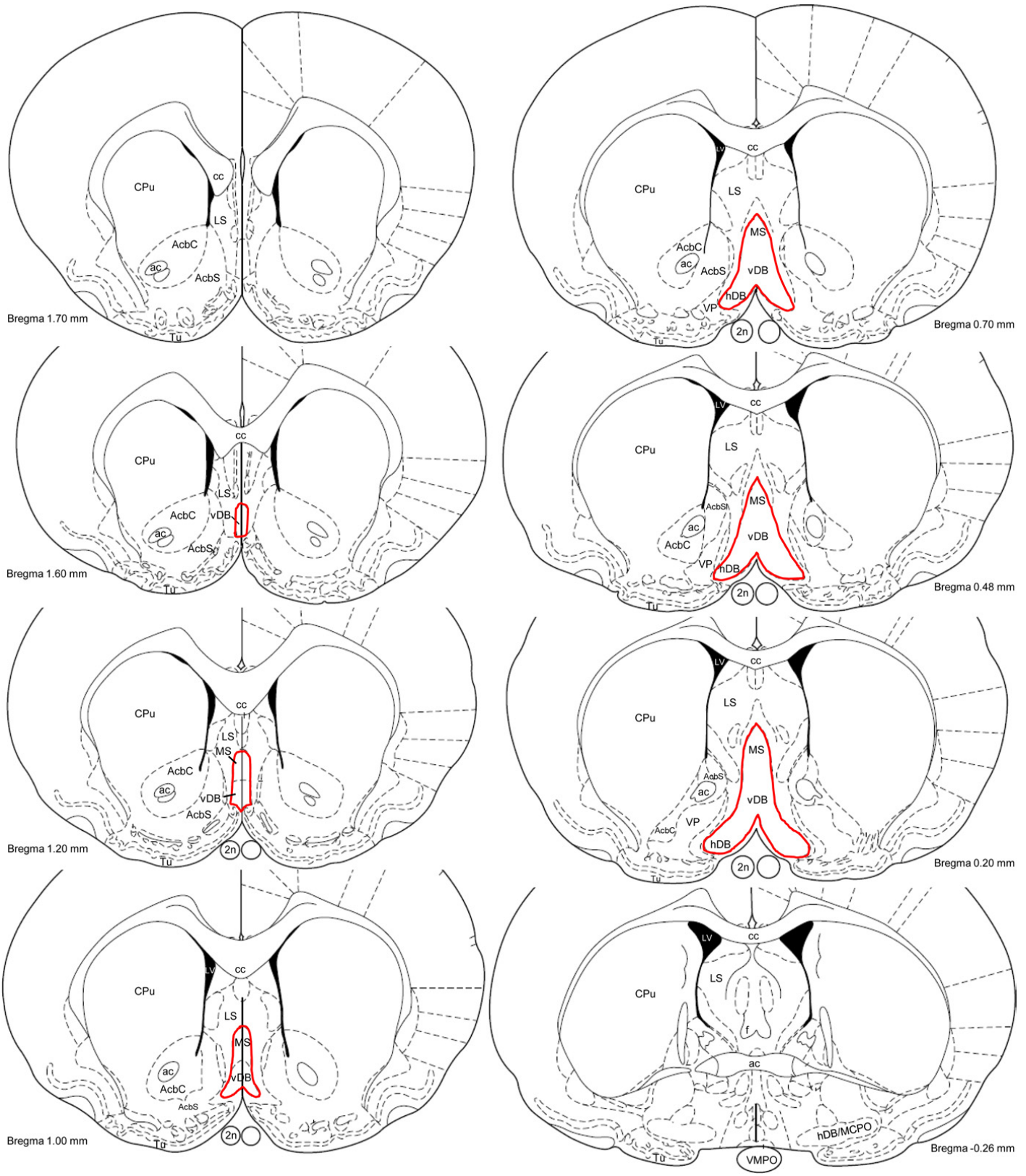

Fig. 1. Rostral basal forebrain boundaries used for cell count estimations. Schematic illustrations modified from Paxinos and Watson (2007) showing the rostrocaudal boundaries (extending from 1.7 mm anterior to −0.26 mm posterior of Bregma) and the delineation of rostral basal forebrain nuclei (red outline) used in the current study. The basal forebrain neurons that innervate the hippocampal formation are primarily localized within the medial septum (MS) and vertical limb of the diagonal band of Broca (vDB). Just caudal to the joining of the corpus callosum, these contiguous nuclei emerge along the midline with the vDB situated ventral to the MS. These nuclei are bordered laterally by the lateral septum and in more caudal sections by the medial edge of the nucleus accumbens shell (AcbS). The vDB extends ventrally to the medial intersection of the 2 hemispheres on the ventral edge of the tissue. In more caudal planes, the rostral-most portion of the horizontal limb of the diagonal band of Broca (hDB) emerges. Contiguous with the vDB, the hDB is bordered laterally by

rostral basal forebrain cholinergic (ChAT), GABAergic projection (GAD67) or total (NeuN) immunopositive neurons (Gundersen and Jensen, 1987). Sections were collected into cold 0.1 M phosphate-buffered saline and stored at 4 °C until stained immunohistochemically.

For immunohistochemistry, free-floating sections were washed several times in 0.1 M Tris-buffered saline (TBS; 100 mM Tris-HCl, 150 mM NaCl, pH 7.5), preincubated in a blocking solution containing 3% normal donkey serum and 0.3% Triton X-100 in 0.1 M TBS for 1 hour at room temperature and then incubated in blocking solution that contained rabbit anti-GAD67 (Bioworld Technology, Louis Park, MN, USA; 1:500); goat anti-ChAT (Millipore, Temecula, CA, USA; AB144P, 1:1000) or mouse anti-NeuN (Millipore; MAB377, 1:500) for 72 hours at 4 °C. After primary incubation, sections were washed in 0.1 M TBS, and incubated in 0.1 M TBS containing 2% normal donkey serum and the appropriate Alexa 488-conjugated secondary antibodies (Invitrogen, Carlsbad, CA, USA; 1:300) for 2 hours at room temperature in the dark. The sections were washed in 0.1 M TBS, and mounted onto Superfrost++ slides (Fisher Scientific, Pittsburgh, PA, USA). The sections were then coverslipped under ProLong Gold (Invitrogen), sealed with clear fingernail polish, and stored at 4 °C until analysis.

2.4. Stereological counts of ChAT, GAD67, and NeuN immunopositive neurons

2.4.1. Delineation of the rostral basal forebrain

The basal forebrain neurons that innervate the hippocampal formation are primarily localized within the medial septum (MS) and the vertical limb of the diagonal band of Broca (vDB) (Dutar et al., 1995; Lewis and Shute, 1967; McKinney et al., 1983; Meibach and Siegel, 1977; Segal and Landis, 1974; Swanson and Cowan, 1979). As shown in Fig. 1, these are contiguous nuclei that emerge along the midline just caudal to the joining of the corpus callosum. The vDB is positioned ventral to the MS and these nuclei are bordered laterally by the lateral septum and the medial edge of the nucleus accumbens shell. The vDB extends ventrally to the medial intersection of the two hemispheres on the ventral edge of the tissue section. In more caudal planes, the rostral-most portion of the horizontal limb of the diagonal band of Broca (hDB) emerges. Contiguous with the vDB, the hDB extends laterally along the medial edge of the nucleus accumbens shell and is bordered ventrally by the ventral pallidum and olfactory tubercle. The caudal-most edge of the vDB is rostral to the joining of the anterior commissure. After the crossing of the anterior commissure, the hDB (sometimes also referred to as the magnocellular preoptic area in this plane) is a clearly defined nucleus located in the ventral and lateral basal forebrain. As such, the crossing of the anterior commissure is often used as a boundary between rostral basal forebrain and more caudal neocortical-innervating basal forebrain nuclei (Colom et al., 2005; McQuail et al., 2011; Peterson et al., 1999; Ypsilanti et al., 2008). In the current study, counts were obtained from equally spaced (140 μm apart) sections throughout the entire rostrocaudal extent of the medial septum and vDB. Because there are not clear boundaries that allow the hDB to be reliably distinguished in the rostral basal forebrain, neurons within the hDB rostral to the crossing of the anterior commissure were also included in the population estimates. The rostral basal forebrain nuclei as a whole can be readily distinguished from surrounding structures (described above) within ChAT, GAD67, and NeuN immunolabeled material (Figs. 2–4).

