Alzheimer's Disease: A Network Perspective

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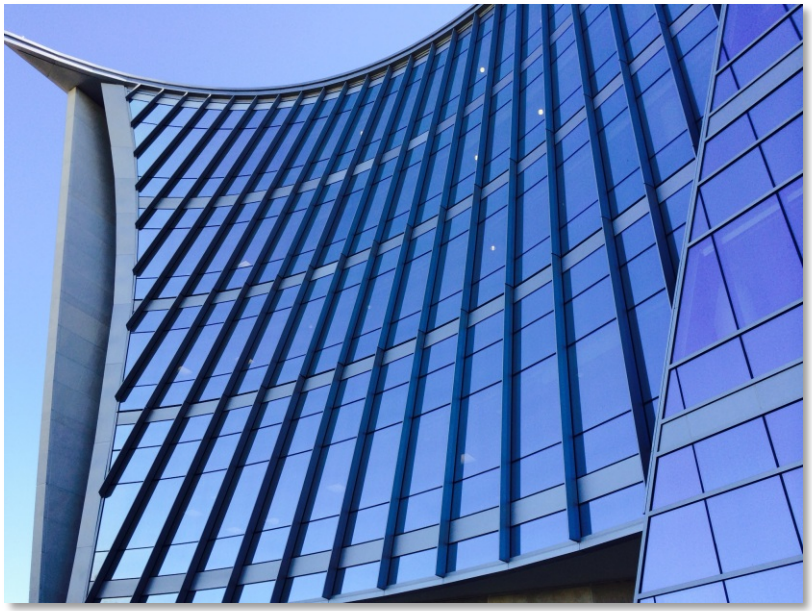
Indiana Alzheimer Disease Center
IU Center for Neuroimaging
Department of Radiology and Imaging Sciences



INDIANA UNIVERSITY SCHOOL OF MEDICINE

IU HEALTH Neuroscience Center

Network Science Seminar

Monday, October 20, 2014

Indiana University Bloomington

asaykin@iupui.edu

Disclosures & Acknowledgements

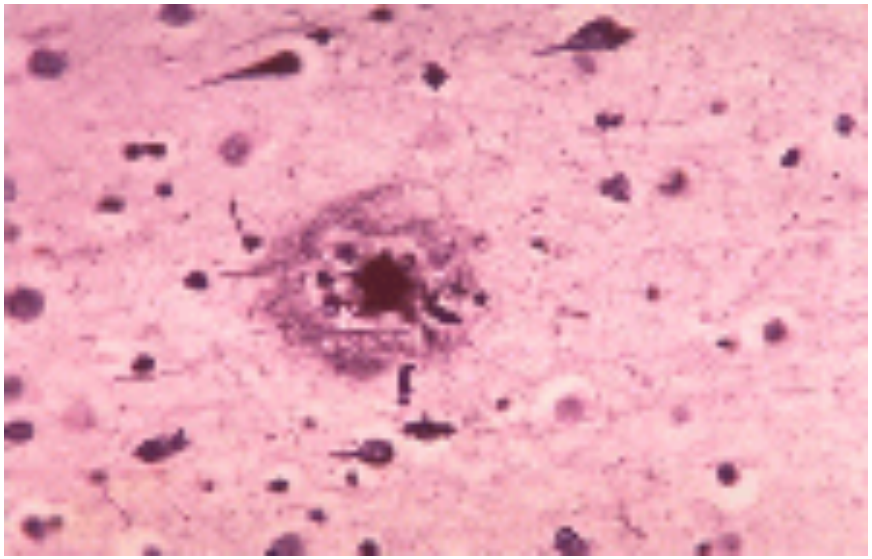
- **National Institute on Aging**
  - ADNI: U01 AG024904 & RC2 AG036535
  - Indiana: R01 AG19771, P30 AG10133 (IADC)
  - U01 AG032984, U24 AG21886, P30 AG010129, K01 AG030514
- Institute of Biomedical Imaging and Bioengineering
- National Library of Medicine: R01 LM011360 and K99/R00 LM011384
- National Science Foundation: IIS-1117335
- Foundation for the NIH (ADNI-1 GWAS)
  - Anonymous Foundation (Challenge Grant)
  - Gene Network Sciences, Merck, Pfizer (DNA extraction)
- Alzheimer's Association & Brin Wojcicki Foundation
  - Whole Genome Sequencing of ADNI-GO/2
- Disclosures:
  - Siemens Healthcare, Eli Lilly, Avid, Pfizer, Arkley BioTek

