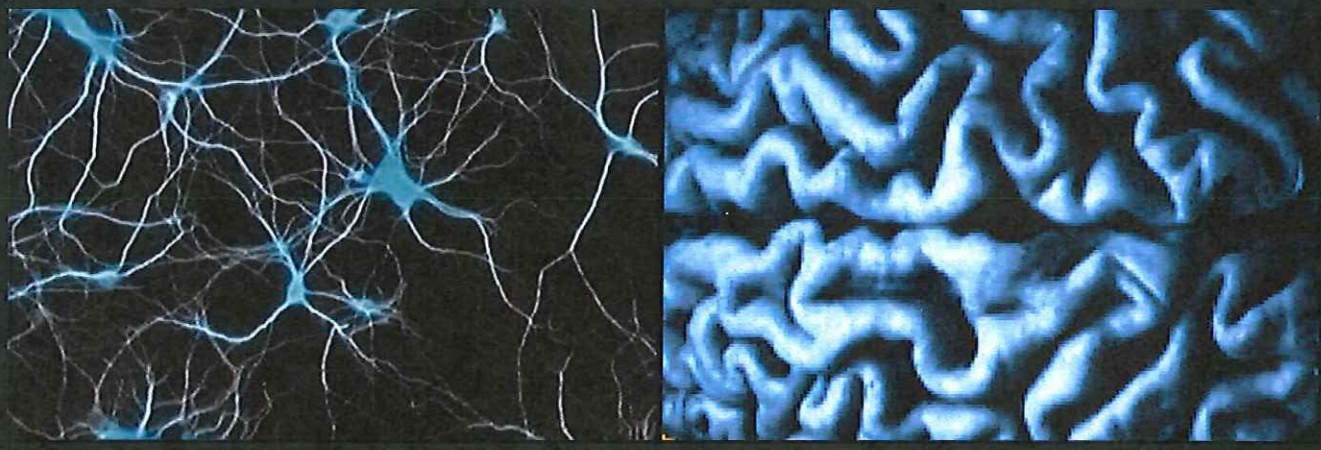


EVELYN F. McKNIGHT BRAIN INSTITUTE

SYMPOSIUM AND PROGRAM UPDATE

FEBRUARY 20, 2013

PRESENTED TO THE
EVELYN F. McKNIGHT BRAIN RESEARCH FOUNDATION
BOARD OF TRUSTEES

MILLER SCHOOL OF MEDICINE

UNIVERSITY OF MIAMI

UNIVERSITY OF MIAMI MILLER SCHOOL OF MEDICINE

EVELYN F. MCKNIGHT BRAIN INSTITUTE

Symposium and Program Update

AGENDA

February 20, 2013

Location: Gordon Center, first floor auditorium
Clinical Research Building, 1120 NW 14th Street, Miami, Fl 33136

Attendees: McKnight Brain Research Foundation Trustees, UM Faculty, Staff and Students

BREAKFAST		8:00AM – 8:30AM
WELCOME AND FACULTY PRESENTATIONS		8:30AM – NOON
8:30 - 8:39	Welcome and Introductions	Dr. Ralph Sacco
8:40 – 8:49	Opening Remarks	Dean Pascal Goldschmidt
8:50 - 8:59	Symposium Agenda and Highlights	Dr. Clinton Wright

Symposium

Each 15 minute segment includes 5 minutes for questions

Update from Animal Behavior Core (moderator, Miguel Perez-Pinzon, Ph.D.)

9:00 – 9:14	Cerebral Ischemia & Cognition in Aged Rats – *Jacob Neumann, Ph.D*
9:15 – 9:29	Cognitive Decline and Cerebral Ischemia – *Charles Cohan, B.S.*

Update on NOMAS projects (moderator, Ralph Sacco, M.D., M.S.)

9:30 – 9:44	White Matter Lesion Location and Cognition - *Clinton Wright, M.D., M.S.*
9:45 – 9:59	Genetics of White Matter Hyperintensity Volume – *Susan Blanton, Ph.D.*
10:00 – 10:14	Sleep Health and Cognition – *Alberto Ramos, M.D., M.S.*

UNIVERSITY OF MIAMI MILLER SCHOOL OF MEDICINE

EVELYN F. MCKNIGHT BRAIN INSTITUTE

Symposium and Program Update

AGENDA

February 20, 2013

15 MINUTE BREAK

Update on Evelyn F. McKnight Registry (moderator, Clinton Wright, M.D., M.S.)

10:30 – 10:44 MDC Registry: Cognitive & Behavior Manifestations – *Bonnie Levin, Ph.D.*

10:45 – 10:59 Blood flow in the Aging Brain: Ultrasound – *Tatjana Rundek, M.D., Ph.D.*

11:00 – 11:14 Blood flow in the Aging Brain: MR Imaging – *Noam Alperin, Ph.D.*

Education Research Update

11:15 – 11:29 Health IT Solutions for Professionals, Patients, and Caregivers – *Richard Isaacson, M.D.*

Update on MRI and Cognitive Assessment Standardization Across Institutes

11:30 – 11:39 MRI Standardization Working Group – *Fatta Nahab, M.D.*

11:40 – 11:49 Cognitive Assessment Standards Working Group – *Bonnie Levin, Ph.D.*

11:50 – 12:00 Wrap-up and Questions

LUNCH *(by invitation only)* 12:15 PM

Location: Clinical Research Building – 10TH Floor, Conference room #1080

Evelyn F. McKnight Brain Institute

Symposium and Program Update

February 20th, 2013

Miller School of Medicine
University of Miami

University of Miami
Miller School of Medicine
Evelyn F. McKnight Brain Institute

Neurology
Ralph L. Sacco, MD, MS
Clinton Wright, MD, MS
Bonnie Levin, PhD
Tatjana Rundek, MD PhD
Richard Isaacson, MD
Fatta Nahab, MD
Miguel Perez-Pinzon, PhD
Kunjan Dave, PhD
Chuanhui Dong, PhD

University of Miami
Miller School of Medicine
Evelyn F. McKnight Brain Institute

Human Genetics
Susan Blanton, PhD

Psychiatry & Behavioral Sciences
Elizabeth Crocco, MD

Radiology
Noam Alperin, PhD

Evelyn F. McKnight Brain Institute

Symposium and Program Update

Opening Remarks

Dean Pascal Goldschmidt

Overview of Institute

Mission

Discover the causes of age-related disorders of brain function and memory, and ways to prevent them

Vision

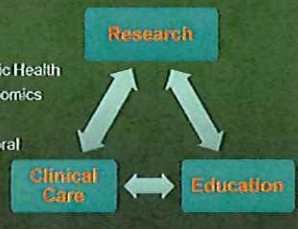
To become a foremost center of research and education into the causes and treatment of age-related cognitive disorders

The Institute will help integrate the University's basic and clinical scientists, enhance its educational programs, and improve care of patients

Evelyn F. McKnight Brain Institute

Reaches across the university, involving many departments both at the Coral Gables campus and the Miller School of Medicine

- Center On Aging
- Dept. Engineering
- Dept. Epidemiology & Public Health
- Hussman Inst. Human Genomics
- Dept. Neurology
- Dept. Psychiatry & Behavioral Sciences
- Dept. Psychology
- Dept. Radiology



Evelyn F. McKnight Brain Institute

Update from Animal Behavior Core

Moderator: Miguel Perez-Pinzon, Ph.D.
Professor & Vice Chair of Basic Research
Department of Neurology

Leonard M. Miller School of Medicine, University of Miami
Department of Neurology
Cerebral Vascular Disease Research Laboratories
Evelyn F. McKnight Brain Institute

Animal Behavior Core

Research Center for Cerebral Vascular Disease

- Established more than 50 years ago

Objective

- Conduct coordinated investigations into the pathophysiology, treatment and prevention of cerebral ischemic injury

Cognitive Dysfunction Following Cerebral Ischemia in Aged Fischer 344 Rats

Dr. Jake Neumann, Ph.D
Charles Cohan, B.S.
Dr. Kunjan Dave, Ph.D
Dr. Clinton Wright, M.D., MS
Dr. Miguel Perez-Pinzon, Ph.D.

Leonard M. Miller School of Medicine, University of Miami
Department of Neurology
Cerebral Vascular Disease Research Laboratories
Evelyn F. McKnight Brain Institute

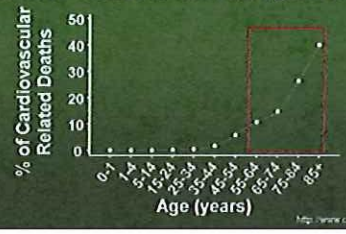
Cerebral Ischemia

- Major Causes:
  - Cardiovascular diseases
  - Cerebrovascular diseases
- Decreased cerebral circulation
  - Decreased supply of oxygen (O_2) and glucose
  - Induce neuronal death

http://www.cdc.gov/nchs/fastats/deaths.htm
Moulaert et al. Resuscitation. 2009; 80: 297-305.

Risk of Cerebral Ischemia versus Life Expectancy

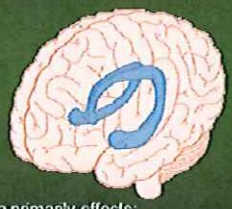
- Increased risk of Cerebral Ischemia in Aged Population
  - 92% of cases are over the age of 55



http://www.cdc.gov/nchs/fastats/deaths.htm

Cognitive Dysfunction & the Hippocampus

- Cognitive dysfunction following cerebral ischemia
  - Memory
  - Attention
  - Executive Function
  - Motor Function
- Hippocampus
  - Important for:
    - Learning
    - Spatial memory
  - Transient Cerebral Ischemia primarily effects:
    - Hippocampus



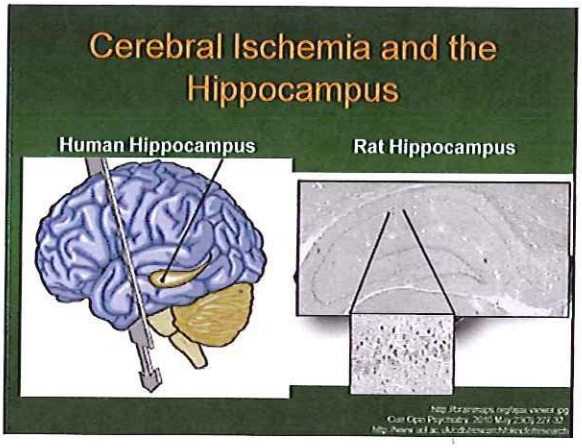
http://brainconnection.positscience.com/
Curr Drug Targets. 2013 Jan; 14(1): 20-35.

Learning, Memory, and Electrophysiology

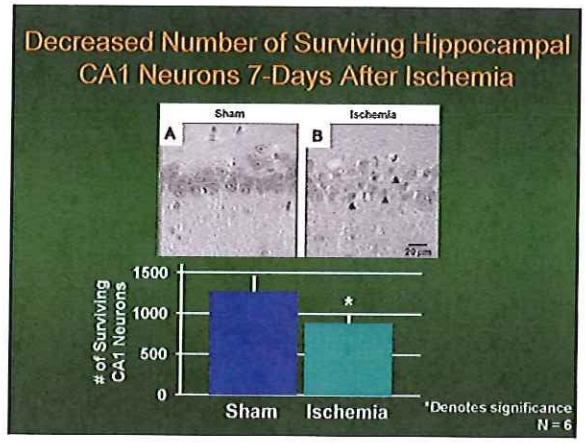
- Memory formation (encoding) occurs through the hippocampus
  - Electrical signals are sent between neurons
- Synaptic plasticity
  - Ability for neurons to change their electrical conductance for learning due to rapid and intense stimulation
  - Long-term potentiation (LTP)

http://photos.the-scientist.com/legacy/ArticleImages/2011/12/neuron.jpg
Physiol Rev. 2004 Jan; 84(1): 87-136.