2.4.2. Estimation of neuron number using the optical fractionator

Starting at a randomly selected level within the first sampling interval, the optical fractionator method (Gundersen, 1986; Peterson, 1999; West et al., 1991) was implemented using an Olympus Fluoview 300 confocal microscope, equipped with the appropriate filter sets, a CCD camera, and a computer-driven x, y, and z Ludl-motorized stage controlled with StereoInvestigator software (version 10; MBF BioScience, Williston, VT, USA). Regional boundaries for the rostral basal forebrain nuclei (shown in Fig. 1) were delineated at low power magnification (4×) in an evenly spaced series of immunolabeled sections. The series spanned the rostrocaudal extent of the MS and vDB, which are the basal forebrain nuclei that innervate the hippocampal formation (Dutar et al., 1995; Lewis and Shute, 1967; McKinney et al., 1983; Meibach and Siegel, 1977; Segal and Landis, 1974; Swanson and Cowan, 1979). This design yielded 7–8 sections for quantification (per 1-in-4 series) from each brain. The motorized stage of the microscope was moved in evenly spaced x-y intervals under the computer control, surveying the regions of interest in each section according to a systematic random sampling scheme (Table 1 for sampling details). Using a 60× oil-immersion objective (with 1.4 numerical aperture), section thickness was measured at each sampling site and z-stacks (comprised of 1 μm z-

the medial wall of the nucleus accumbens shell, and in more caudal sections, by the ventral pallidum and olfactory tubercle. The caudal-most edge of the vDB is just rostral to the joining of the anterior commissure (just prior to the Bregma −0.26 mm). At the crossing of the anterior commissure, the hDB (often referred to as magnocellular preoptic area in this plane of section) is located toward the ventral edge of the tissue and no basal forebrain nuclei remain along the midline. Because there are not clear boundaries reliably distinguishing the hDB from vDB in the rostral basal forebrain, immunopositive neurons localized within the hDB situated rostral to the crossing of the anterior commissure were included in the population estimates. Abbreviations: 2n, optic nerve; ac, anterior commissure; AcbC, nucleus accumbens core; cc, corpus callosum; CPu, caudate putamen; LS, lateral septum; LV, lateral ventricle; MCPO, magnocellular preoptic area; Tu, olfactory tubercle.

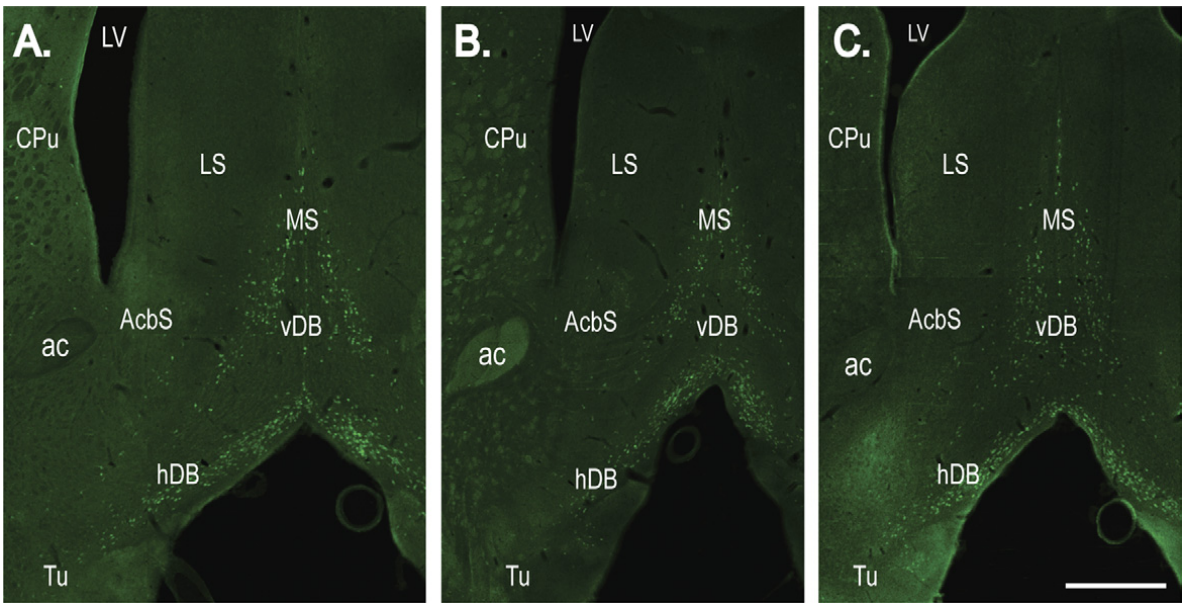

Fig. 2. Distribution of choline acetyltransferase (ChAT) immunopositive cells in rostral basal forebrain. Low magnification photomicrographs of ChAT immunolabeling in coronal sections taken through the rostral basal forebrain (approximately 0.5 mm anterior to bregma) of representative young (A), aged spatially unimpaired (B) and aged spatially impaired (C) rats. Staining was robust in individual neurons localized to rostral basal forebrain nuclei including the medial septum (MS), vertical limb of the diagonal band of Broca (vDB) and horizontal limb of the diagonal band of Broca (hDB), and was also evident in scattered interneurons distributed throughout the caudate putamen (CPu), nucleus accumbens (Acb) and olfactory tubercle (Tu). The dense immunolabeling of the ChAT immunopositive neurons within the MS, vDB, and hDB made these nuclei readily distinguishable from neighboring structures (including lateral septum, the medial wall of the nucleus accumbens shell [AcbS] and the olfactory tubercle) across age and cognitive groups. For orientation, white matter regions (i.e., corpus callosum and anterior commissure) and the lateral ventricle (LV) are labeled. Scale bar = 200 μm. Abbreviations: ac, anterior commissure; cc, corpus callosum; LS, lateral septum.

slices) were acquired through the full section thickness at the appropriate emission wavelengths. The mean section thickness was measured at 30.62 μm (coefficient of variation = 0.13), indicating an approximate 12.5% tissue shrinkage in the z-plane. This degree of shrinkage is significantly less than that observed from immunohistological procedures that require dehydration and is consistent with other reports of immunofluorescent tissue processing (Hart and Terenghi, 2004; Prasad and Richfield, 2010). Quantification was performed offline on the acquired z-stacks and was confined to an optical disector 25 μm in height which was positioned 3 μm below the surface of the tissue. The top-most nucleus associated with an immunopositive neuron was counted only when it first came into focus within the optical disector, provided it did not encroach on the exclusion lines of the counting frame (Gundersen, 1986; Sterio, 1984). The sufficiency of the guard zone was confirmed by plotting the distribution of the cells counted for each marker in the z-axis (Andersen and Gundersen, 1999; Dorph-Petersen et al., 2001, 2009). The number of cells counted was highly consistent across the disector height, indicating that the guard zone of 3 μm was sufficient to minimize the effects of superficial damage associated with tissue sectioning (i.e., to avoid lost caps [Gundersen, 1986], Supplementary Fig. 1). Moreover, the distribution of cells along the z-axis did not differ between age or cognitive groups (Gardella et al., 2003; Supplementary Fig. 1), confirming good antibody penetration throughout the full section thickness (see representative examples of cell positions within the disector in the orthogonal windows shown in Supplementary Fig. 1). The total number of ChAT, GAD67, and NeuN immunopositive cells in rostral basal forebrain was estimated using the optical fractionator method (West et al., 1991) in which the product of the cells counted in a known, uniformly random sample of the region of interest is multiplied by the reciprocal of the sampling fraction. The shrinkage robust version of the optical fractionator based upon the number weighted mean section thickness was used (Dorph-Petersen et al., 2001). Additional details, including stereological sampling parameters are provided in Table 1.

The precision of the stereological estimates was determined by estimating the coefficients of error (CE) using methods described by Gundersen et al. (1999). Equations used to generate the CEs are based on Gundersen's smoothness classification $m = 1$, as the areas defined for the cell counts changed smoothly from the rostral entrance of the MS to the caudal conclusion of the vDB. These CEs (ranging from 0.04 to 0.06) were less than half of the observed variation across subjects (coefficients of variation ranging from 0.16 to 0.2; Table 1), indicating that the sampling and counting parameters were sufficiently precise to detect frank biologically driven differences in neuronal population estimates among experimental groups (Boyce et al., 2010;

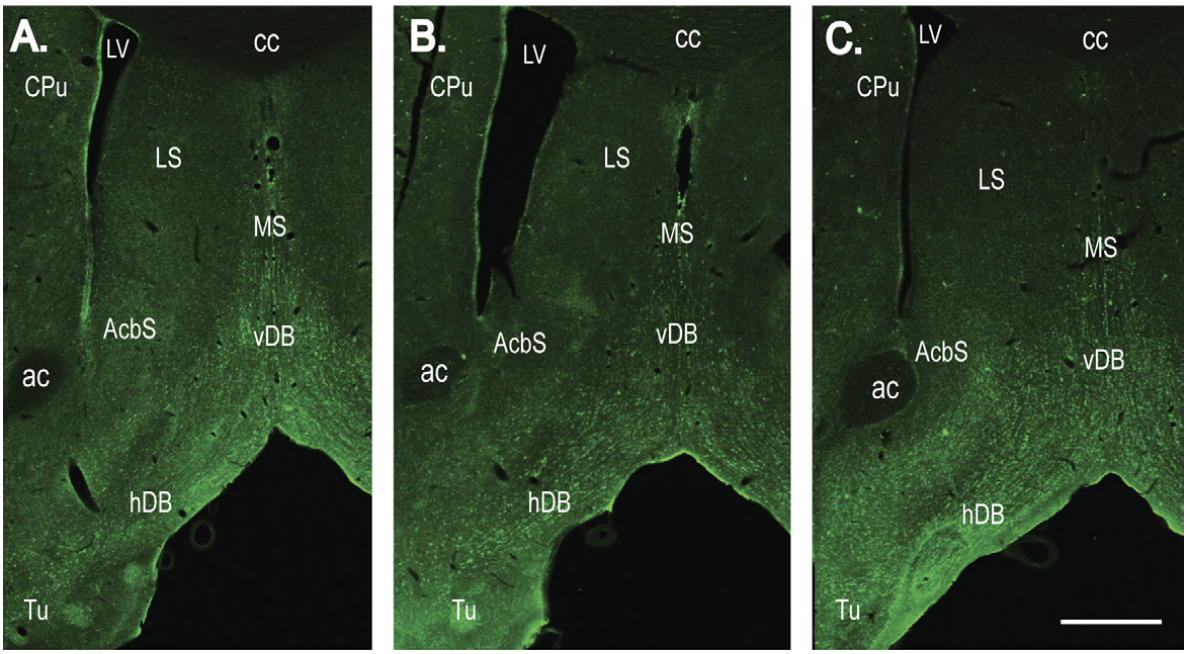

Fig. 3. Distribution of glutamic decarboxylase (GAD)67 immunopositive cells in rostral basal forebrain. Low magnification photomicrographs of GAD67 immunolabeling in coronal sections taken through the rostral basal forebrain (approximately 0.5 mm anterior to bregma) of representative young (A), aged spatially unimpaired (B) and aged spatially impaired (C) rats. GAD67 labeling was robust throughout rostral basal forebrain nuclei, including medial septum and the vertical and horizontal limbs of diagonal band of Broca (vDB and hDB, respectively). Somewhat diffuse GAD67 immunolabeling was also observed in lateral septum (LS) and in nucleus accumbens (Acb), whereas scattered individual GAD67 immunopositive cells were observed in the caudate putamen (CPu) and olfactory tubercle (Tu). Across age and cognitive groups, dense labeling within basal forebrain nuclei allowed these regions to be readily delineated from surrounding nuclei. For orientation, white matter regions (i.e., corpus callosum and anterior commissure) and the lateral ventricle (LV) are labeled. Scale bar = 200 μm. Abbreviations: ac, anterior commissure; AcbS, nucleus accumbens shell; cc, corpus callosum; MS, medial septum.

Dorph-Petersen et al., 2001; Gundersen and Jensen, 1987; Gundersen and Osterby, 1981; West, 1999).

3. Results

3.1. Cognitive performance in young and aged rats

In the spatial water maze task, a comparison of performance on training trials using the cumulative search error measure (two-factor ANOVA; age × trial block) indicated that both young and aged rats improved performance over the course of training trials (main effect of training trial block, $F(3,66) = 35.8$; $p < 0.0001$) but that aged rats were significantly impaired in finding the platform in comparison with young (main effect of age, $F(1,22) = 9.8$; $p < 0.005$, Fig. 5A). Notably, these differences were not present on the very first training trial ($F(1,22) = 0.77$; not significant [n.s.]), indicating that aged rats' initial search strategies were comparable with those of young rats. Performance on probe trials as assessed with the mean search error measure (two-factor ANOVA; age × probe trial) revealed results similar to those on training trials, in that search for the platform became more accurate as training progressed (main effect of probe trial, $F(3,66) = 13.8$; $p < 0.0001$) but aged rats were overall less proficient in their search than young rats (main effect of age, $F(1,22) = 7.34$; $p < 0.05$). In contrast to the spatial task, there was no impairment in the ability of aged rats to locate the visible escape platform during cue (visible platform) training (one-factor ANOVA, $F(1,22) = 1.4$; n.s.), indicating intact sensorimotor and motivational processes.

In order to relate population estimates to cognitive abilities, mean search error during probe trials was used to calculate a SLI for each rat as described above (Bizon et al., 2009; Gallagher et al., 1993). This measure, specifically designed to maximize individual differences in water maze performance within the context of aging, has been shown to correlate with age-related changes in numerous neurobiological substrates of spatial memory (Bizon et al., 2001, 2004; Colombo et al., 1997; Nicolle et al., 1999; Smith et al., 2000). Fig. 5B shows individual spatial learning indexes of young and aged rats. For some analyses, aged rats were subgrouped based on their SLI such that aged rats performing more than two times the standard deviation of the mean SLI of the young group (SLI > 275) were classified as "aged spatially impaired" ($n = 8$) and all other aged rats (SLI ≤ 275) were classified as "aged spatially unimpaired" ($n = 8$). A repeated measures ANOVA (training trial block × cognitive group) confirmed that cumulative search error across training blocks differed between these subgroups ($F(2,21) = 9.91$; $p < 0.01$) and Tukey's post hoc analyses indicated that aged spatially impaired rats performed significantly worse than both young and aged spatially unimpaired

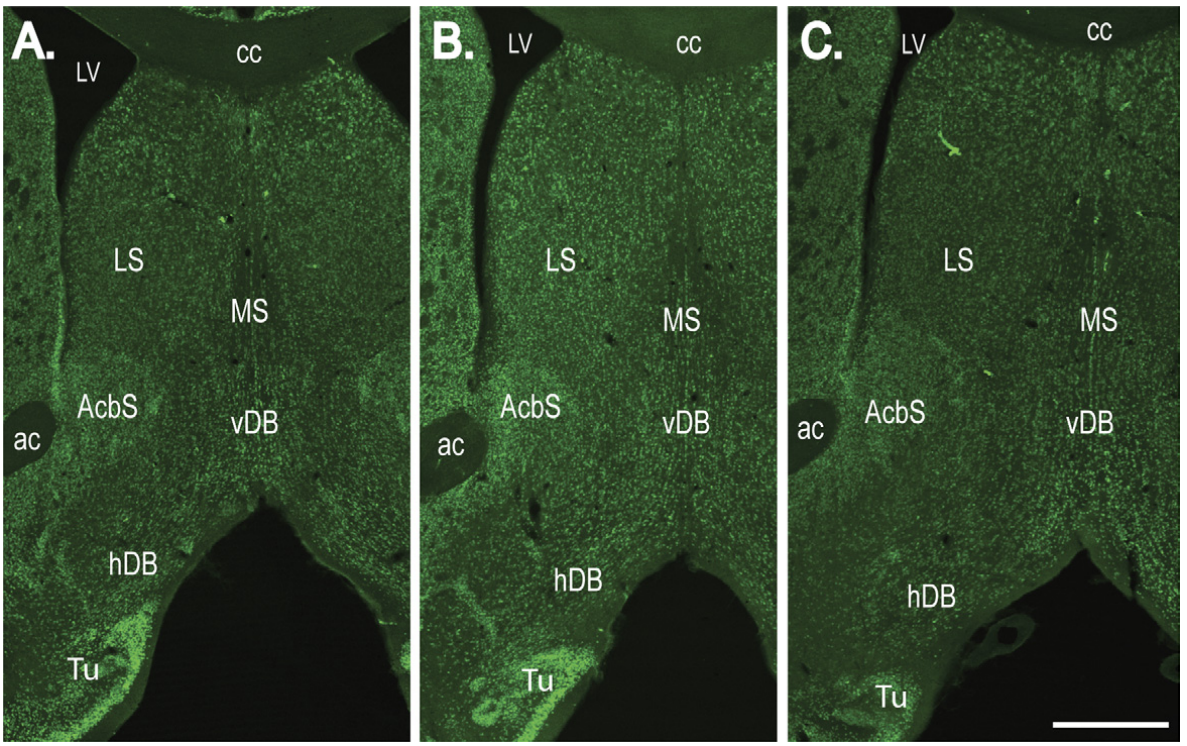

Fig. 4. Distribution of NeuN immunopositive cells in rostral basal forebrain. Low magnification photomicrographs of NeuN immunolabeling in coronal sections taken through the rostral basal forebrain (approximately 0.5 mm anterior to bregma) of representative young (A), aged spatially unimpaired (B), and aged spatially impaired (C) rats. NeuN expression is prominent in most neurons through rat forebrain, although differences in density and intensity of expression allow discrete nuclei to be clearly distinguished. NeuN immunolabeling is robust throughout the medial septum (MS) and the vertical and horizontal limbs of the diagonal band of Broca (vDB and hDB, respectively). It is also particularly prominent in lateral septum (LS) and the nucleus accumbens shell (AcbS), as well as in olfactory tubercle (Tu), allowing the boundaries of basal forebrain nuclei to be clearly delineated across age and cognitive groups. For orientation, white matter regions (i.e., corpus callosum [cc] and anterior commissure [ac]) and the lateral ventricle (LV) are labeled. Scale bar = 200 μm. Abbreviations: 2n, optic nerve; AcbC, nucleus accumbens core; CPu, caudate putamen; MCPO, magnocellular preoptic area.

rats ($ps < 0.05$); however, performance of young and aged spatially unimpaired rats did not differ (n.s.).