Cerebral Ischemia and the Hippocampus

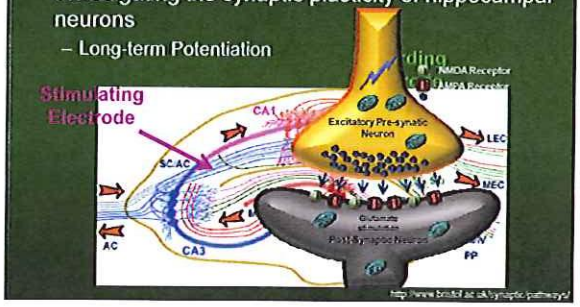


Decreased Number of Surviving Hippocampal CA1 Neurons 7-Days After Ischemia

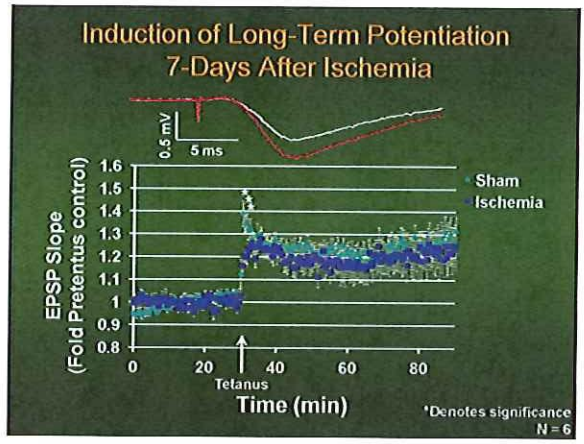


Acute Brain Slice Electrophysiology 7-Days After Ischemia

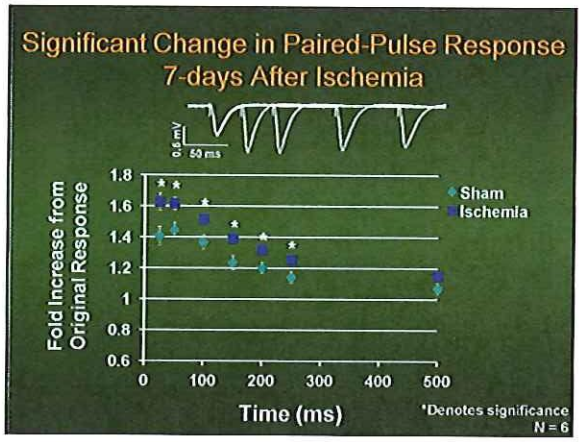
- Investigating the synaptic plasticity of hippocampal neurons
  - Long-term Potentiation



Induction of Long-Term Potentiation 7-Days After Ischemia



Significant Change in Paired-Pulse Response 7-days After Ischemia



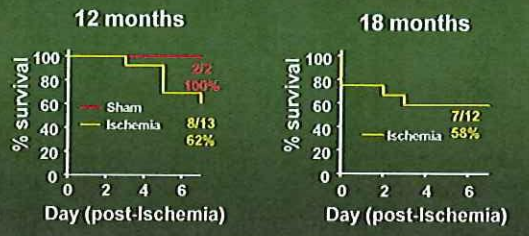
Summary

- Successful induction of cerebral ischemia in 9 month old rats
- Cerebral ischemia decreased the number of surviving hippocampal CA1 neurons
- Cerebral ischemia promotes synaptic dysfunction

- Behavior Studies → Charles Cohan

Future Studies

- Continue investigating the effects of cerebral ischemia and cognitive dysfunction on aged Fischer 344 rats



Acknowledgements

- Evelyn F. McKnight Brain Institute
- NIH grants:
  - NS45676
  - NS054147
  - NS34773
  - NS073779

Cognitive Dysfunction following Cerebral Ischemia in Aged Fischer 344 Rats: Behavioral Assays and Future Directions

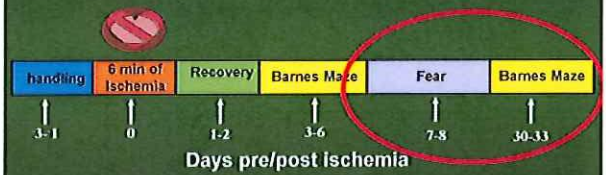
Charles Cohan B.S.
Dr. Jake Neumann Ph.D.
Dr. Kunjan Dave Ph.D.
Dr. Clinton Wright M.D.
Dr. Miguel Perez-Pinzon Ph.D.

Leonard M. Miller School of Medicine
University of Miami

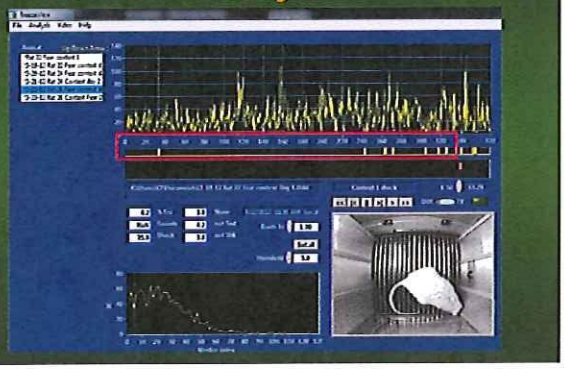
Measuring Behavioral Deficits After Cerebral Ischemia

- Spatial memory
  - Hippocampal dependent
- Behavioral assays
  - Contextual fear conditioning
  - Barnes circular platform maze

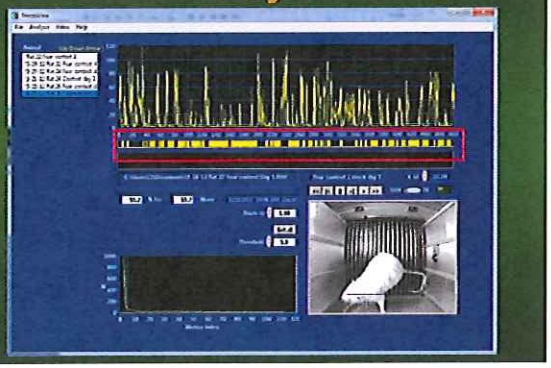
Experimental Paradigm and Tests of Spatial Memory



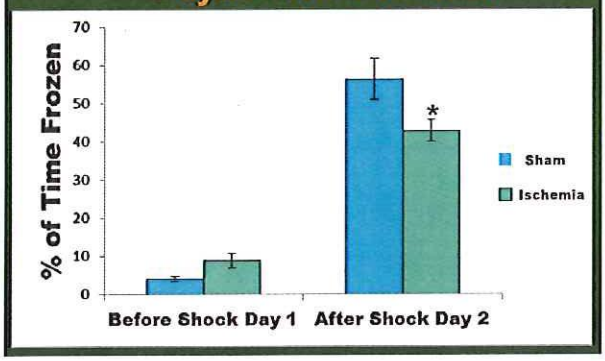
Contextual Fear Conditioning Day 1



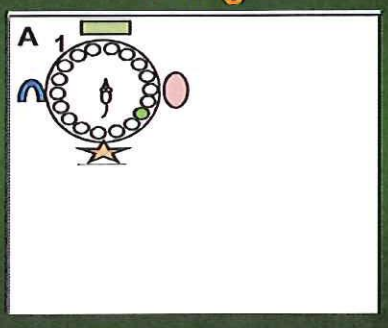
Contextual Fear Conditioning Day 2



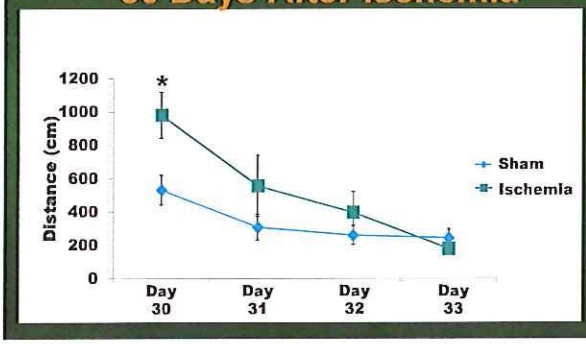
Spatial Memory is Impaired 7 Days After Ischemia



Barnes Maze Experimental Paradigm



Spatial Memory Is Impaired 30 Days After Ischemia



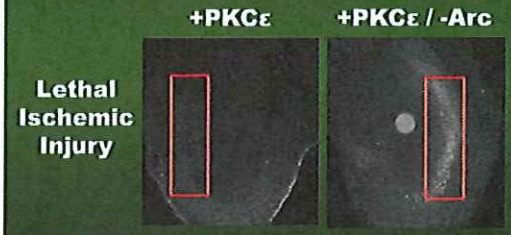
Behavioral Results Summary

- Rat spatial memory is impaired
  - 7 days after ischemia
  - 30 days after ischemia

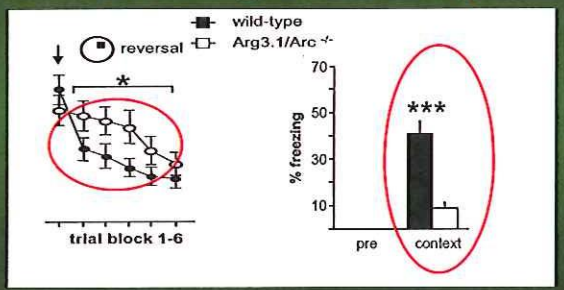
How can we protect the brain to prevent cognitive deficits in the elderly?

PKCε Activation Prior to a Lethal Ischemic Event Prevents Hippocampal Cell Death

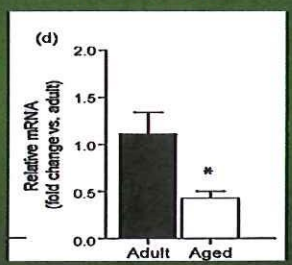
PKCε-mediated Neuroprotection Depends Upon Arc Expression



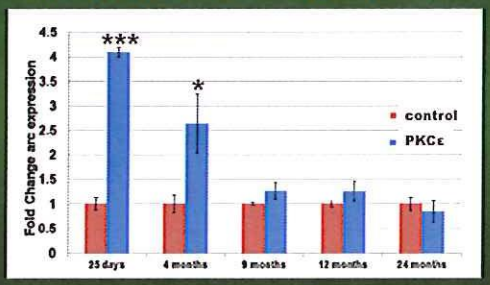
Arc is Necessary For Learning and Memory



Activity Induced Arc Transcription is also Decreased in Aging



Aging Decreases PKCε Activated Arc Expression



Future directions

Can increasing arc expression in the elderly protect from ischemia or age-related cognitive deficits?

Thanks!

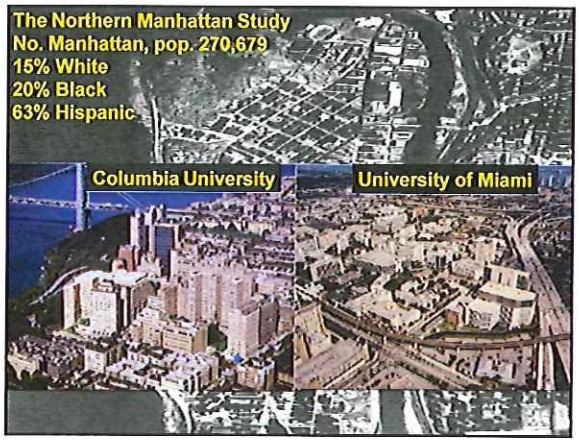
- Dr. Carol Barnes Ph.D.
- Funding Sources
  - Evelyn F. McKnight Brain Institute
  - NIH grants NS45676, NS054147, NS34773, and NS073779.

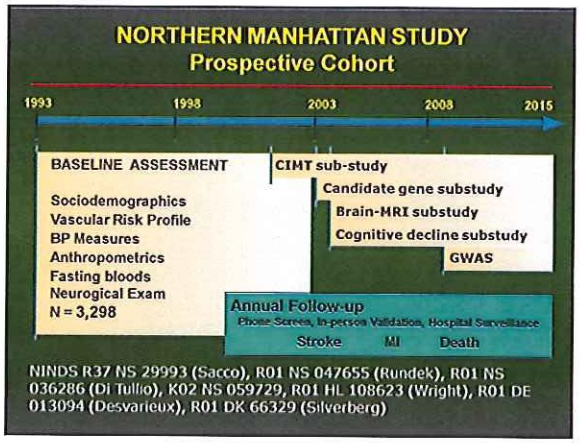
Evelyn F. McKnight Brain Institute

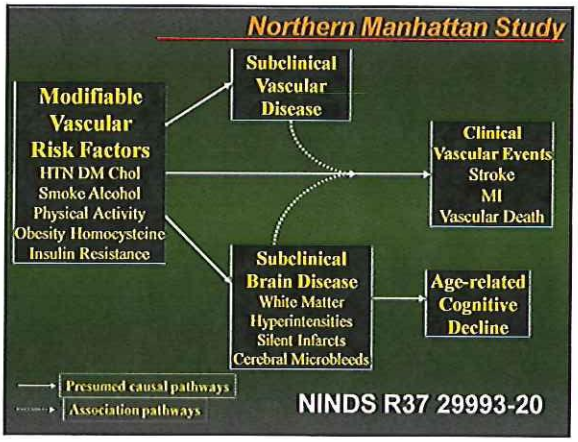
Update on NOMAS projects

Moderator: Ralph L. Sacco, M.D., M.S.

Leonard M. Miller School of Medicine, University of Miami
Department of Neurology
Evelyn F. McKnight Brain Institute







White Matter Hyperintensity Location and Cognition

Ahmet M. Bagci, PhD[1], Chuanhui Dong, Ph.D., Noam Alperin, PhD[1], Clinton Wright, MD[2]

Advanced Image Processing Lab, Radiology[1] and Neurology[2]
February 20 2013

Leonard M. Miller School of Medicine
University of Miami

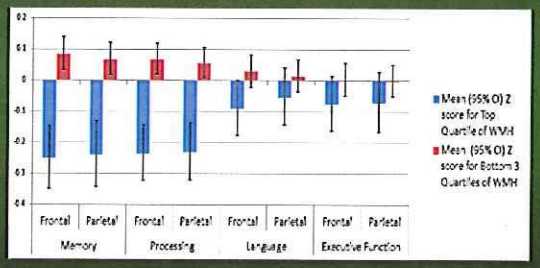
Background

- WMH load is an important risk factor for cognitive decline in "normal" and pathological aging
- Previous work has focused on WMH volume regardless of its functional location and anatomical distribution
- To look into this we began by examining our Visual Rating Scale to examine associations between WMH in particular locations and cognitive performance

WMH and Cognition: Descriptives

Variable	N, % (Total N=1286)
Male sex	507, 39%
White	190, 15%
Black	223, 17%
Hispanic	844, 66%
High school completion	590, 46%
Maximum frontal score 0-3	963, 75%
Maximum frontal score 4-6	323, 25%
Maximum parietal score 0-3	1003, 78%
Maximum parietal score 4-6	283, 22%
	Mean ± SD
Age at scan	70.59 ± 8.98
Brain volume/cranial volume %	72.42 ± 4.26

WMH Location by VRS and Cognitive Domains



Unadjusted associations

WMH Location by VRS: Memory and Processing Speed

Lobe	N	Memory Domain Z score Effect estimate (in SD)*	p-value	Processing Speed Domain Z score Effect estimate (in SD)*	p-value
Frontal Lobe Top Quartile vs. Bottom 3 Quartiles	323	**-0.153**	**0.03**	**-0.141**	**0.04**
Parietal Lobe Top Quartile vs. Bottom 3 Quartiles	283	0.0018	0.98	-0.033	0.65
Top Quartile Frontal + Parietal	217	**-0.154**	**0.02**	**-0.181**	**0.01**
Top Quartile Frontal only	106	-0.145	0.10	-0.121	0.16
Top Quartile Parietal only	66	0.015	0.89	-0.0036	0.97
Neither Lobe	897	ref		ref	

*Controlling for age, sex, race/ethnicity, education, brain atrophy (brain volume/cranial volume), and mutually controlling for the WMH volume in the other lobe

Background

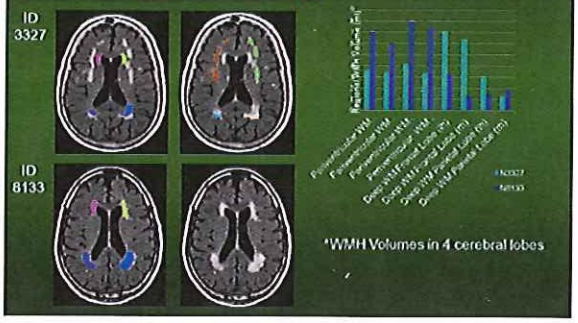
- WMH load is an important risk factor for cognitive decline in normal aging
- Previous works focus on WMH volume regardless of its functional location and anatomical distribution
- We developed new methodologies for assessment of WMH load that account for both anatomical and functional locations

Three types of localization:

1. Lobar
2. By specific white matter tract
3. Distance from lateral ventricle

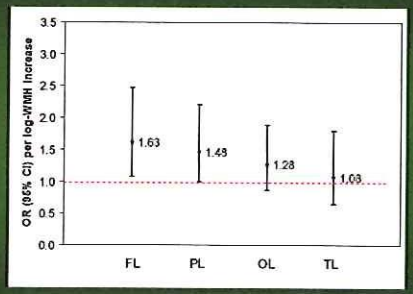
Lobar WMH Volumes

Periventricular WMH (distance to ventricle <10mm)	Deep WMH (distance to ventricle >10mm)



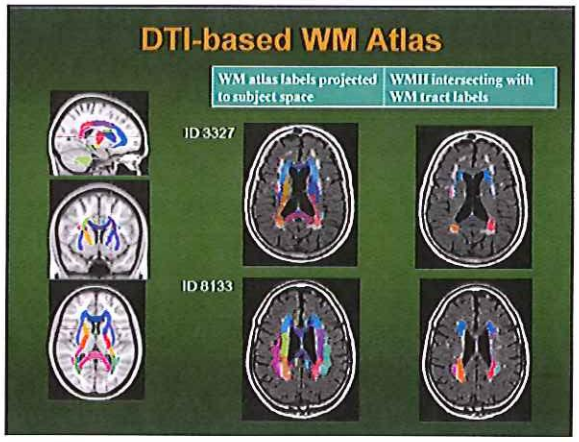
*WMH Volumes in 4 cerebral lobes

Regional WMH Volumes

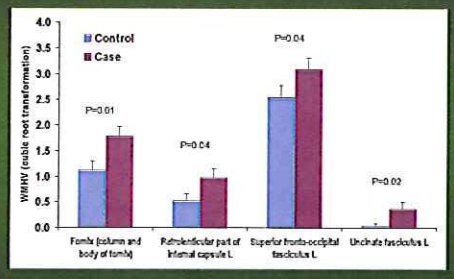


Odds ratios (OR) and 95% confidence intervals (CI) for per log-WMH greater in frontal lobe (FL), parietal lobe (PL), occipital lobe (OL) and temporal lobe (TL) among 59 cases with memory impairment and 50 controls, adjusted for age and education

DTI-based WM Atlas

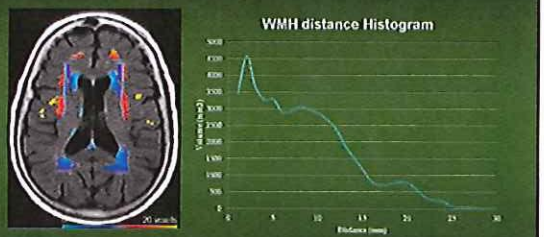


DTI-based WM Atlas



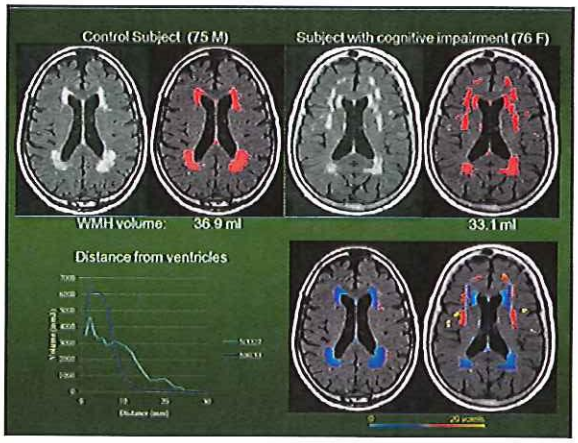
Among 48 DTI based white matter tracts, four showed larger WMHV in cases compared to controls, adjusted for age and sex. Data presented as means (SE)

Distance Weighted WMH

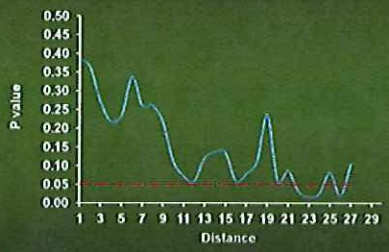


Each WMH voxel is weighted by its distance from the ventricular boundary

The histogram provides a global characterization of the WMH load distribution



Association of Distance Weighted WMH with Case Control Status



Association between WMH volume and case status by the distance of WMHV from the ventricle, adjusted for age and education

Genetics of White Matter Hyperintensity Volume

Susan Halloran Blanton, Ph.D.

Hussman Institute for Human Genomics
Dr. John T. Macdonald Department of Human Genetics

Sample Characteristics

Variable	Hispanics (n=759)	White (n=154)	Black (n=170)
Age at MRI, mean ± SD	69.1 ± 8.3	72.7 ± 9.2	73.4 ± 8.9
Male, %	37.90%	50.65%	37.70%
WMH, mean ± SD	6.9 ± 8.6	6.5 ± 6.9	11.1 ± 13.1
WMH, median [IQR]	3.8 [5.5]	4.1 [5.5]	6.1 [10.8]
Ln(WMH), mean ± SD	1.5 ± 0.9	1.5 ± 0.9	1.9 ± 1.0
TCV, mean ± SD	1139 ± 113	1224 ± 139	1140 ± 125
TCV, median [IQR]	1133 [165]	1209 [202]	1131 [170]

Basic Model for Association

Outcome

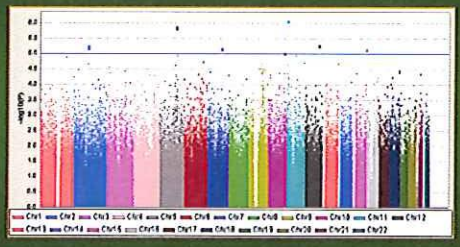
ln White Matter Hyperintensity Volume

Univariate Predictors

Genetic Marker
Age
Sex
Ancestry
Total Cranial Volume

$$\ln WMH = \beta_0 + \beta_1 * ADD + \beta_2 * Age + \beta_3 * Sex + \beta_4 * PCA1 + \beta_5 * PCA2 + \beta_6 * TCV$$

Significance of Genetic Effect in Hispanics



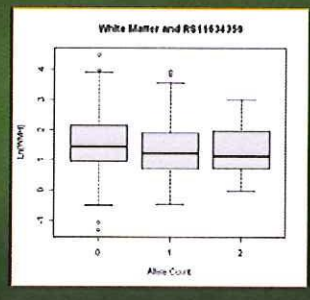
Significance of Genetic Effect in Hispanics

			Hispanic Base Model		Hispanic Base Model + Brain Volume		Black Base Model		White Base Model			
CHR	SNP	BP	BETA	P	BETA	P	BETA	P	BETA	P	Gene	Location
11	rs10541791	85688858	-0.1979	8.49E-07	-0.1972	9.52E-07	-0.017	8.24E-01	-0.06	5.82E-01	RICS	flanking
5	rs37451078	115558257	0.2401	1.30E-06	0.2383	1.57E-06	-0.051	6.54E-01	-0.25	3.95E-02	PRR26	flanking
5	rs33563523	115581247	0.2401	1.54E-06	0.2383	1.83E-06	-0.061	6.02E-01	-0.26	3.14E-02	PRR26	flanking
2	rs17650888	136779658	-0.5741	5.51E-06	-0.5718	6.17E-06			-0.2	4.86E-01	STRAP2	flanking
12	rs11115825	106416141	0.3333	5.61E-06	0.3316	6.18E-06						
2	rs17641565	106787958	-0.5631	8.83E-06	-0.5671	7.32E-06			-0.21	3.36E-01	STRAP2	UTR3
7	rs41262	105401733	0.3062	8.85E-06	0.3053	7.61E-06	-0.03	9.07E-01	0.201	3.20E-01	CDHR3	intron
15	rs11634350	96529366	-0.216	7.32E-06	-0.2161	7.31E-06	-0.253	1.21E-01	-0.12	2.24E-01		
10	rs7915358	116421357	0.2544	9.34E-06	0.2558	8.44E-06	-0.138	3.06E-01	0.163	3.34E-01	ABLIM1	intron

Chromosome 15 Association

Region previously associated with late onset Alzheimer Disease

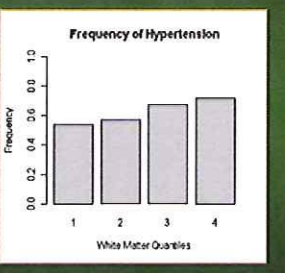
Distribution of White Matter Lesions by RS11634350 in Hispanics



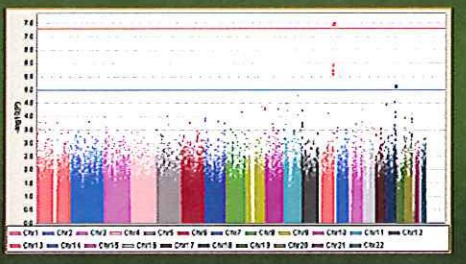
Gene - Hypertension Interaction

Outcome
ln White Matter Hyperintensity Volume
Univariate Predictors
Genetic Marker
Age
Sex
Ancestry
Total Cranial Volume
Hypertension (yes/no)
Interaction
Genetic Marker * Hypertension (yes/no)

Frequency of Hypertension in Hispanics



Significance of Genetic Effect in Hispanics after adjustment for Gene*Hypertension Interaction



Significance of Genetic Effect in Hispanics after adjustment for Gene*Hypertension Interaction