3.2. Distribution of ChAT, GAD67, and NeuN immunopositive neurons

Figs. 2–4 show low power photomicrographs of representative immunolabeling for ChAT (Fig. 2), GAD67 (Fig. 3), and NeuN (Fig. 4) in independent series of sections through the rostral basal forebrain of representative young, aged spatially unimpaired, and aged spatially impaired rats. Both cholinergic (ChAT immunopositive; Fig. 2) and GABAergic projection (GAD67 immunopositive, Fig. 3) neurons were distributed heterogeneously throughout the rostral basal forebrain nuclei and represented clear subpopulations of those neurons immunolabeled for NeuN (Fig. 4). For each label and across age and cognitive

Table 1
Sampling parameters used for estimating total number of rostral basal forebrain neurons

Object	Sampling grid (μm × μm)	Counting frame (μm × μm)	Disector height (μm)	Average object counted ± SD	Average CE[a]	CV
ChAT+ cells	336 × 448	140 × 140	25	292 ± 42.89	0.05	0.16
GAD67+ cells	448 × 448	110 × 100	25	679 ± 101.14	0.06	0.20
NeuN+ cells	400 × 400	89 × 89	25	781 ± 175.33	0.04	0.16

Total cell numbers were estimated using the formula: N (total number) = 1/section sampling fraction (ssf) × 1/area sampling fraction (asf) × 1/height sampling fraction (hsf) × number of immunopositive cells counted. The total number of cells counted for each subject and the sampling grid and counting frame used to generate the asf for each label are provided above. The ssf in the current study equaled ¼ in every case. The hsf was calculated using the mean weighted thickness (with section thickness measured at each sampling site).

Key: +, positive; SD, standard deviation; CE, coefficient of error; ChAT, choline acetyltransferase; CV, coefficient of variation; GAD, glutamic decarboxylase.

N = 24 total rats for ChAT and N = 23 for GAD67 and NeuN.

[a] Gundersen's CE, $m = 1$.

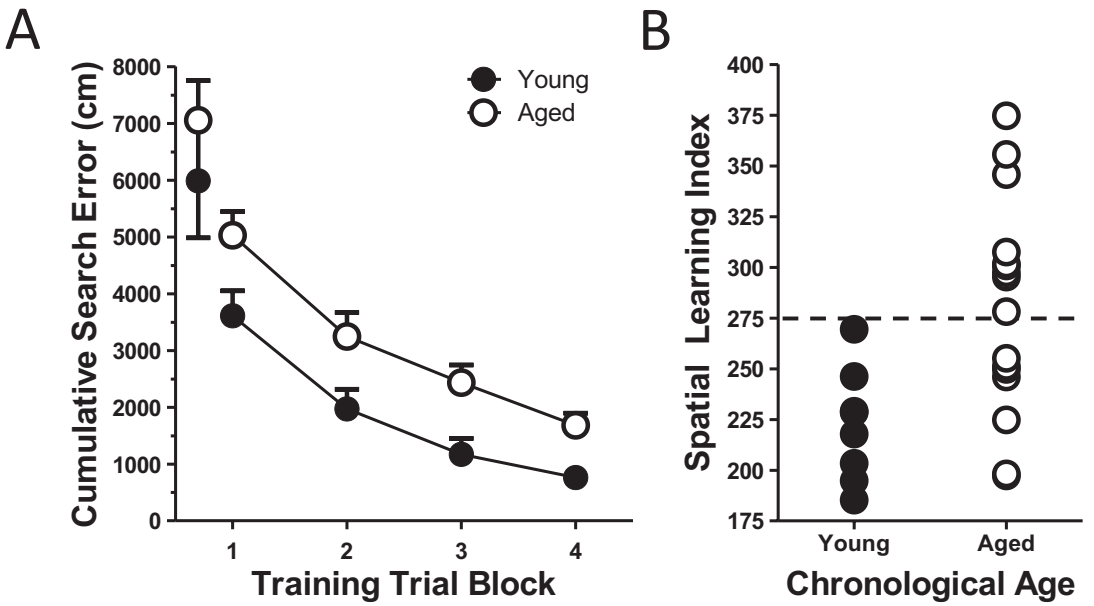

Fig. 5. Spatial learning in young and aged rats. (A) Young and aged rats did not differ on the first training trial, and both groups improved over the course of training. As a group, aged rats were significantly impaired relative to young in learning to swim to a hidden (submerged) platform within the water maze. (B) Spatial learning index (SLI) scores were calculated from probe trial performance to provide an overall index of spatial learning ability for each subject. Note that there was considerable variability among aged rats, with many performing within the range of young (aged spatially unimpaired rats; SLI $\leq$ 275) and others performing more than two times the standard deviation of mean young rat performance, demonstrating impairment (aged spatially impaired rats, SLI $>$ 275). See text for statistical analysis.

groups, the rostral basal forebrain nuclei could be readily distinguished from bordering structures (including the lateral septum, nucleus accumbens, and olfactory tubercle).

High magnification immunofluorescent labeling of ChAT, GAD67, and NeuN immunopositive neurons is shown in Fig. 6. ChAT immunopositive cells (Fig. 6A–C) were robustly labeled with well-defined nuclei and tended to be polygonal and fusiform in shape. Overall, ChAT immunopositive neurons appeared larger but less densely distributed than GAD67 immunopositive cells (Fig. 6D–F) in the same region. In agreement with previous reports (Brashear et al., 1986; Colom, 2006; Gritti et al., 2003, 2006), the GAD67 immunopositive cells exhibited diverse morphologies (oval, fusiform, or polygonal cell bodies were observed) and sizes (ranging from small oval cells to large multipolar cells). Labeling of ChAT and GAD67 was consistent with numerous neuroanatomical studies that have demonstrated that ChAT and GAD immunopositive neurons in the rostral basal forebrain are distinct nonoverlapping neuronal populations (Brashear et al., 1986; Formaggio et al., 2011; Gritti et al., 1993; Köhler et al., 1984; Semba, 2000). While the ChAT immunopositive cells were primarily clustered within the medial septum and along the ventral edge of the hDB, the GAD67 immunopositive cells were distributed more homogenously throughout the rostral basal forebrain subfields. As expected, NeuN immunopositive cells (which include both ChAT and GAD67 immunopositive neurons as well as a variety of other projection and interneurons) had discernible nuclei, were located throughout the rostral basal forebrain, and exhibited diverse sizes and morphologies; Fig. 6G–I). No obvious morphological differences in ChAT, GAD67, or NeuN immunopositive cells were detected at either low or high magnification in sections obtained from rats that differed in age or cognitive status.

3.3. Age and cognitive comparisons of ChAT, GAD67, and NeuN immunopositive cell numbers in the rostral basal forebrain

3.3.1. ChAT immunopositive neurons

A comparison between young and aged rats yielded a significant but modest decline in the number of ChAT immunopositive cells in aged rats relative to young (−12.5%; $t(22) = 2.00$; $p < 0.05$; Fig. 7A; Table 2). A comparison of ChAT immunopositive cells among young and aged rats subgrouped based upon spatial learning ability indicated a similar trend toward decreased ChAT immunopositive cell number with age ($F(2,21) = 2.23$; $p = 0.13$) but the magnitude of reduction in aged rats was comparable across aged spatially unimpaired (−14%) and aged spatially impaired (−12%) subgroups (Fig. 7B). In agreement with the observation that ChAT immunopositive cell number was reduced by a similar magnitude in both aged spatially unimpaired and aged spatially impaired rats, there was no reliable relationship between ChAT immunopositive cell number and spatial learning index among aged rats ($r = -0.10$; n.s.; Fig. 7D). Notably, however, a significant correlation between ChAT immunopositive cell number and spatial learning index