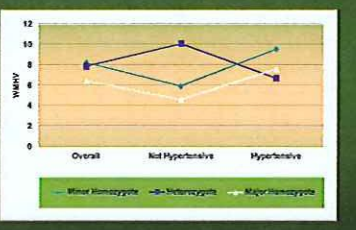
			Hispanic			Black			White				
CHR	SNP	BP	A1	BETA	P	A1	BETA	P	A1	BETA	P	Gene	Location
13	rs17196604	99659263	T	0.5428	3.02E-08	T	1.95E-01	3.12E-01	T	9.45E-02	6.14E-01	PCCA	Intron
13	rs9585381	99663324	G	0.4655	1.10E-06	G	2.23E-01	2.31E-01	G	1.71E-01	3.51E-01	PCCA	Intron
13	rs1556800	99607806	G	0.4537	1.80E-06	G	2.80E-01	2.80E-01	G	-1.02E-01	6.31E-01	PCCA	Intron
13	rs1124035	99608559	T	0.4668	2.43E-06	T	2.38E-01	3.59E-01	T	9.53E-02	6.10E-01	PCCA	Intron
18	rs2935065	74522236	C	-0.3087	7.27E-06	T	6.42E-02	7.70E-01	C	1.64E-02	9.12E-01		

PCCA

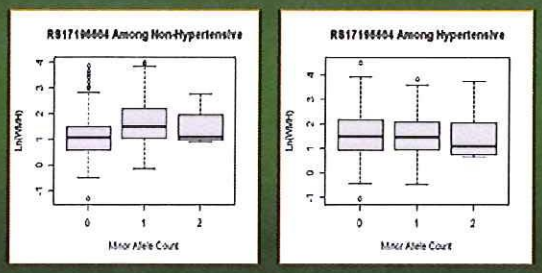
Propionyl-CoA carboxylase (PCC):
Catalyzes the first step in the catabolism of propionyl-CoA

Propionyl-CoA:
Intermediate in the metabolism of several amino acids
Produced by oxidation of odd-numbered fatty acids

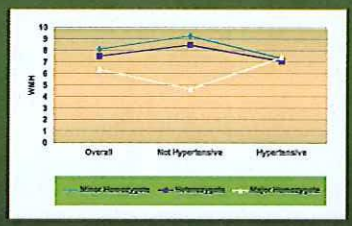
Distribution of White Matter Lesion Volume by RS17197604 and Hypertension in Hispanics



Distribution of White Matter Lesion Volume by RS17197604 and Hypertension in Hispanics



Distribution of White Matter Lesion Volume by RS9585381 and Hypertension in Hispanics



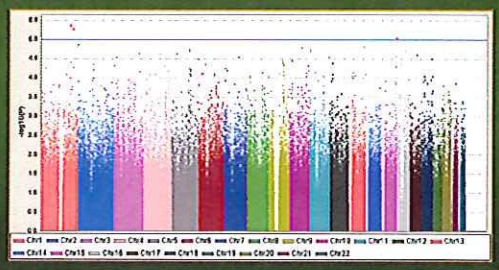
Gene - Executive Function Interaction

Outcome
- *ln* White Matter Hyperintensity Volume

Univariate Predictors
- Genetic Marker
- Age
- Sex
- Ancestry
- Total Cranial Volume
- Executive Function

Interactions
- Genetic Marker * Executive Function

Significance of Genetic Effect in Hispanics after adjustment for Gene * Executive Function Interaction



Significance of Genetic Effect in Hispanics after adjustment for Gene * Executive Function Interaction

			Hispanic		Black		White			
CHR	SNP	BP	BETA	P	BETA	P	BETA	P	Gene	Location
1	rs17548640	192209129	0.4693	4.03E-06	-0.4299	5.28E-01	-0.5308	2.31E-01		
1	rs4551495	209291737	-0.2265	5.05E-06	0.0276	8.07E-01	0.0095	9.58E-01	KCNH1	Intron
15	rs11634350	96529366	-0.2395	8.90E-06	-0.3209	6.50E-02	-0.4907	6.52E-03		

KCNH1

Expression: myoblast formation
Brain

Function: (voltage activated)

Future Directions

Follow-up: Chromosome 15 LOAD region KCNH1

NOMAS: Other cognitive domains

Collaborators

Department of Neurology

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Ashley Beecham, MS

Sleep Health and Cognition

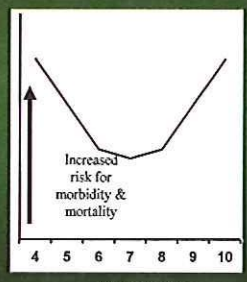
Alberto Ramos, MD MSPH

Assistant Professor of Neurology and Sleep Medicine

Leonard M. Miller School of Medicine

Sleep Habits/Patterns

- Sleep duration has a curvilinear U-shaped relation with mortality, cardiac disease and stroke
- About one third of older adults report extreme sleep durations (<6 or > 10 h) and over 50% have sleep difficulties
- Aim: To evaluate the association between self reported sleep duration and cognitive performance



Demographic, vascular risk factors and Mini-Mental Exam scores across categories of sleep hours

Mean±SD or N (%) or as indicated	Total N=927	< 6 h (n=224, 24%)	6 - <9 hours (n=616, 66%)	≥ 9 h (n=87, 9%)
Age, years	75 ± 9	74 ± 8	74 ± 9	77 ± 9 *
Moderate alcohol	363 (39)	69 (31)	259 (42)	35 (41) *
Hypertension	634 (68)	140 (63)	429 (70)	65 (75) *
Diabetes	131 (14)	34 (15)	75 (12)	22 (25) **
Mini Mental Score, median (interquartile range)	28 (10-30)	28 (3)	28 (4)	26 (6) ***
Low MMSE score (Based on age/education cutoff)	93 (10)	18 (8)	59 (10)	16 (18) *

* $p < 0.05$, ** $p < 0.001$, *** $p < 0.0001$

Association between sleep hours and Mini-Mental Score

	Model 1		Model 2		Model 3	
sleep hours	β (se)	p	β (se)	p	β (se)	p
< 6 hours	0.005 (0.02)	0.74	0.01 (0.02)	0.46	0.01 (0.02)	0.39
6-8.9 hours	Reference	--	--	--	--	--
≥ 9 hours	- 0.07 (0.02)	0.0012	-0.05 (0.02)	0.0187	- 0.06 (0.03)	0.0120

Model 1: univariate

Model 2: adjusted for age, sex, race-ethnicity, education, Medicaid or no insurance status

Model 3: adjusted for covariates in model 2 and reported alcohol consumption, depression, diabetes mellitus, hypertension, high risk for SDB, and medications

Odds Ratio and 95% Confidence Interval among categories of sleep duration and low MMSE score.

	Model 1	Model 2	Model 3
<6 hours	0.8 (0.5-1.4)	0.8 (0.4-1.4)	0.8 (0.4-1.6)
≥9 hours	2.1 (1.2-3.9)	1.9 (1.02-3.7)	2.4 (1.1-5.0)

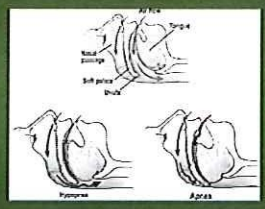
Reference: 6-8.9 hours Based on age/education cutoff

Model 1: unadjusted.

Model 2: adjusted for age, sex, race-ethnicity, education, insurance status.

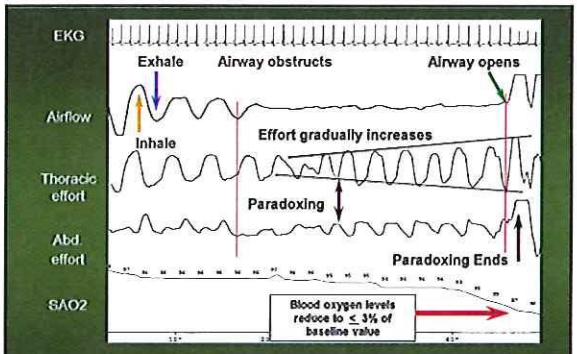
Model 3: as model 2 and alcohol, depression, diabetes, hypertension, high risk for sleep apnea and medications.

Obstructive Sleep Apnea



Associated with Increased:

- *Mortality*
- *Ischemic Stroke*
- *Hypertension*
- *Type 2 diabetes*
- *Cardiac Arrhythmias*
- *Obesity*



AHI 5-15 mild; 15-30 moderate; >30/hr severe OSA

Sleep Apnea in the Hispanic Community Health Study

- Aim/Purpose: To evaluate the association between apnea-hyponea index (OSA) and neurocognitive function in Hispanics.
- HCHS/SOL: Multicenter, prospective, population-based study of Hispanics/Latinos in Bronx, Chicago, Miami, San Diego from 2008-2011. N=16,415
- Obstructive sleep apnea (OSA) was evaluated with the ARES Unicorder system
- Apnea-hyponea index (AHI): apneas (pauses in breathing) and hypopneas (partial obstructions in breathing)
- Neurocognitive function was evaluated in participants ≥ 45 years

Demographic, apnea-hyponea index and cognition in Hispanics ≥ 45 years (N= 9,396)

Mean (SD) or n%	
Age, years	56 (10)
Female	5815 (54.3)
Male	3569 (45.7)
Education , years	10.8 (5.8)
Daytime sleepiness	1892 (20)
Apnea-Hypopnea Index	6.2 (14.4)
Cognitive Outcomes	
Spanish English Verbal Learning Test	8.1 (3.5)
Word Fluency Test	18.2 (8.9)
Digit Symbol Substitution	33.7 (16.7)

Univariate association between daytime sleepiness, apnea-hypopnea index and neurocognitive function

	SEVLT			Digit symbol substitution			Word Fluency		
	β	se	P	β	se	P	β	se	P
Sleepiness	-0.12	0.10	0.235	0.14	0.28	0.617	-0.15	0.46	0.738
Apnea-Hyponea index	-0.01	0.00	***	-0.05	0.020	***	-0.03	0.01	***

***P<0.01

Multivariate Analysis

Spanish English Verbal learning Test (SEVLT)- Memory, Recall	Model 1		Model 2		Model 3	
	β	se	β	se	β	se
Apnea/Hypopnea Index	-0.01**	0.00	0.00	0.00	0.00	0.00
Male			-1.11***	0.08	-1.14***	0.08
Age (Centered at 45)			-0.06***	0.01	-0.06***	0.01
Education			0.14***	0.01	0.14***	0.01
Baseline oxygen level					-0.02*	0.01
Word Fluency- Executive Function						
	β	se	β	se	β	se
Apnea/Hypopnea Index	-0.02**	0.01	-0.02**	0.01	-0.02**	0.01
Male			-0.61**	0.24	-0.65***	0.24
Age (Centered at 45)			-0.03**	0.02	-0.04**	0.02
Education			0.62***	0.03	0.62***	0.03
Baseline oxygen level					-0.04	0.03
Digit Symbol Substitution- Sustained attention						
	β	se	β	se	β	se
Apnea/Hypopnea Index	-0.05***	0.02	-0.01	0.02	-0.01	0.02
Male			-2.70***	0.35	-2.73***	0.35
Age (Centered at 45)			-0.50***	0.02	-0.50***	0.03
Education			1.46***	0.04	1.46***	0.04
Baseline oxygen level					-0.03	0.03

Conclusion

- Summary: Sleep disturbances are highly prevalent and can adversely impact cognition and the development of cognitive impairment.
- Future Directions: Longitudinal studies are with the aim to identify at risk populations. Development of prevention and intervention strategies.

Evelyn F. McKnight Brain Institute

Update on McKnight Memory Clinic Registry Projects

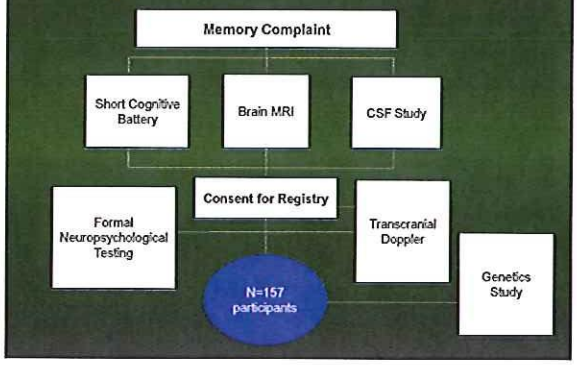
Moderator: Clinton Wright, M.D., M.S.

Leonard M. Miller School of Medicine, University of Miami
Department of Neurology
Evelyn F. McKnight Brain Institute

McKnight Cognitive Disorders Registry

- Collaboration between Neurology, Psychiatry & Behavioral Sciences, Human Genomics, Radiology, and Brain Endowment Bank
- Clinical program funded by grant from State of Florida Department of Elder Affairs
- Research program funded by McKnight Brain Institute
- Program includes state of the art neuroimaging, blood and cerebrospinal fluid collection, cognitive testing, and brain bank capabilities

McKnight Cognitive Disorders Registry



McKnight Cognitive Disorders Registry

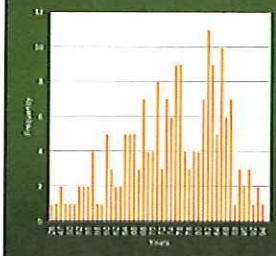
Cognitive & Behavioral Manifestations

February 20, 2013

Leonard M. Miller School of Medicine
University of Miami

McKnight Cognitive Disorders Registry

Age



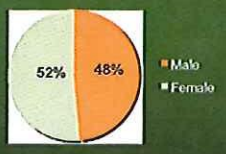
Descriptive Statistics

Statistics	
Mean	73
Stand. Deviation	11
Minimum	28
Maximum	93
Frequencies (n)	
<60 years old	16
60-69 years old	35
70-79 years old	52
80-89 years old	48
90+ years old	6

*65+ years, n = 26

McKnight Cognitive Disorders Registry

Gender



Gender by Age Group

Age Group	Male (N)	Female (N)
<60	10	6
60-69	19	17
70-79	21	31
80-89	23	25
90+	4	2
Total	77	81

McKnight Cognitive Disorders Registry

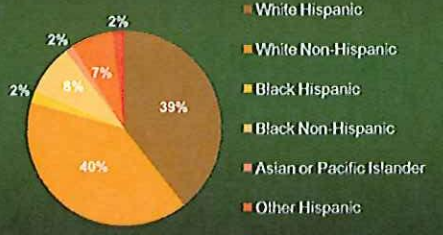
Education

Descriptive Statistics

Statistics	
Mean	14
Stand. Deviation	3
Minimum	2
Maximum	20
Frequencies (n)	
<12	20
12	31
12-15	24
16	35
>16	31

McKnight Cognitive Disorders Registry

Race and Ethnicity



McKnight Cognitive Disorders Registry

Uniform Data Set (UDS) Neuropsychological test Battery

Domain	Tests
Dementia Severity	Mini-mental State Examination (MMSE)
Attention	Digit Span Forward- Longest Sequence
	Digit Span Backwards- Longest Sequence
Processing Speed	Digit Symbol
	Trail Making Test Part A
Executive Function	Trail Making Test Part B
Memory	Logical Memory Story A- Immediate and Delayed Recall
Language	Animal Fluency (categorical)
	Vegetable Fluency (categorical)
	Boston Naming Test

McKnight Cognitive Disorders Registry

NACC Uniform Data Set (UDS) Neuropsychological Battery (n=157)

Test	Range	Mean	SD	UDS Control's Mean	UDS Control's SD
Gross Cognitive Functioning- *MMSE*	0-30	22	7	29	1
Immediate Recall- *Logical Memory I*	0-25	6	5	14	4
Attention- *Digit Span Forward*	0-8	6	2	7	1
Working Memory- *Digit Span Backwards*	0-8	4	1	5	1
Verbal Fluency- *Animals*	0-77	15	16	20	6
Processing Speed-*Trail Making Test A*	0-300"	64	39	47	13

McKnight Cognitive Disorders Registry

NACC Uniform Data Set (UDS) Neuropsychological Battery (n=157)

Test	Range	Mean	SD	UDS Control's Mean	UDS Control's SD
Executive Function- *Trail Making Test B*	0-300"	193	122	90	50
Psychomotor Speed- *WAIS-R Digit Symbol*	0-93	27	18	47	13
Delayed Recall- *Logical Memory II*	0-25	4	5	13	4
Confrontation Naming- *Boston Naming Test*	0-30	20	8	27	3
Depression- *Geriatric Depression Scale*	0-15	3	3	--	--
Activities of Daily Living – *FAQ*	0-30	11	11	--	--

McKnight Cognitive Disorders Registry

Neuropsychological Battery for Subjects with MMSE ≥ 28 (n=46)

Test	Range	Mean	SD	UDS Control's Mean	UDS Control's SD
Gross Cognitive Functioning- *MMSE*	0-30	29	1	29	1
Immediate Recall- *Logical Memory I*	0-25	10	4	14	4
Attention- *Digit Span Forward*	0-8	6	1	7	1
Working Memory- *Digit Span Backwards*	0-8	5	1	7	2
Verbal Fluency- *Animals*	0-77	19	11	20	6
Processing Speed-*Trail Making Test A*	0-300"	44	25	47	13

Memory Disorders Clinic Registry

Neuropsychological Battery for Subjects with MMSE ≥ 28 (n=46)

Test	Range	Mean	SD	UDS Control's Mean	UDS Control's SD
Executive Function- *Trail Making Test B*	0-300"	126	77	90	50
Psychomotor Speed- *WAIS-R Digit Symbol*	0-93	41	15	47	13
Delayed Recall- *Logical Memory II*	0-25	8	4	13	4
Confrontation Naming- *Boston Naming Test*	0-30	26	4	27	3
Depression- *Geriatric Depression Scale*	0-15	2	3	--	--
Activities of Daily Living – *FAQ*	0-30	3	5	--	--

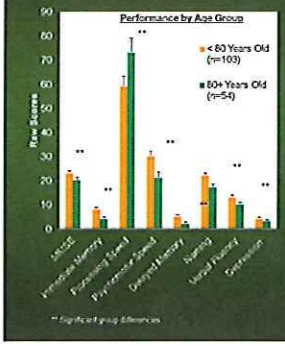
McKnight Cognitive Disorders Registry

Gender Differences by Age Group

- Female = 81
- Males = 77
- No overall significant group differences:
  - Neuropsychological performance
  - Psychiatric symptoms
  - Activities of daily living

Age Group	Significant Differences
<70	None
70-79	None
≥80 & ≤ 85	Female: Higher MMSE, Naming

McKnight Cognitive Disorders Registry



Performance by Age

- Select neuropsychological impairments for oldest old
- No differences in depression scores

McKnight Cognitive Disorders Registry

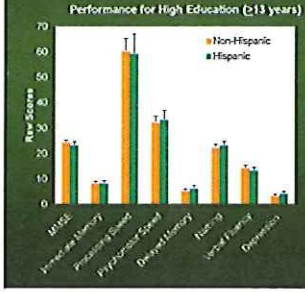
Depressive Symptoms (GDS)

Score (0-15)	Depression Level	N	Percentage
0-4	Normal	99	73%
5-10	Mild	28	21%
≥ 11	Severe	9	6%

- Majority of subjects do not report depression symptoms
- GDS score also not correlated with age, nor is it more prevalent among the oldest old (80+ years)

McKnight Cognitive Disorders Registry

High Education and Ethnicity: Neuro-cognitive Variables



No differences between highly educated Hispanics and Non-Hispanics on:

- Neuro-cognitive test scores
- Behavioral symptoms

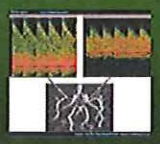
McKnight Cognitive Disorders Registry

Neuropsychiatric Inventory (NPI)

- Symptoms more prevalent among oldest old (80+): irritability, anxiety, and aggression
- No differences between Hispanic and Non-Hispanic subjects except for motor disturbances (H>NH)
- No gender differences except nighttime behaviors (F>M)
- No differences between well-educated (>13 years) and less well educated subjects
- Greater functional impairment is associated with widespread psychiatric symptoms except for depression

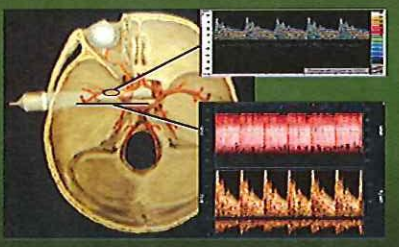
Blood Flow in the Aging Brain: Transcranial Doppler (TCD) Study in the McKnight Cognitive Disorders Registry

TATJANA RUNDEK, MD PhD
DIGNA CABRAL , RDMS



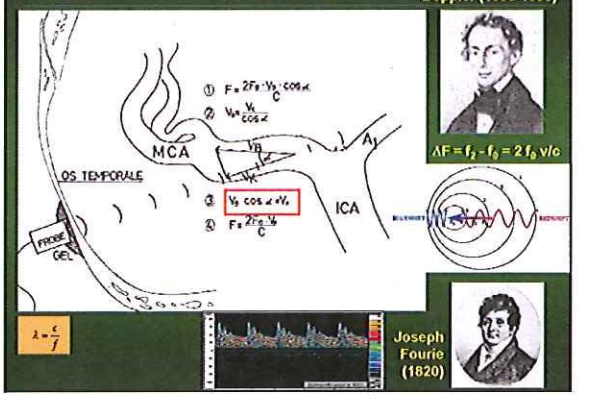
Transcranial Doppler (TCD)

What is TCD ?



Transcranial Doppler (TCD)

Christian Andreas Doppler (1803-1853)



Transcranial Doppler (TCD)

Thomas Willis, 1675

Acustic "Windows"

Runo Aaslid, 1982
Berne, Switzerland

Transcranial Doppler (TCD)

Motivation

- Reduced cerebrovascular perfusion has been associated with cognitive decline, MCI and dementia.
- It is unclear whether cognitive changes with aging have chronic vascular-ischemic etiology (functional- increased arterial stiffness and/or structural - small vessel disease)
- Few data regarding the relation of cerebrovascular perfusion to cognitive performance in non-demented elderly population exist (in part due to feasibility and cost of imaging, e.g., PET, MRI in large samples)
- **TCD has emerged as a viable option**

Transcranial Doppler (TCD)

Preliminary Data

Derby CA, Elizza A, Katz MJ, Zimmerman ME, Lipton RB, Rundek T. (2013) TCD and Cognition: The Einstein Aging Study (NIA 2P01 AG003949)

- Prior to the onset of dementia, **TCD-BFV are more highly correlated with executive function and language** than with tests of memory.
- This suggests that TCD may be useful for distinguishing persons at risk for MCI early in the course of cognitive decline.
- Longitudinal data are needed to confirm this hypothesis.

	Spearman's Correlation Coefficient (p-value) N=97 EAS participants				
MCV	FCSRT-FR	LM	CF	DSST	TMTB Speed
PCA	0.14 (0.17)	0.12 (0.25)	0.41 (<0.001)	0.23 (0.03)	0.23 (0.03)
ACA	0.14 (0.19)	-0.03 (0.80)	0.35 (0.001)	0.30 (0.004)	0.25 (0.14)
MCA	-0.02 (0.82)	-0.10 0.36)	0.14 (0.17)	0.06 (0.59)	0.09 (0.41)

FCSRT-FR= Free recall from Free and Cued Selective Reminding Test; LM= Logical memory I subtest of WMS-R; CF= category fluency (semantic memory); DSST= WAIS-III digit symbol substitution test (executive function); TMTB Speed= Trail making Test B (executive function)

Transcranial Doppler (TCD)

Aim:

- To examine the cross-sectional associations of TCD measures (BFV, PI, VMR) with cognitive performance among unselected individuals examined in the McKnight Cognitive Disorders Registry

UM IRB approved the study; all participants signed inform consent

TCD done in the McKnight Cognitive Disorders Registry: Since October 2011

As of Feb 2013

- N= 83 participants
- Mean Age (SD): 73 (11) y; range 37-92y
- 54% Women

Mean SPB/DBP= 131(21)/74(10)mmHg

TCD: Performed by a trained sonologist using a standardized/ validated TCD protocol during the clinic visits (neuropsychological testing/neuro exams)

16 (19%) incomplete windows

"0" with no windows

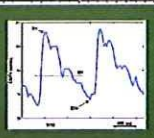
Transcranial Doppler (TCD)

Indices for Doppler Flow waveform analysis

PSV, EDV, MFV

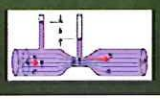
MCA/ICA ratio (Lindergaard)

PI: PSV – EDV (Gosling)
Mean V

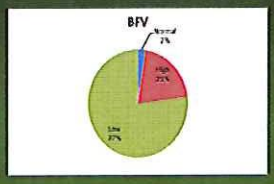


RI: $\frac{PSV - EDV}{PSV}$ (Pourcelot)

Q = V x A



Transcranial Doppler (TCD)



BFV Categorical

Normal Range	2%
Decreased	77%
Increased	21%

Arteries	Depth (mm)	*PSV	*Mean V
MCA	35 - 60	50 - 110	30 - 75
ACA	60 - 75	50 - 100	20 - 75
PCA	60 - 70	50 - 80	15 - 55
VA	50 - 80	50 - 70	13 - 66
BA	80 - 100	50 - 80	13 - 66
ICA / S	60 - 66	50 - 80	20 - 70

Stenosis (>120)	6 (7%)
MCA	4 (5%)
MCA+ACA+BA	1 (1%)
MCA+...	1 (1%)

*Tegeler CH, Rundek T, Katsnelson M. J Neuroimaging. 2012; 1552-9.

Transcranial Doppler (TCD)

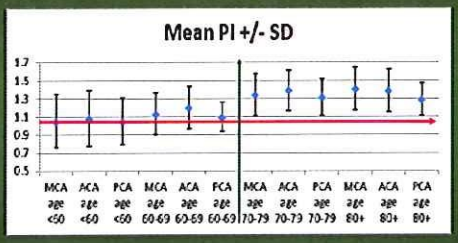
	PI (SD)
MCA	1.27 (0.28)
ACA	1.29 (0.27)
PCA	1.21 (0.23)
VA	1.28 (0.22)
BA	1.30 (0.26)
ICA / S	1.35 (0.27)

*0.6-1.0

*Tegeler CH, Rundek T, Katsnelson M. J Neuroimaging. 2012; 1552-9.