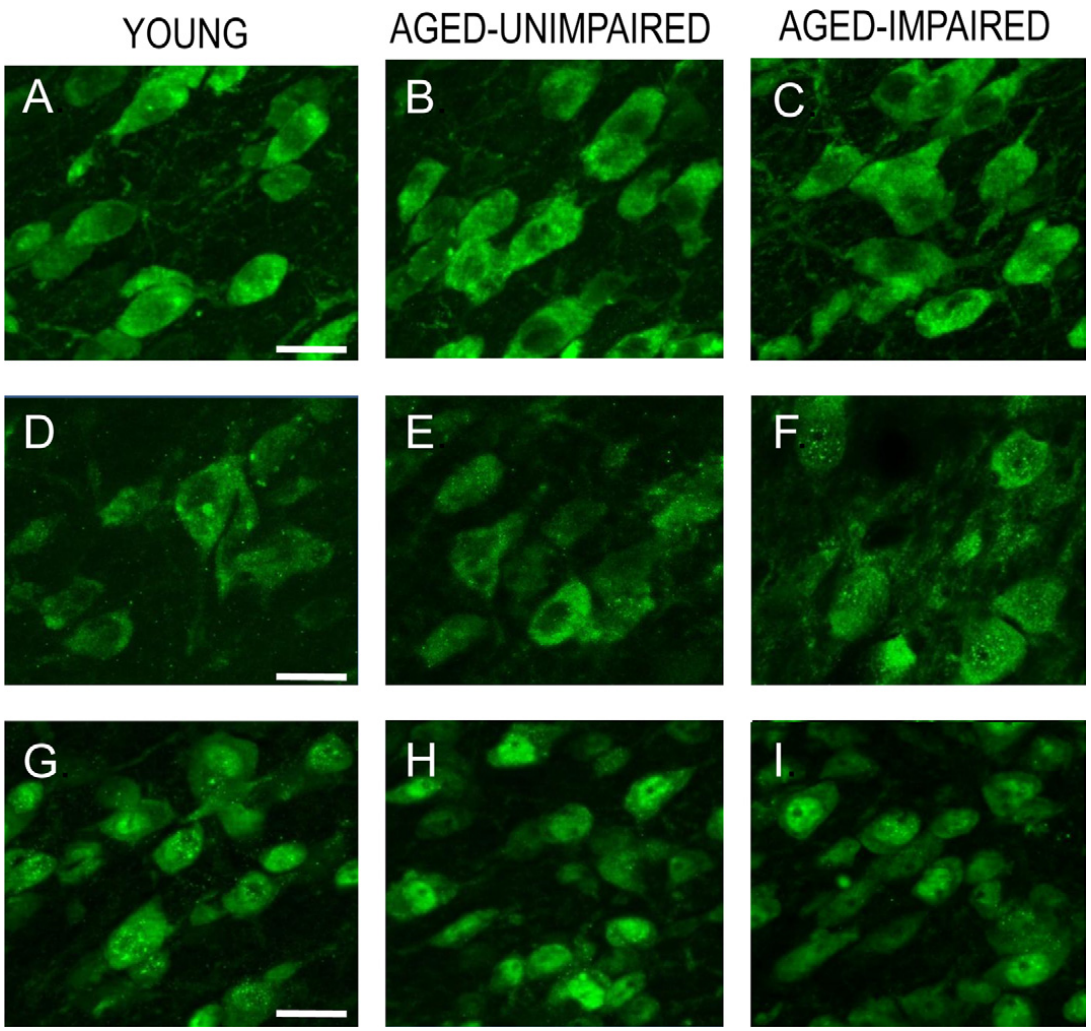

Fig. 6. High magnification immunofluorescent labeling of choline acetyltransferase (ChAT), glutamic decarboxylase (GAD)67, and NeuN immunopositive neurons. Representative ChAT (A–C), GAD67 (D–F), and NeuN (G–I) immunopositive cells in young (left), aged spatially unimpaired (middle), and aged spatially impaired rats (right). Across ChAT, GAD67, and NeuN material, immunopositive cells were robustly labeled and contained a well-defined nucleus. Overall, ChAT immunopositive cells tended to be polygonal and fusiform shaped whereas GAD67 immunopositive cells exhibited diverse morphologies and sizes (ranging from small oval cells to large multipolar cells). The NeuN immunopositive cells (which would include both ChAT and GAD67 immunopositive neurons as well as a variety of other projection and interneurons) had discernable nuclei and exhibited diverse sizes and morphologies. No obvious morphological differences between ChAT, GAD67, or NeuN immunopositive cells were detected from rats that differed in age or cognitive status. Scale bar = 20 μm.

was evident in young rats, such that higher ChAT immunopositive cell numbers were associated with better spatial learning performance ($r = -0.76$; $p < 0.05$; Fig. 7C).

3.3.2. GAD67 immunopositive neurons

A very different pattern of results was obtained from estimates of total GABAergic projection (GAD67 immunopositive) neuron numbers in the same subfields. As shown in Fig. 8A, GAD67 immunopositive cell number was greater in aged relative to young rats, although this difference was not statistically reliable ($t(21) = 0.74$; n.s.). However, a one-factor ANOVA comparing GAD67 immunopositive cell number in young and aged rats subgrouped on the basis of spatial learning ability revealed a highly significant difference among cognitive groups ($F(2,20) = 16.2$; $p < .0001$; Fig. 8B; Table 2). Post hoc comparisons confirmed a robust statistically significant increase in the number of GAD67 immunopositive cells specifically in aged spatially impaired rats relative to both young (+ 18%; $p < 0.005$) and aged spatially unimpaired (+ 25%; $p < 0.0001$) rats. The number of GAD67 immunopositive cells did not differ significantly between young and aged spatially unimpaired rats (n.s.). The strong relationship between elevated GAD67 immunopositive cell number and cognitive impairment was supported by a significant correlation among aged rats ($r = 0.60$; $p < 0.05$), such that higher numbers of GAD67 immunopositive cells were associated with higher spatial learning indexes (i.e., worse learning; Fig. 8D). Among young rats the relationship between spatial learning ability and GAD67 immunopositive cell number was in the same direction but did not reach statistical significance ($r = 0.49$; $p = 0.22$; Fig. 8C).

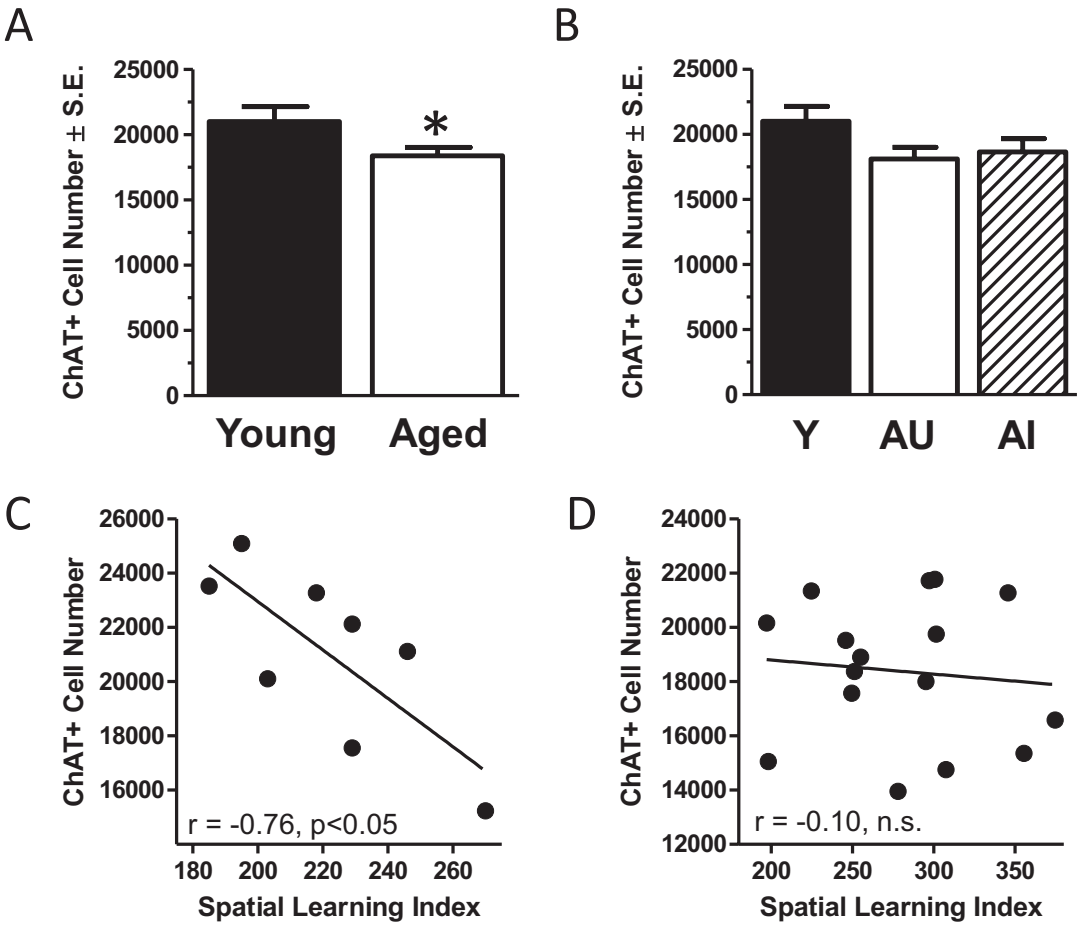

Fig. 7. Cholinergic (choline acetyltransferase [ChAT] immunopositive) cell number in the rostral basal forebrain of young (Y) and aged rats. (A) The number of ChAT immunopositive cells was modestly but significantly decreased in aged relative to young rats. (B) The reduction in ChAT immunopositive cells was of a similar magnitude (approximately −12.5%) in both aged spatially unimpaired (AU) and aged spatially impaired (AI) rats. (C) Scatter plot illustrating a strong relationship between ChAT immunopositive cell number and spatial learning index among young rats. (D) This relationship was not present among aged rats. See text for statistical analyses. * $p < 0.05$.

3.3.3. NeuN immunopositive neurons

To investigate whether age- and cognition-related alterations in ChAT immunopositive and GAD67 immunopositive cell estimates contributed to an overall difference in neuron number in rostral basal forebrain, NeuN immunopositive cells were also quantified. As shown in Fig. 9A, the mean estimated number of NeuN immunopositive cells was numerically lower in aged rats relative to young but this difference was not reliable ($t(1,21) = 1.2$; n.s.; Table 2). Likewise, no significant differences were evident using a one-factor ANOVA performed on young and aged rats subgrouped by cognitive ability ($F(2,20) = 0.78$; n.s.; Fig. 9B). As expected based on these analyses, no reliable correlations were observed between NeuN cell number and spatial learning indexes in young ($r = -0.13$; n.s.; Fig. 9C) or aged rats ($r = 0.26$; n.s.; Fig. 9D).