Transcranial Doppler (TCD)

Mean PI by AGE



Transcranial Doppler (TCD)

Predictors of BFV

MCA	Beta	SE	p
AGE	-0.4495	0.1253	0.001
Male SEX	0.7364	2.7276	0.79
SBP	0.0868	0.0831	0.30
DBP	-0.1898	0.1714	0.27
HR	-0.0198	0.1264	0.88

AGE

Predictors of PI

MCA-PI	Beta	SE	p
AGE	0.0093	0.0023	0.0001
MALE	0.0337	0.0498	0.50
SBP	0.0054	0.0015	0.001
DBP	-0.0167	0.0031	<0.0001
HR	0.0037	0.0023	0.11

AGE
BP

Transcranial Doppler (TCD)

Cerebral MFV (PI in PCA) associated with MMSE

	MMSE Cont (range 4-30) Mean 22; Median 24			MMSE ≤24 vs. >25
	Beta*	SE	p	OR (p*)
MFV MCA	0.26	0.12	0.04	0.96 (0.22)
MFV PCA	0.40	0.21	0.07	0.94 (0.30)
MFV VA	0.45	0.18	0.02	0.93 (0.22)
PI MCA	-7.51	5.62	0.19	3.09 (0.48)
PI PCA	-12.46	7.77	0.12	67.98 (0.07)
RI MCA	-26.41	17.73	0.15	63.3 (0.41)
RI PCA	-23.38	19.78	0.25	5.06 (0.78)

* Controlling for age, sex, SBP, DBP, HR, education level

Transcranial Doppler (TCD)

Conclusion

TCD provides an estimate of brain hemodynamic status in aging by:

- Evaluation of BFV (hypoperfusion, stenosis)
- Evaluation of cerebral arterial stiffness (PI)
- Evaluation of functional collateral circulation
- Correlation with cognitive status

TCD may provide early identification of individuals with pre-clinical cognitive decline.

Transcranial Doppler (TCD)

Future plans:

Include VMR testing of cerebral VM capacity
Correlate TCD parameters with:

- other measures of cognitive performance
- MRI markers (WMH, ASL)
- clinical outcomes (dementia, depression)

Investigate predictors of TCD hypoperfusion and stiffness in aging

To perform a well designed/powered case-control (or cohort) longitudinal study in order to assess:

- Cerebral perfusion (TCD and extracranial US) and the rate of change in normal aging
- Association of cerebral perfusion with cognitive change/ and clinical outcomes
- Identify early predictor (environmental, biologic/ genetic) of cerebral perfusion changes with aging

Transcranial Doppler (TCD)

Thank you !

Blood Flow, Perfusion, and Autoregulation by MRI:
MRI VS. Transcranial Doppler

Noam Alperin, PhD
Ahmet M. Bagci, PhD
Sang H. Lee, MS
Taljana Rundek, MD, PhD
Clinton Wright, MD, MS

Motivation

- Cerebral blood flow (CBF) and brain tissue volume both decrease with age: which one is the "egg"?
- Blood flow to the human brain has three main regulatory mechanisms:
  1. Cerebral autoregulation
  2. Flow-metabolism coupling
  3. Neurogenic regulation
- Noninvasive measurements of blood flow, perfusion and autoregulation are critical for understanding normal aging

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Content

1. MRI measures of velocity and Flow: comparison with TCD
2. MRI measurement of Perfusion
3. MRI mapping of cerebral autoregulation

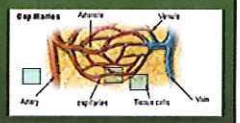
12
7

Flow Vs. Perfusion

Blood flow and perfusion are often used interchangeably

- Blood flow = volume of blood passing through vessel per unit of time (e.g., mL/min)
- Measure by MR velocity imaging

- Perfusion= Delivery of arterial blood to a capillary bed. It is measured in units of volume/time per tissue weight (e.g., mL/min/100 gram)



- Measured by diffusible tracer

MRI measurement of Cerebral Blood Flow

MR Angiography of the head and neck vessels

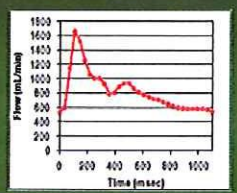
Velocity encoded MRI

12
9

MRI measurement of Cerebral Blood Flow

3D rendering of flow velocities

CBF by MR Velocity Imaging



Volumetric Flow = Velocity X Lumen area

Total CBF = LICA +RICA +LVA +RVA

Alperin N, Lee S. Magn. Reson. in Med. 49:934-944 (2003)

TCD vesus MRI

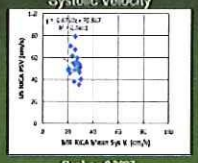
Subjects
Total of 32 subjects from the McKnight Cognitive Disorders Registry underwent both TCD and MR flow
Mean age of 73 ± 10years, ranging from 49 to 89

Vessels compared
Left/ right Internal Carotid Artery (LICA, RICA)
Left/ right vertebral Artery (LVA, RVA)

Measurements compared
1. Systolic velocity
2. Diastolic velocity
3. Mean velocity
4. PI (Pulsatility Index) = (S-D)/Mean

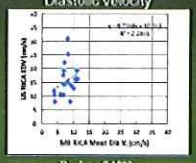
US vs. MRI measures (RICA)

Systolic Velocity



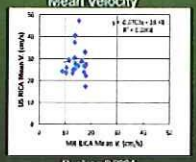
P-value = 0.3697

Diastolic Velocity



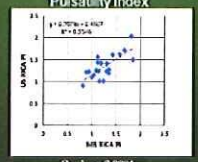
P-value = 0.1828

Mean Velocity



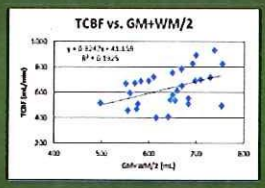
P-value = 0.0004

Pulsatility Index



P-value = 0.0001

CBF vs. Brain Tissue Volume



p-value < 0.02

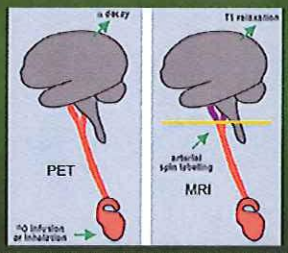
Cerebral Perfusion by MRI

Arterial Spin Labeling (ASL)

Non invasive tracer based method

Diffusible Tracer: water

Source of signal: T1 ("activated" by inversion pulse = magnetic labeling)

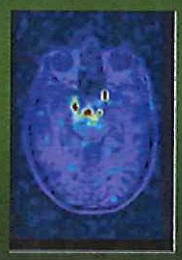


T1 decay is about 100 faster than radioactive decay rate of ^{15}O

Principle of ASL

The 3 main important components of ASL imaging are:

1) Labeling
2) Transient Time
3) Imaging



Mapping Autoregulation

1. Measure total CBF to the brain (by velocity encoding) at baseline, and in several reduced CBF states (CO_2 manipulation)
2. Performed ASL perfusion measurements in each CBF state
3. Calculate rate of decrease in perfusion for selected brain region relative to global CBF decrease

1. Aspern N, Bagci A, et al. Comparison between Total CBF Values Measured by ASL and Phase Contrast Over Increased Range of CBF Values. ISMRM Annual Meeting in Stockholm, Sweden, 2010
2. Aspern N, Bagci A, et al. Assessment of Regional Rate of Change in CBF in Response to Changes in PaCO2: A Combined ASL and Phase Contrast Study. Oral presentation ISMRM 2012

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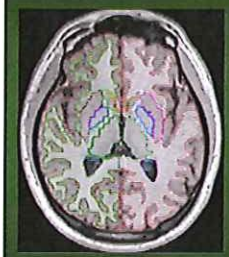
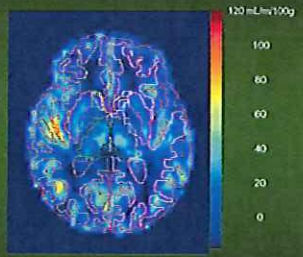
Calculating region specific perfusion



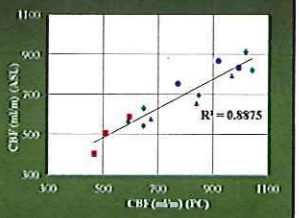
T1-weighted image overlaid with subcortical segmentation map.



The corresponding regions in the perfusion image.

Results- Whole brain

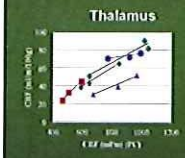
- ASL-derived whole brain CBF and the PC-CBF relationship
- 5 subjects shown in different colors
- Value for the 3 states of CO2 levels are shown

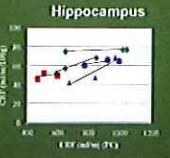


- High correlation (R=0.94) demonstrates the reliability of PCMR based ICBF measurement as a surrogate measure for the change in PaCO2.

Results –Regional CBF

- Regional CBF regulation is estimated by the slope of the mean regional ASL derived CBF vs. ICBF.
- Steeper the slope, the less is the degree of flow regulation.





Region	Mean Slope
Thalamus	0.075
Cerebral GM	0.051
Cerebral WM	0.034
Hippocampus	0.033
Putamen	0.023
Pallidum	0.008

Conclusions

- Large differences in CBF response to changes in PaCO2 were found across different brain regions.
- Larger slope (0.075) was found for thalamus compared with putamen (0.023).
  - Thalamus supplied by vertebro-basilar arterial system (posterior circulation)
  - Putamen supplied by branches of the middle cerebral arteries (anterior circulation)

Evelyn F. McKnight Brain Institute

Education Research: Health IT Solutions for Healthcare Professionals, Patients, and Caregivers

Richard S. Isaacson, MD
Education Director, Evelyn F. McKnight Brain Institute
Vice Chair of Education
Associate Professor of Clinical Neurology
February 20, 2013

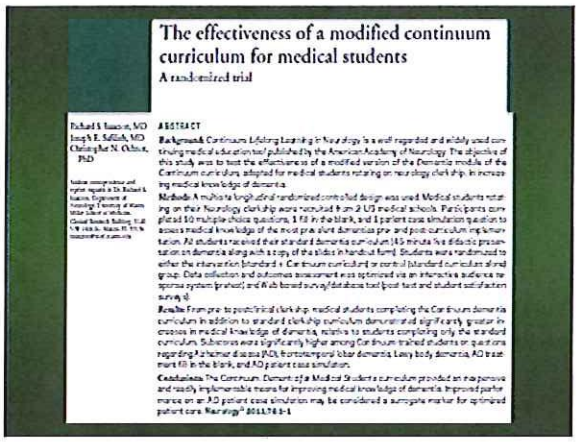
Leonard M. Miller School of Medicine
University of Miami

Education Overview

- Pilot Data: Lessons learned
  - First randomized trial in age–related memory loss informs future research
- Patient and Caregiver Education using Web-based technology
- Healthcare Provider Education using Health IT

Medical Student Education

- Evaluating the Effectiveness of Continuum: Dementia as a Teaching Tool for Medical Students: A Randomized, Multi-Center Trial
- Education research grant from the American Academy of Neurology and support of the McKnight Brain Institute



The effectiveness of a modified continuum curriculum for medical students

A randomized trial

Richard S. Isaacson, MD
Joseph E. Saffiotti, MD
Christopher N. Ochner, PhD

ABSTRACT

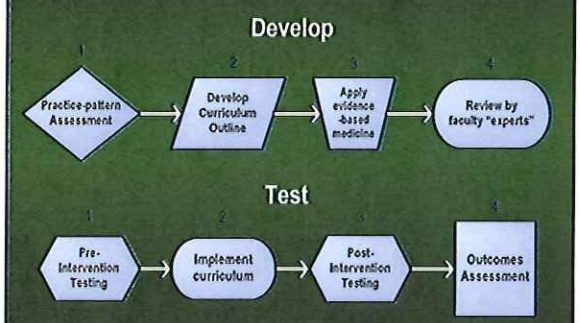
Background: Continuum Lifelong Learning in Neurology is a well regarded and widely used continuing medical education tool published by the American Academy of Neurology. The objective of this study was to test the effectiveness of a modified version of the Dementia module of the Continuum curriculum, adapted for medical students rotating on neurology clerkship, in increasing medical knowledge of dementia.

Methods: A multisite longitudinal randomized controlled trial design was used. Medical students rotating on their Neurology clerkship were recruited from 2 US medical schools. Participants completed 50 multiple choice questions, 1 fill in the blank, and 1 patient case simulation question to assess medical knowledge of the most prevalent dementias pre- and post-curriculum implementation. All students received their standard dementia curriculum (45 minute to 4 didactic presentation on dementia along with a copy of the slides in handout form). Students were randomized to either the intervention (standard + Continuum curriculum) or control (standard curriculum alone) group. Data collection and outcomes assessment was optimized via an interactive audience response system (pretest) and Web-based survey/database tool (post-test and student satisfaction survey).