4. Discussion

This study was designed to test the hypothesis that coordinated age-related alterations in rostral basal forebrain cholin-

Table 2
Estimates of ChAT, GAD67, and NeuN immunopositive cells in rostral basal forebrain of young and aged behaviorally characterized rats

	Young	Aged, Total	Aged-SU	Aged-SI
ChAT+ cells (SD, *n*)	21003.47 (3284.54, 8)	**18383.71*** **(2626.83, 16)**	18113.89 (2515.56, 8)	18653.53 (2879.54, 8)
GAD+ cells (SD, *n*)	48586.17 (5564.82, 8)	51118.00 (8721.43, 15)	44459.45 (4408.62, 8)	**58727.78**** **(5317.29, 7)**
NeuN+ cells (SD, *n*)	140007.13 (19561.76, 8)	128798.47 (21035.71, 15)	124938.86 (22388.96, 7)	132175.63 (20674.01, 8)

Key: +, positive; ChAT, choline acetyltransferase; GAD, glutamic decarboxylase; SI, spatially impaired; SU, spatially unimpaired.
* $p < 0.05$ relative to young.
** $p < 0.001$ relative to both young and aged unimpaired.

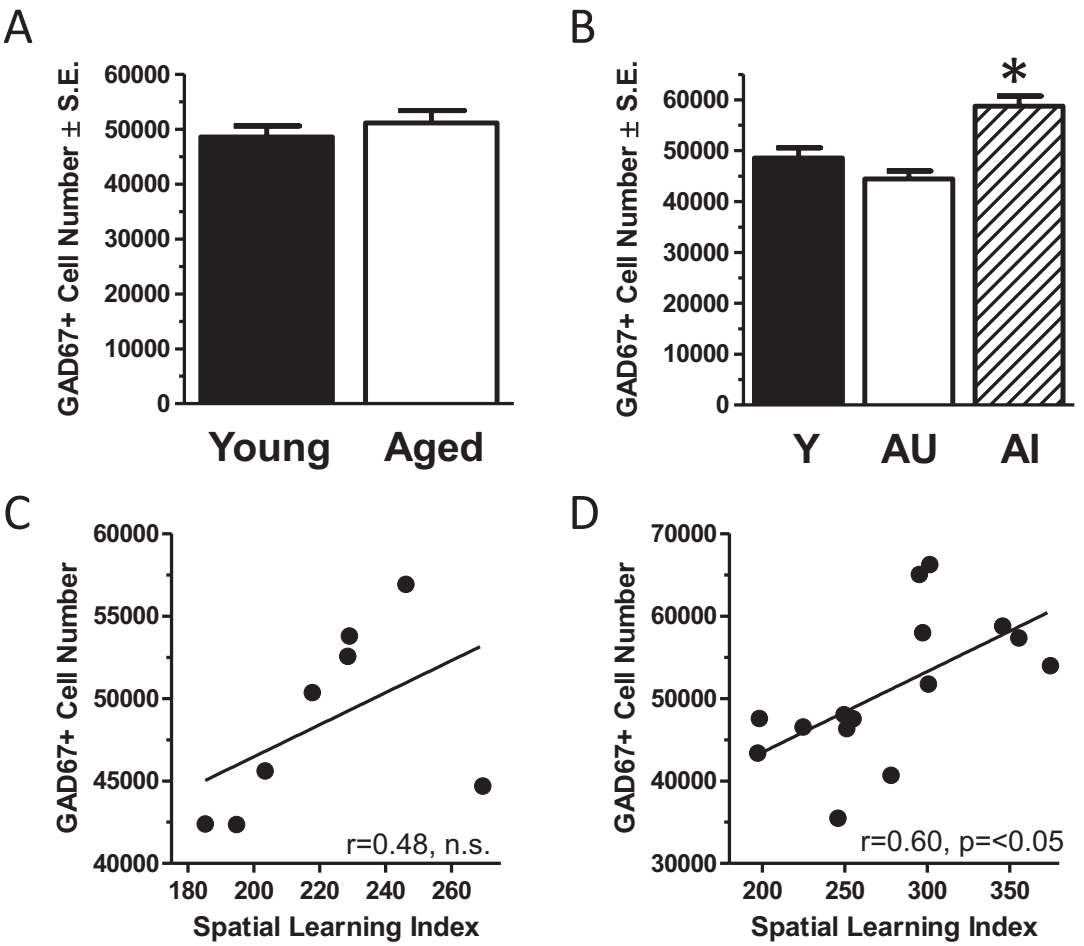

Fig. 8. GABAergic (glutamic decarboxylase [GAD]67 immunopositive) cell number in the rostral basal forebrain of young (Y) and aged rats. (A) GAD67 immunopositive cell number was numerically but not significantly greater in aged rats in comparison with young. (B) A significant difference in GAD67 immunopositive cell number was evident between cognitive age groups, such that aged spatially impaired (AI) rats exhibited a marked, reliable elevation in GAD67 immunopositive cells in comparison with both young and aged spatially unimpaired (AU) rats. (C) Scatter plot shows a trending though nonsignificant relationship between GAD67 immunopositive cell number and spatial learning index in young rats such that higher numbers were associated with worse learning. (D) Scatter plot shows that the same relationship was observed among aged rats, but in this case, greater GAD67 immunopositive cell number was significantly associated with worse spatial learning ability. See text for statistical analyses. * $p < 0.05$ relative to Y and AU rats.

ergic and GABAergic neurons that project to the hippocampus contribute to hippocampal-dependent spatial learning abilities in aged rats. Indeed, age-dependent changes were evident in both cholinergic and GABAergic neuronal populations, but the direction of these changes and their relationships to cognitive abilities were distinct. A modest but significant decline in cholinergic (ChAT immunopositive) neuron number occurred in the rostral basal forebrain with age, although this reduction was not related to spatial learning ability in aged rats. However, there was a strong relationship between cholinergic cell number and spatial learning abilities in young rats. In contrast to findings with cholinergic neurons, a robust increase in the number of GABAergic projection (GAD67 immunopositive) neurons was observed selectively in the rostral basal forebrain of aged rats with impaired spatial abilities. These phenotypically-specific alterations were not reflected in the total number of rostral basal forebrain neurons, as NeuN immunopositive cell number was stable with age and across cognitive groups.

4.1. Cholinergic (ChAT immunopositive) neurons

Cholinergic signaling in the hippocampus and neocortex has been heavily implicated in cognitive functioning, including learning, memory, and attention (Deutsch, 1971; Dunnett and Fibiger, 1993; Everitt and Robbins, 1997; Fragkouli et al., 2005; McKinney and Jacksonville, 2005; Ormerod and Beninger, 2002; Sarter and Bruno, 1997; Sarter et al., 2003; Schliebs and Arendt, 2006, 2011; Woolf, 1997). A number of cholinergic indexes decline with age, and the cholinergic system remains a primary target of drugs currently used to treat age-related cognitive impairment (Giacobini, 2004; Lane et al., 2004, 2006; Nordberg, 2006). Indeed, degeneration of cholinergic neurons in the nucleus basalis of Meynert and concomitant depletion of acetylcholine in cortical targets is a hallmark of Alzheimer's disease (Whitehouse et al., 1982), suggesting that degeneration of cholinergic neurons may be an important contrib-

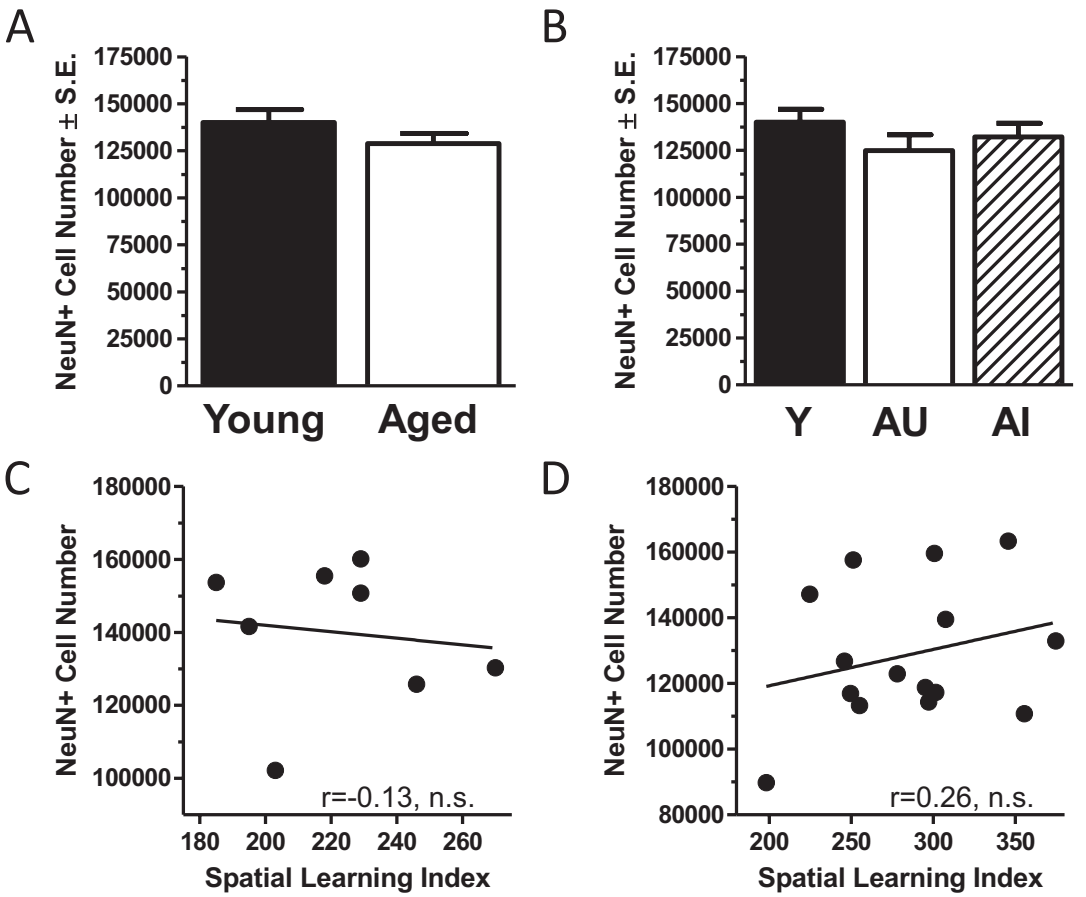

Fig. 9. Total (NeuN immunopositive) cell number in the rostral basal forebrain of young and aged rats. NeuN immunopositive cell number in the rostral basal forebrain did not differ as a function of age (A) or cognitive ability (B). Moreover, the total number of NeuN immunopositive cells did not predict spatial learning ability in either young (C) or aged (D) rats. See text for statistical analyses. AI, aged spatially impaired; AU, aged spatially unimpaired; Y, young.