Results: From pre- to post-clinical clerkship, medical students completing the Continuum dementia curriculum in addition to standard clerkship curriculum demonstrated significantly greater increases in medical knowledge of dementia, relative to students completing only the standard curriculum. Subscores were significantly higher among Continuum trained students on questions regarding behavioral disease (FDD, frontotemporal lobar dementia, Lewy body dementia, AD treatment fill in the blank, and AD patient case simulation.

Conclusions: The Continuum Element of a Medical Student's curriculum provided an inexpensive and readily implementable means for improving medical knowledge of dementia. Improved performance on an AD patient case simulation may be considered a surrogate marker for optimized patient care. *Neurology*® 2011;76:1–6

Practice-pattern-based Curriculum Development in Neurology



Results

- Students who received, vs. did not receive *Continuum* scored higher on post-testing
  - 67.97% ± 14.17 vs 42.78% ± 10.78
- Also had greater score increases
  - 25.19% ± 14.36 vs 5.74% ± 12.87
- Both *p*'s < 0.0005

Cost Analysis (Estimated)

- Question: Case of age-related memory loss with mild depression, *not* AD
- **1= Regular f/u with PCP/Neurologist (correct)**
- 2= cost of unnecessary AChI = $1920/year
- 3= cost of unnecessary NMDA-antagonist =$2760/yr
- 4= cost of unnecessary neuroimaging = $1300 [$1000 (scan) + $300 (contrast)]
- 5= cost of unnecessary APOE4 genetic test = $300

- **Conclusion:** *Continuum* is an effective teaching tool for medical students and offers potential cost-savings for patients
- **Future Directions:** Implement as a teaching curriculum for medical students rotating on their neurology clerkship
- **Outcome:** Now available for free to medical students on AAN website

Patient and Caregiver Education

- Age-Related Memory Loss and AD Web-based Educational Intervention
- Goal: Develop and test intervention
  - Web-based interactive video plus pamphlet vs. pamphlet alone (English)
- Module created on Articulate software

Patient and Caregiver Education

- Patients and caregivers have difficult time navigating the plethora of resources
- Researchers have uncovered gaps in the quality of current educational resources available for patients and their caregivers

Study Design

- Participants: Patients, caregivers, and medical students
- Randomized
  - Two Educational pamphlets from Alzheimer's Association
  - Pamphlets + Online Interactive Video
- Pre / Post Multiple Choice Question Test
- Pre-survey questions assess interest in topic, confidence in knowledge, degree of concern about memory loss, frequency of computer use
- Follow-up survey to evaluate learning tool satisfaction and changes in initial statements

Video And Survey Clips

- http://neurology.med.miami.edu/interactive/Learning_aboutMem/player.html

(INTERIM) RESULTS
(IRB AMENDMENT FOR FACEBOOK AND WEBSITE RECRUITMENT)

Quiz Scores

- Pamphlet Only Group:
  - Pre-test: 47%
  - Post-test: 56%
- Pamphlet + Video Group:
  - Pre-test: 49%
  - Post-test: 72%

Subjective Statements

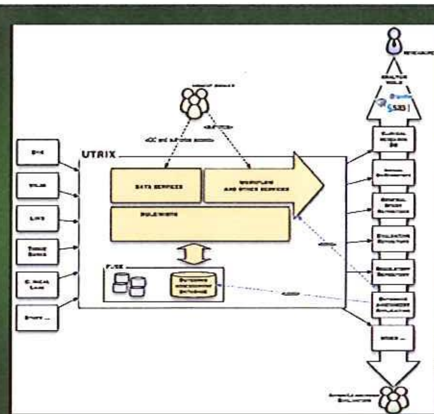
- Level of satisfaction with material presented significantly higher in video group (3.4 vs. 4.3, $p<.05$)
- "I understand the difference between Age-Related Memory Loss and Alzheimer's Disease."
- "I know how to find good educational resources for learning about memory loss."

Global Initiatives

- Can we enhance Health Information Technology infrastructure via the Electronic Health Record to improve education?
- Collaborative project with UM Center of Computational Science, Upenn, Cornell, Harvard, Urochester, Umiami (Neurology/IM)

Project Overview:

- Developing software that automates evidence-based teaching curricula for neurology residents using EMR data
- A variety of neurologic conditions will be studied, including age-related memory loss and other cognitive disorders
- Will lead to a proportionate increase in related items in the curriculum



Automated Education?

Unrated Articles	Rate It	Help you change your practice?
Antiplatelet agents in stroke prevention: acute and long-term treatment strategies.	☆☆☆☆☆	Yes ◻ No ◻
Vigabatrin: a comprehensive review of drug properties including clinical updates following recent FDA approval.	☆☆☆☆☆	Yes ◻ No ◻
Functional role of cannabinoid receptors in urinary bladder.	☆☆☆☆☆	Yes ◻ No ◻

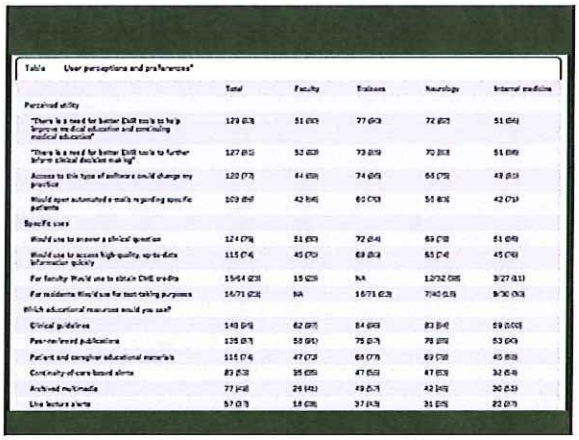


Table User perceptions and preferences*

	Total	Faculty	Trainees	Neurology	Internal medicine
Perceived utility					
"There is a need for better EMR tools to help improve medical education and continuing medical education"	129 (83)	51 (80)	77 (85)	72 (87)	51 (84)
"There is a need for better EMR tools to further inform clinical decision making"	127 (81)	52 (82)	73 (81)	70 (84)	51 (84)
Access to this type of software could change my practice	120 (77)	44 (69)	74 (82)	66 (79)	43 (71)
Would open automated e-mails regarding specific patients	103 (66)	42 (66)	60 (67)	55 (66)	42 (70)
Specific uses					
Would use to answer a clinical question	124 (79)	51 (80)	72 (80)	69 (83)	51 (84)
Would use to access high-quality, up-to-date information quickly	115 (74)	45 (70)	69 (77)	65 (78)	45 (74)
For faculty: Would use to obtain CME credits	15/64 (23)	15 (23)	NA	12/52 (23)	3/27 (11)
For residents: Would use for test-taking purposes	16/71 (23)	NA	16/71 (23)	7/40 (18)	9/30 (30)
Which educational resources would you use?					
Clinical guidelines	140 (91)	62 (97)	84 (93)	83 (94)	59 (100)
Peer-reviewed publications	135 (87)	58 (91)	75 (83)	78 (89)	53 (90)
Patient and caregiver educational materials	115 (74)	47 (73)	68 (76)	69 (78)	45 (76)
Continuity of care based alerts	83 (53)	35 (55)	47 (52)	47 (53)	32 (54)
Archived multimedia	77 (49)	26 (41)	49 (54)	42 (48)	30 (51)
Live lecture alerts	57 (37)	18 (28)	37 (41)	31 (35)	22 (37)

Education Team

- Marytery Fajardo, Thomas Hugues, Kevin Fu
  - Patient and Caregiver Education
- Alon Seifan MD, MA (Neuro Resident, RCRT)
  - Global Initiatives using the EMR
- Sergio Lanata MD (Brown)
  - Neurology/Internal Medicine Resident Education
- Joseph Safdieh MD (Cornell)
- Chris Ochner PhD (Columbia)
  - Medical Student Education
- Neurology Residents (Miami)

Thank you!

A very, very special thank you to the Trustees of the McKnight Brain Research Foundation for your support

"Education is the most powerful weapon that you can use to change the world."

- Nelson Mandela

McKnight Inter-institutional MRI Standardization Initiative

UM	UF	UA	UAB
N. Alperin, Ph.D.	R. Cohen, Ph.D.	G. Alexander Ph.D.	D. Knight, Ph.D.
F. Nahab, M.D.		L. Ryan, Ph.D.	K. Visscher, Ph.D.
P. Pattany, Ph.D.		T. Trouard, Ph.D.	
C. Wright, M.D.			

February 20, 2013

Leonard M. Miller School of Medicine
University of Miami

MRI Standardization

- Despite decades of Dementia Research, little is known about:
  - Features of the aging brain
  - Association between brain structure and function
  - The value of neuroimaging in pre-symptomatic people

MRI Standardization

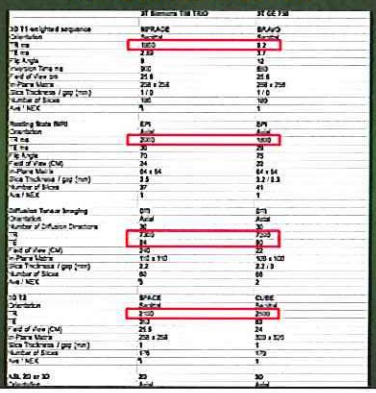
- McKnight Inter-Institutional Neuroimaging Collaboration Goal: To develop standardized neuroimaging methods across institutions for the study of Healthy Aging
- Develop a rich data repository for hypothesis-driven research within and across Institutes
- Test and refine the limits of inter-institutional collaborations

MRI Standardization

STATUS UPDATE

- **August 1-3, 2012**: Inter-institutional meeting of neuroimaging experts to discuss goals, framework, and deliverables.
- **Mid-December**: Preliminary drafts of manuscripts reviewing the topic of 'MRI of the Aging Brain' initiated
- **January 2013**: Inter-Institutional standardization of MRI initiated
- **March 2013**: Planned data collection across 4 Institutes, including an MRI Phantom and human subject to test data quality and variability
- **April 2013:** meeting of MRI Group in Houston to Discuss future plans

MRI Standardization



MRI Standardization – Future Directions

- **Complete Inter-institutional Neuroimaging Inventory**
- **Carry out Inter-institutional pilot data collection**
  - **Compare MRI findings across modalities**
  - **Analyze data to measure data variability**
  - **Finalize sequences and parameters across Institutes for future data collection**
- **Complete Literature Review and Consensus guidelines for cross-site MRI data collection in Healthy Aging cohort**
- **Develop and Implement infrastructure to allow for reliable, accessible data storage**
- **Hypothesis-driven research…**

Cognitive Test Battery Working Group

Update: Bonnie Levin, PhD

Future Directions

Animal Behavior Core

- Study ischemia in 18 month old rats to examine interaction with aging, and effects on physiology and behavior
- Targets for translation to prevent age related memory loss

NOMAS

- Continue genetics studies
- Begin in depth processing of brain scans for regional brain volume and white matter lesion volume
- Examine sleep in relation to brain morphology
- Analysis of vitamin D and phosphorus pathway

McKnight Cognitive Disorders Registry

- Continue MR/ultrasound correlations and study of large vessel disease in normal aging, MCI, and dementia
- Study of inflammation, brain morphology, and cognitive performance
- Examine earliest and most sensitive cognitive tests to distinguish normal aging from pathology in this diverse cohort

Noam Alperin, PhD
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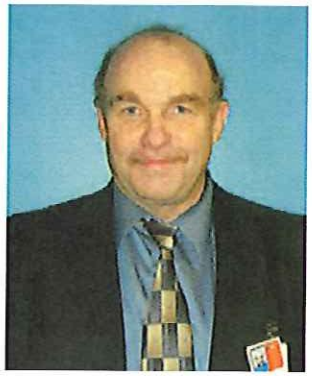

Noam Alperin came to the University of Miami in May 2009 from the University of Illinois at Chicago. He obtained his Graduate Degree from the University of Chicago's Medical Physics program. Dr. Alperin's work is supported by the National Institute of Health. Dr. Alperin's research focuses on the interplay between blood and CSF flow dynamics using flow sensitive MRI techniques. A primary aim of the research is to provide noninvasively, important physiologic parameters among which are cerebral blood perfusion and intracranial pressure. These parameters play an important role in a wide range of neurological problems, including hydrocephalous and stroke. Since joining the University of Miami, Dr. Alperin's Advance Image Processing laboratory is working closely with the Evelyn F. McKnight Center for Age Related Memory Loss, using different MRI modalities to characterize and quantify morphologic and physiologic changes in the brain associated with aging as well as the coupling between age related brain tissue volume loss and cerebral blood flow decrease.