utor to cognitive deficiencies observed in normal aging. However, across species, findings regarding cholinergic neuronal integrity at advanced ages have been mixed. A number of studies, employing a variety of counting techniques, report a decline in cholinergic neuron number in aging (Altavista et al., 1990; Armstrong et al., 1993; Bartus et al., 1982; Baskerville et al., 2006; Fischer et al., 1989, 1992; Lee et al., 1994; Stroessner-Johnson et al., 1992), although others report no or only a modest decline (Bigl et al., 1987; McQuail et al., 2011; Ypsilanti et al., 2008). While the current findings provide support for a significant loss of rostral basal forebrain cholinergic neurons in normal aging, it should be noted that this reduction was modest, even with the relatively large sample size used. Indeed, some of the reported differences in findings across studies comparing cholinergic neuron numbers between young and aged rats may be attributable to the numbers of subjects employed relative to the numbers necessary to achieve sufficient statistical power for detecting small-magnitude group differences.

In addition to the modest but significant decline in cholinergic neuron number with advancing age, there is considerable evidence that age-related decline in cholinergic neuronal function and signaling contributes to cognitive impairment. For example, age-associated dysregulation in calcium signaling in cholinergic neurons could affect a range of neuronal functions that include neurotransmitter release and synaptic plasticity (Disterhoft et al., 1996; Foster et al., 2001; Kumar et al., 2009). Specifically, Murchison and Griffith (1998) reported increased intracellular calcium buffering in cholinergic basal forebrain neurons in aged rats, and more recently, that age-related calcium dysregulation in basal forebrain cholinergic neurons strongly predicts impaired hippocampal-dependent cognition using the same rat model employed here (Murchison et al., 2009). Other evidence indicates that aging may disrupt cholinergic signaling at the receptor level. Specifically, muscarinic signaling in the hippocampus, a principal target of rostral basal forebrain projection neurons, is significantly altered in aged rats. Whereas muscarinic receptor-mediated phosphoinositide turnover is blunted in hippocampal CA1, CA3, and subiculum across aged rats (Nicolle et al., 2001), G protein coupling to muscarinic receptors in hippocampus is specifically associated with compromised hippocampal-dependent spatial learning (Zhang et al., 2007). Together with the current data, these findings suggest that age-related alterations in cholinergic signaling not only result from the loss of

acetylcholine-synthesizing neurons in basal forebrain but also reflect suboptimal functioning of these neurons and/or postsynaptic signaling associated with the cholinergic receptors in hippocampus and other cortical targets. This interpretation is consistent with the finding that cholinergic cell number strongly correlated with cognitive abilities in young but not aged rats (see Fig. 7). In young rats, the cellular machinery and environment is largely intact and functioning optimally, and, thus, the overall number of cholinergic neurons might provide an accurate index of acetylcholine signaling in target fields. In aged rats, however, disruption in cholinergic signaling at multiple levels might result in a functional decoupling, such that cell number is a less accurate predictor of overall cholinergic function.

4.2. GABAergic projection (GAD67 immunopositive) neurons

A major finding from the current work is the selective and significant increase in GABAergic projection neurons (indicated by greater numbers of GAD67 immunopositive cells) in the rostral basal forebrain of spatially impaired rats. Notably, the 67 isoform of GAD is preferentially expressed by GABAergic neurons in rostral basal forebrain that project to cortical targets, whereas the 65 isoform is expressed by rostral basal forebrain interneurons (Castañeda et al., 2005). Very few prior studies have quantified rostral basal forebrain GABAergic neurons in aging, and to our knowledge, no other studies have quantified this specific GAD67 immunopositive neuronal population. Using a nonisoform-specific GAD antibody, Smith and Booze (1995) reported no age-related change in GAD immunopositive neurons in caudal neocortical projecting basal forebrain nuclei (Smith and Booze, 1995). The current findings are consistent with this previous report in that no significant difference in GABAergic projection neuron number was evident in rostral basal forebrain when age groups were compared in the absence of cognitive subgrouping. Together, these data indicate that GABAergic neurons do not degenerate with advancing age, an important finding for interpreting phenotypic and functional age-related alterations in basal forebrain. For example, the calcium binding protein parvalbumin is highly coexpressed in GABAergic projection neurons and reduced parvalbumin cell number has been reported in aging (Krzywkowski et al., 1995). The present findings would support an interpretation that reduced parvalbumin cell number with age is indicative of cellular dysregulation of Ca^{2+} signaling akin to that described above for cholinergic neurons rather than overt neuronal loss (Murchison and Griffith, 1998). Additional characterization of age-related changes in the signaling properties and function of these GABAergic neurons represents an important direction of future work.

Importantly, the increase in GAD67 immunopositive cell number observed in aged spatially impaired rats did not appear due to an overall increase in total neuron number in rostral basal forebrain, as stereological estimates of NeuN immunopositive cells in adjacent sections did not differ with age or as a function of cognitive ability. Although the specific mechanisms responsible for the elevation in GABAergic cell number observed in spatially impaired aged rats remains an outstanding question, it seems plausible that this change might reflect an age-related upregulation of GAD67 protein expression in a subset of rostral basal forebrain neurons which might otherwise express only nominal levels of GAD67. Such an upregulation would increase the detectability of these neurons, which in turn would be reflected as an increase in the total number of GAD67 immunopositive neurons. Indeed, GAD67 expression can be regulated by a number of factors including activity, stress, estrous cycle, and caloric restriction (Carta et al., 2008; Cashion et al., 2004; Cheng et al., 2004; Liang et al., 1996). Moreover, altered GAD expression has been reported in a number of brain disorders, including epilepsy, Parkinson's disease, and schizophrenia (Briggs and Galanopoulou, 2011; Lanoue et al., 2010; Lewis et al., 2005).

Alternatively, it is important to consider that the neurons in rostral basal forebrain are quite heterogeneous and the full extent of distinct neuronal subtypes in these fields remains undetermined and was not exhaustively evaluated in the current study. In addition to cholinergic and GABAergic projection neurons, other cell types include GABAergic interneurons and a recently identified subpopulation of hippocampal-projecting glutamatergic neurons (Colom et al., 2005; Manseau et al., 2005). As such, it is possible that the failure to detect differences in numbers of NeuN immunopositive cells between age and cognitive groups reflects differential effects of age on multiple phenotypically distinct neuronal populations in this region. Notably, the rostral basal forebrain glutamatergic neurons share size and certain neurochemical characteristics with GABAergic projection neurons (Colom et al., 2005; Manseau et al., 2005) and some basal forebrain neurons have been identified that have the capacity to synthesize both GAD67 and phosphate-activated glutaminase, a mitochondrial enzyme used in the production of glutamate (Gritti et al., 2006). In addition, reverse transcription polymerase chain reaction studies have shown that mRNA for the glutamate vesicular transporter 2 may be coexpressed with ChAT and GAD67 messenger RNA in young and adult rats (Danik et al., 2005). These findings make it intriguing to speculate that the present results represent a functional shift from excitatory to inhibitory signaling in a subpopulation of hippocampal-projecting neurons as has been shown in kindling models in which stimulation induces the production of GAD67 in hippocampal granule cells (Gómez-Lira et al., 2005; Sloviter et al., 1996). It will be important in future studies to determine the effects of age on glutamatergic projections as well as on GABAergic interneuronal populations, in order to better understand how age-related changes in basal forebrain dynamics contribute to a loss of hippocampal-dependent learning and memory.

It is becoming increasingly clear that corticopetal basal forebrain GABAergic neurons influence neural transmission and cognitive functions linked to their terminal fields (Freund and Antal, 1988; Kiss et al., 1990b; Pang et al., 2001). GABAergic neurons are well-positioned to modulate cortical circuitry, both through their direct input to cortical structures and via the highly interconnected cholinergic and GABAergic neuronal networks within the rostral basal forebrain itself (Freund and Antal, 1988; Freund and Buzsáki, 1996). Neuronal tracing studies indicate that GABAergic hippocampal interneurons are a primary target of GABAergic afferents from rostral basal forebrain (Freund and Antal, 1988; Gulyás et al., 1991). As such, an increase in the inhibitory influence from rostral basal forebrain would be expected to result in enhanced excitability of the hippocampal principal neurons. Indeed, many studies have reported hyperexcitability in the hippocampus with advanced age, and such alterations have been linked to hippocampal dysfunction and a decline in hippocampal-supported cognition (Dickerson et al., 2005; Gallagher and Koh, 2011; Wilson et al., 2005; Yassa et al., 2010). The present findings support the hypothesis that age-related alterations in inhibitory signaling within septohippocampal circuitry might contribute to this reported shift in the inhibitory-excitatory dynamics of the aged hippocampal formation.

Overall, the findings from the current work add to the evidence that rostral basal forebrain systems are significantly altered in aging. In particular, these studies support a growing literature which indicates that inhibitory networks are particularly vulnerable to dysfunction in aging and that such dysfunction can profoundly impact cognition. Future work in which the present findings are extended to determine the innervation patterns of both inhibitory and excitatory afferents from rostral basal forebrain and that better characterize the intrinsic dynamics within basal forebrain of aged behaviorally characterized rats will help to further elucidate the role of this system in age-related cognitive decline.

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Disclosure statement

The authors report no actual or potential conflicts of interest.

The Institutional Animal Care and Use Committee approved all protocols described in this report.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2012.06.013.

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COMMENTARY

COGNITIVE FRAILTY: FRONTIERS AND CHALLENGES

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An international consensus group comprised of investigators from the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) recently convened in Toulouse, France to establish a definition for cognitive frailty in older adults. This effort was motivated by growing awareness that many people with physical frailty are also prone to cognitive problems. In "Cognitive Frailty: Rationale and Definition" (1), an initial working definition was developed, and a framework proposed for future studies of cognitive frailty.

This group should be commended for addressing the construct of cognitive frailty and an obvious gap in the clinical gerontology literature. Physical frailty is a widely recognized problem in the elderly. While age-associated cognitive dysfunction has been studied for many years, for the most part it was not conceptualized in a manner that is consistent with current definitions of physical frailty. In fact, cognition has typically not been conceptualized in this manner, and only recently has the term cognitive frailty been employed. Rockwood et al published one of the first studies to examine factors associated with frailty in the elderly (2). Frailty was conceptualized as a multidimensional construct with both physical and cognitive origins. Panza et al. used the term cognitive frailty in the title of their review of pre-dementia syndrome vascular risk factors (3). In a subsequent paper, Panza et al, attempted to specify different models of frailty in pre-dementia and dementia syndrome (4). The prognostic accuracy of frailty assessment inventories for mortality among hospitalized elderly people was examined subsequently, with results suggesting that both cognitive and physical factors were important in predicting outcome (5). We reviewed 199 manuscripts cited in PubMed in which cognitive frailty was mentioned in either the title or as a keyword. In the vast majority of these manuscripts, frailty was examined as a manifestation of cognitive dysfunction. Only recently has cognitive frailty itself become the focus of inquiry.

The term cognitive frailty is attractive as it suggests a parallel with physical frailty. The concept of physical frailty is relatively well understood in the context of aging, and has been operationalized in studies conducted over the past two decades (6-8). However, as Kelaiditi et al. point out, the operational definition of physical frailty remains unresolved (1). The situation is even more problematic for cognitive frailty, as past investigators have focused on a variety of different phenomena. The term has often been used as a general descriptor for cognitive impairment occurring as people reach advanced age. Sometimes cognitive frailty refers to cognitive disturbances or pre-dementia occurring in association with other medical conditions (9). However, Kelaiditi et al. state that cognitive frailty must be considered as being independent of dementia or pre-existing brain disorders (1). Accordingly, there seems to be several different perspectives on the nature of cognitive frailty. The fact that the construct is ambiguous and lacking a precise operational definition clearly reinforces the authors' effort to establish a common language for future studies of cognitive frailty.

An obvious question emerges: How is cognitive frailty different from cognitive reserve? Cognitive reserve refers to the capacity of a given individual to resist cognitive impairment or decline. Educational level and prior cognitive abilities have been shown to be important determinants of cognitive reserve (10-12). Cognitive reserve has been linked with resilience of brain function and structure in the presence of disease, injury, or other factors that alter physiological functioning (13). While cognitive and brain reserve undoubtedly have some common underpinnings, the relationship between these types of reserve is still not fully understood.

Kelaiditi et al maintain that "cognitive frailty is characterized by reduced cognitive reserve". Accordingly, cognitive frailty could be viewed as simply the inverse of cognitive reserve. The authors indicate that while cognitive reserve is an important element of cognitive frailty, it is also dependent on the existence of physical frailty; i.e., "the simultaneous presence of both physical frailty and cognitive impairment". They distinguish this category of older non-demented adults from cognitive impairment in the absence of physical frailty. The importance of this categorization is that it emphasizes an important and often under-recognized relationship between systemic physical illness, brain dysfunction, and cognitive impairment. It is now well established that cognitive disturbances occur secondary to various medical conditions, such as cardiovascular disease, diabetes and HIV (14-19).

The value of excluding brain disorders from cognitive frailty may be less well justified. By limiting cognitive frailty to people with physical frailty, Kelaiditi et al create four discrete categories of older non-demented adults, which may have some clinical value. However, with respect to the concept of

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cognitive frailty, there are many examples of people who are vulnerable to subsequent functional decline based on the existence of subtle cognitive and/or brain abnormalities below the threshold for clinical detection. In fact, a major thrust of current research on neurodegenerative disease focuses on the discovery of vulnerability and early markers of future functional decline. While physical disorders such as diabetes and cardiovascular risk factors contribute to this vulnerability, a variety of neurobiological and behavioral risk factors also exist that create functional vulnerability (20-22), and ultimately cognitive frailty. In fact, excluding people with brain disturbances from the definition of cognitive frailty fails to account for the fact that the effects of physical illnesses are exacerbated by the existence of a neural predisposition to cognitive decline or prior brain disturbances that reduce cognitive reserve. Furthermore, people with physical frailty who develop cognitive frailty presumably do so as their brain begins to develop neuropathological changes. Accordingly, there is value in dichotomizing cognitive frailty between people with or without pre-existing brain dysfunction, or alternatively treating brain vulnerability as a mediator of the effects of physical illness on cognitive frailty.

Defining cognitive frailty depends on determining its diagnostic criteria. Other than physical frailty, the primary criteria proposed by Kelaiditi et al. is the presence of mild cognitive impairment as defined by a clinical dementia rating (CDR) score of 0.5, without Alzheimer's disease or another progressive brain disturbance that would lead to dementia. Using these criteria, it is not clear whether people with cerebrovascular disturbances would meet these criteria or not. The authors make a point of also noting that "under different circumstances cognitive frailty may also represent a precursor of neurodegenerative processes". This is a critical point that reinforces the need to go beyond the definition of cognitive frailty as occurring in the absence of brain dysfunction. It is also likely that a CDR = 0.5 is too narrow to fully capture the heterogeneity of cognitive frailty. For example, people without cognitive impairment that rises to the level of a CDR= 0.5 may still be vulnerable to functional decline under certain conditions. This occurs commonly during hospitalization, in response to extreme stress, or to changes in the physical environment in the elderly.

In fact, it is the vulnerability to alterations in cognitive function under such conditions that may be the essential determinant of cognitive frailty. There are many people in society with cognitive limitations who would not be considered to be frail, unless they exhibit a tendency to functionally decompensate when their resources are challenged. The key to operationalizing cognitive frailty may ultimately depend of developing diagnostic challenges that would enable clinicians to determine this tendency. This will depend on determining which neurocognitive measures are most useful for detecting this vulnerability and for assessing the severity of cognitive frailty.

In sum, "Cognitive Frailty: Rationale and Definition" (1) provides a valuable starting point for the development of a coherent operational definition and for future studies of cognitive frailty. While closely linked to cognitive reserve, the construct of cognitive frailty goes beyond cognitive reserve, particularly because of its association with physical frailty and the fact that it often becomes evident in the context of acute physical illness. There seems to be considerable value in distinguishing vulnerability to cognitive functional decline among people with or without physical frailty, though there is evidence that both cognitive and physical frailty share several common pathophysiologic mechanisms and risk factors. Growing and consistent epidemiologic evidence shows that impaired physical performance, which is a component of physical frailty, measured with walking speed or the Short Physical Performance Battery (SPPB) (23), is independently associated with cognitive decline (24-36). The SPPB tests, including walking, balance and chair stands, require the complex interplay of sensory, cognitive, and motor functions. These systems may be altered early in the path to cognitive decline (36, 37), and possibly to cognitive frailty. Low walking speed and low SPPB score are also associated with elevated inflammatory cytokines and low Brain-Derived Natirurectic Factor (BDNF) (38-40), all of which are predictors of cognitive decline (41, 42).

Future research is needed to determine how phenotypic differences among people and the existence of a wide variety of preexisting manifestations of brain structure and function affect this vulnerability. Following the expert consensus, prospective studies will be needed to assess the reliability and predictive validity of the operational measure of cognitive frailty. We laud the efforts of the IANA/IAGG consensus group in laying the foundation for the emerging concept of cognitive frailty and strongly encourage future studies aimed at advancing this clinical domain.

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