Susan Halloran Blanton, Ph.D.
Executive Director, Hussman Institute for Human Genomics
Associate Professor of Human Genetics and Neurology
Dr. John T. Macdonald Department of Human Genetics
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Dr. Blanton received her PhD in Human Genetics from Virginia Commonwealth University/Medical College of Virginia. She obtained post-doctoral training in Biostatistics (University of Pittsburgh) and Population Oncology (Fox Chase Cancer Center). Her primary research has focused on the mapping of genes for Mendelian and complex diseases; she has been instrumental in studies identifying over twenty genes/loci for Mendelian disorders. Stroke and the underlying genetics of its risk factors, deafness, retinal diseases, skeletal dysplasias, cleft lip/palate, and clubfoot are among the diseases which she currently studies. She collaborates with Drs. Sacco, Wright and Rundek to identify genetic factors influencing white matter and cognition and their relation to ageing. She has also been involved in developing and implementing genetic education materials for Federal and appellate level judges and science writers in an ELSI sponsored project. Her current research also involves developing methods for integrating genetics into the private practice setting. Dr. Blanton is the Executive Director of the Hussman Institute for Human Genomics as well as the Associate Director of Communications and Compliance. She is an Associate Professor in the Dr. John T. Macdonald Foundation Department of Human Genetics.

Richard S. Isaacson, MD
Associate Professor of Clinical Neurology
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A graduate of the accelerated 6-year B.A. / M.D. program at the University of Missouri at Kansas City School of Medicine, Dr. Isaacson currently serves as the Vice Chair for Education and Director of the Neurology Residency Program in the Department of Neurology at the University of Miami, Miller School of Medicine. He completed his residency in Neurology at Beth Israel Deaconess Medical Center/Harvard Medical School, and his medical internship at Mount Sinai Medical Center in Miami Beach, FL. Prior to joining the University of Miami, he served as Director of the Research Unit in Medical Education and Associate Medical Director of the Wien Center for Alzheimer's disease and Memory Disorders at Mount Sinai.

Dr. Isaacson chaired the American Academy of Neurology (AAN) Undergraduate Education Subcommittee working group in dementia, which is responsible for making recommendations of what is taught to medical students around the country. He is the recipient of the AAN Education Research Grant for his project "Evaluating the effectiveness of *Continuum*: Dementia as a teaching tool for medical students" which was selected for the "Scientific Highlights" session of the 2009 AAN Annual Meeting (Top 30 Abstracts of Program). He was funded by National Institutes of Health Clinical Research LRP and the McKnight Brain Institute for his education research on Neurology using the EMR and Health IT, and he was senior author on "Education Research: Can my Electronic Health Record Teach Me Something? A multicenter pilot study" which will be published in *Neurology* on March 5, 2013. He is the author of numerous abstracts and publications, his research in neurology and medical education has been presented at scientific meetings nationally and internationally, and he was recently awarded the AAN A.B. Baker Teacher Recognition Award, a national award, for his contributions to improving neurologic education.

Bonnie E. Levin, PhD.
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Dr. Bonnie Levin is the Alexandria and Bernard Schoninger Professor of Neurology and Director of the Division of Neuropsychology in the Department of Neurology at the University of Miami, Miller School of Medicine. She received her BS from Georgetown University and her Ph.D. from Temple University. She completed an internship at the Boston Children's Hospital where she was a clinical fellow in Psychiatry at Harvard Medical School and an externship at the Boston VA Hospital.

Dr. Levin is a neuropsychologist whose research examines neurocognitive and affective changes associated with neurodegenerative disease and the normative aging process. Her work examines the role of cardiometabolic risk factors in cognitive decline. Another focus has been the inter-relationship between behavioral and motor symptoms in Parkinson's disease and the neural circuitry underlying memory and age related cognitive change. Her current work is aimed to advance our understanding of frontal striatal circuit function in cognition and to generate data that will improve our knowledge of key clinical parameters associated with differential rates of cognitive decline. Current projects include: examining which components of the metabolic syndrome predict cognition, identifying imaging and clinical correlates of white matter changes associated with the aging process and linking structural and metabolic markers underlying different symptom profiles in neurodegenerative disease.

Fatta B. Nahab, M.D.
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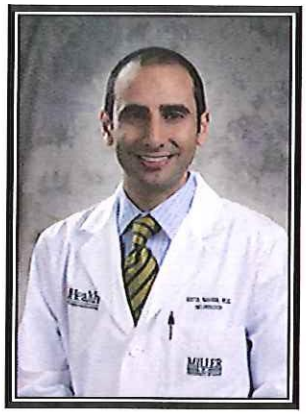

Dr. Nahab is a board-certified neurologist with fellowship training the neurological movement disorders and functional neuroimaging. He is the director of the Laboratory for Functional Imaging of Neurodegenerative Disorders. The FIND lab is focused on the use of neuroimaging to understand the mechanisms of neurodegeneration and normal aging. Current projects included the study of Essential Tremor, Parkinson disease, and gait dysfunction and the role of cognitive impairment in aged individuals.

Jacob T. Neumann, Ph.D.
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Department of Neurology

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Dr. Neumann received his Ph.D. in Pharmacology from Southern Illinois University School of Medicine and is currently being trained by Dr. Miguel Perez-Pinzon at the University of Miami Miller School Of Medicine. His research is focused on the electrophysiological synaptic changes that occur in the hippocampus after cerebral ischemia or cardiac arrest. He is interested in potential therapies to prevent the neurological decline from these insults. Dr. Neumann is collaborating with the McKnight Brain Research Foundation researching the relationship between age-related memory loss and cardiac arrest.

Alberto Ramos, M.D., MSPH
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Dr. Alberto Ramos is Assistant Professor of Clinical Neurology and Co-Director of the Sleep Disorders program at the University of Miami, Miller School of Medicine.
Dr. Ramos' research focus is on sleep and cerebrovascular disease. Dr. Ramos was the recipient of a Research Supplement in Health Related Research - an NIH/NINDS funded supplement grant to the ongoing Northern Manhattan Study, to study the relationship between sleep and risk factors for stroke.
Dr. Ramos is the site Principal Investigator for the Sleep Patterns as a Risk Factor for Disease in the Hispanic Community Health Study – Field Center at the University of Miami. An NHLBI funded, ancillary study to the Hispanic Community Health Study to evaluate sleep patterns and cardiovascular risk in Hispanics. He is a member of the American Academy of Sleep Medicine and the Sleep Research Society.

Tatjana Rundek, MD, Ph.D.
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Dr. Tatjana Rundek is a Professor of Neurology, Epidemiology and Public Health with tenure, Vice Chair of Clinical Research, and a Director of Clinical Translational Research Division in the Department of Neurology of the University of Miami, Miller School of Medicine. She also holds a secondary faculty appointment at the Department of Neurology at Columbia University in New York. Dr. Rundek is a stroke neurologist, clinical researcher and principal investigator of several large longitudinal NIH/NINDS funded R01 grants on genetic determinants of carotid atherosclerosis and stroke epidemiology. Dr. Rundek is also a recipient of a NINDS K24 mid career development award. She participates in large stroke genetic consortiums such as the NINDS SiGN (Stroke Genetic Network), ISGC (International Stroke Genetic Consortium) and CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology). Dr. Rundek was the Fulbright Scholar and the recipient of the research awards from the Hazel K. Goddess, the Dr. Gilbert Baum Fund and the American Institute in Ultrasound in Medicine (AIUM) for best clinical application of medical ultrasound. Dr. Rundek serves on the editorial boards of several scientific journals including Stroke, Neurology, Journal of Ultrasound in Medicine and Cerebrovascular Diseases. She has published over 200 scientific publications, editorials, reviews, and book chapters. She is a member of the American Heart Association, American Academy of Neurology, and AIUM. She is currently President of the Neurosonology Communitiesof Practice of the AIUM, the largest professional medical ultrasound organization in the US. in 2012 Dr. Rundek was elected to the Intersocietal Accreditation Commission (IAC) Vascular Testing Board of Directors, a national organization which accredits clinical echocardiography, nuclear/PET, MRI, CT and Dental laboratories and carotid stenting programs.

Ralph L. Sacco, MD, MS, FAHA, FAAN
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Chairman, Department of Neurology
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Ralph L. Sacco, MD, MS, is the Chairman of Neurology, Olemberg Family Chair in Neurological Disorders, Miller Professor of Neurology, Public Health and Epidemiology, Human Genetics, and Neurosurgery, and Executive Director of the Evelyn McKnight Brain Institute at the Miller School of Medicine, University of Miami. He is Chief of the Neurology Service at Jackson Memorial Hospital. He was the former Professor of Neurology and Director of the Stroke and Critical Care Division at the Neurological Institute of Columbia University College of Physicians and Surgeons, the Mailman School of Public Health, and the Sergievsky Center.

Dr. Sacco graduated from Cornell University with distinction, received his medical degree cum laude from Boston University School of Medicine in Massachusetts, and a master's degree in epidemiology from Columbia University, School of Public Health. Dr. Sacco completed a residency in neurology at Presbyterian Hospital of the City of New York. He completed his postdoctoral training in stroke and Epidemiology at Columbia under a NINDS-funded neuroepidemiology training grant.

Dr. Sacco's clinical research activities began in 1980 when he participated in the Framingham Heart Study. Since 1990, he has been the Principal Investigator of the Northern Manhattan Study an NIH-funded community-based, epidemiologic study designed to determine stroke incidence, risk factors, and prognosis in an elderly, multi-ethnic, urban population living in northern Manhattan in New York City. This study now includes a separate NINDS-funded project, the Northern Manhattan Family Study, to evaluate potential genetic determinants of stroke risk factors. He is the PI of the NINDS U54 Stroke Prevention and Intervention Research Program to support the Florida Puerto Rico Stroke Registry and reduce stroke disparities.

Dr. Sacco was also the founding principal investigator of the NY Columbia Collaborative Specialized Program in Translational Research in Acute Stroke. He is also co-investigator of six other NINDS grants. He has been involved in the design and conduct of multiple randomized trials including the co-principal investigator of the Warfarin Aspirin Recurrent Stroke Study, the principal investigator of the Glycine Antagonist in Neuroprotection Trial, and the co-chair of the international PRoFESS Study (Prevention Regimen for Effectively avoiding Second Strokes). He serves on the Data Safety and Monitoring Boards of a number of NIH and pharmaceutical-sponsored clinical trials. In addition, Dr. Sacco is the Senior Consulting Editor for *Stroke,* and on the editorial boards of *Cerebrovascular Diseases, Neuroepidemiology*, and *Nature Clinical Practice Neurology.* He has published extensively in the areas of stroke prevention, treatment, risk factors and stroke recurrence, with more than 700 original articles,

case reports, book chapters, abstracts and communications to his credit. He has been a principal author on numerous evidence-based guidelines from the AHA and ACCP.

Dr. Sacco has helped train numerous fellows in stroke and epidemiology and was co-director of a T32 entitled Neuroepidemiology Training Program to train neurologists in epidemiology. He has been awarded the 2006 Feinberg Award for Excellence in Clinical Stroke and the 2007 Chairman's Award from the American Heart Association. In 2008, he received the NINDS Javits Award in Neuroscience and was inducted into the American Association of Physicians. He has given numerous lectures including the David Sherman Lecture, the HJM Barnett Lecture, Chaim Mayman Memorial Lecture, the Daniel C. Gainey Lecture, and the AAN Wartenberg Lecture.

Dr. Sacco is a fellow of the Stroke and Epidemiology Councils of the American Heart Association, a Fellow of the American Academy of Neurology, a member of the American Neurological Association, past chair of the Clinical Research Committee of the American Academy of Neurology, and on the Medical Advisory Board of the Hazel K. Goddess Fund for Stroke Research in Women. He is a past member of the Epidemiology and Disease Control-3 NIH Study Section, NINDS Neuroscience Training Review Committee, CMS Medicare Evidence Development and Coverage Advisory Committee, and FDA Advisory Panel for Central and Peripheral Nervous System Drugs. He is a former member of the Board of Directors for the American Heart Association, the Board for the American Academy of Neurology, and current Board member of the World Stroke Organization. Dr. Sacco was the first neurologist to serve as President of the American Heart Association/American Stroke Association in 2010-2011 and is Vice-President elect for the American Academy of Neurology 2013-15.

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Dr. Wright is Associate Professor of Neurology, Epidemiology & Public Health, and Neuroscience and Scientific Director for the McKnight Brain Institute. He is Chief of the Division of Cognitive Disorders in the Department of Neurology and Co-Director of the University of Miami Memory Disorders Center. Dr. Wright's research focus is on the effects of vascular risk factors on brain structure and function, with an emphasis on subclinical damage such as covert infarcts, white matter lesions, and brain atrophy. His research also focuses on vascular cognitive impairment with an emphasis on early cognitive changes and the interaction between aging, vascular damage, and Alzheimer disease.