Alzheimer's Disease: Network Perspectives

- Alzheimer's Disease
  - A complex disorder: Snapshot of the science
  - Prodromal stages: Subjective Cognitive Decline & Mild Cognitive Impairment
- Brain Networks – The Connectome
- Biomarker Networks (phenotype clusters)
- Gene Pathways, Networks & Systems Biology
- Social Networks
  - Families, Communities, Healthcare systems, Provider networks, Social media, Science of Science, ELSI issues

ALOIS ALZHEIMER (1864-1915)

- German scientist, initially a professor of Psychology in Breslau. Later in Munich he worked on histopathology. With Franz Nissl, worked to establish the neuropathological basis of mental illness. Alzheimer published on cerebral arteriosclerosis in 1904 and Huntington's chorea in 1911. **In 1907 he published the pathology of AD**.



← Senile plaque (silver stain)

Louis D. Boshes, M.D. Archives (UIC)

The Memory, Aging & Alzheimer's Puzzle

Disease mechanism, Earlier detection, Personalized therapeutics

Subjective Cognitive Decline

Informant Perception

Cognitive Performance

Lifestyle & environment

- Cognitive stimulation, diet, exercise, sleep, social networks

Biomarkers

- CSF, blood, others

Genomics

- DNA

- RNA

- Epigenetics

Therapeutics & Prevention

Amyloid PET/CSF

Tau PET/CSF

MRI - structure

MRI - function

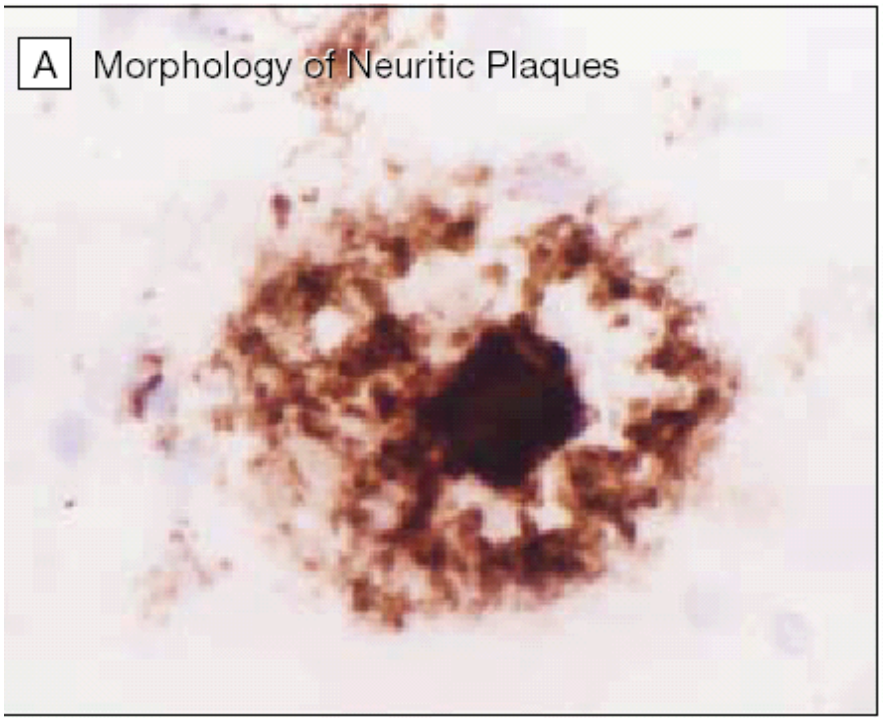
Connectome

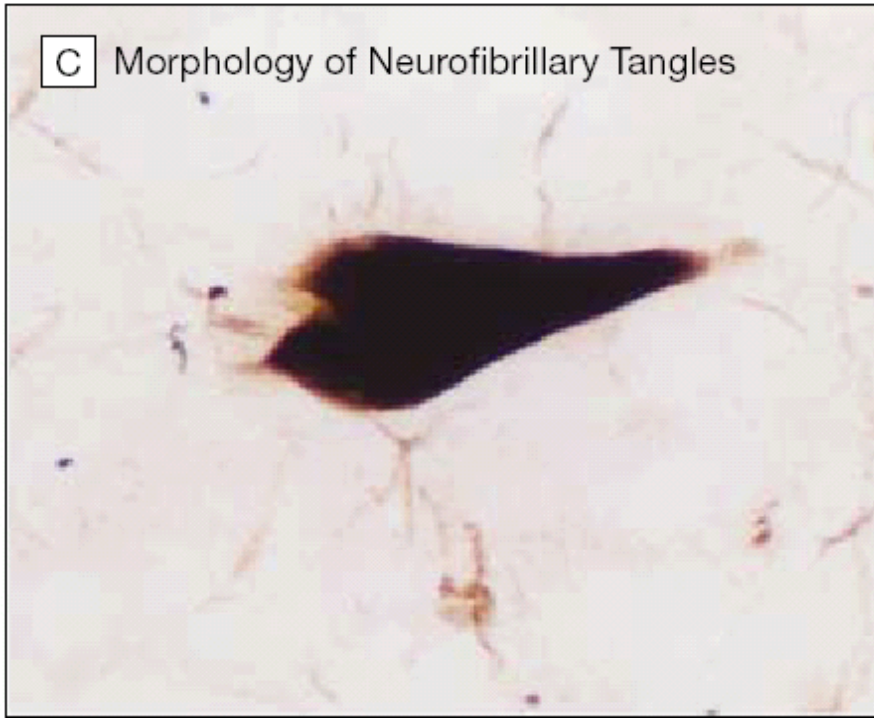
Vascular function & disease

Immune System, Inflammation & Oxidative Stress

Saykin 2014

Neuropathology, Plaques, Tangles & Abnormal Proteins (*Disease Trigger is Still Unresolved*)





Amyloid Beta Protein

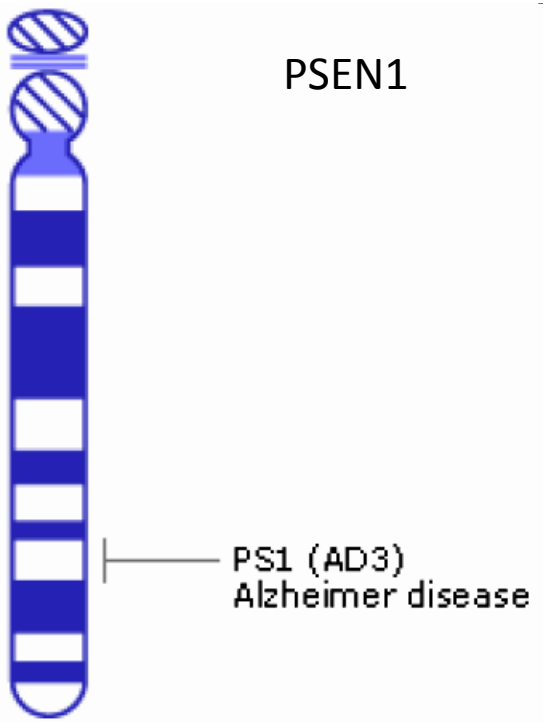
Tau Protein

Cummings & Cole, JAMA May 18, 2002, 2335-8

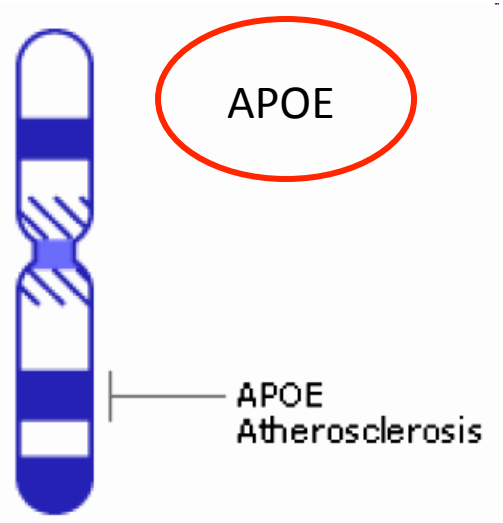
Major AD Genes: EOAD & LOAD

LOAD: genetic factors account for ~60-80% of risk (Gatz et al 2006); APOE accounts for up to 50% (Ashford & Mortimer 2002); so up to 30% remains to be found.

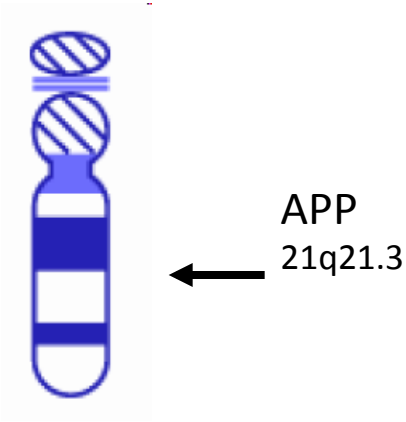
Chromosome 1



Chromosome 14



Chromosome 19



Chromosome 21

The DIAN Consortium

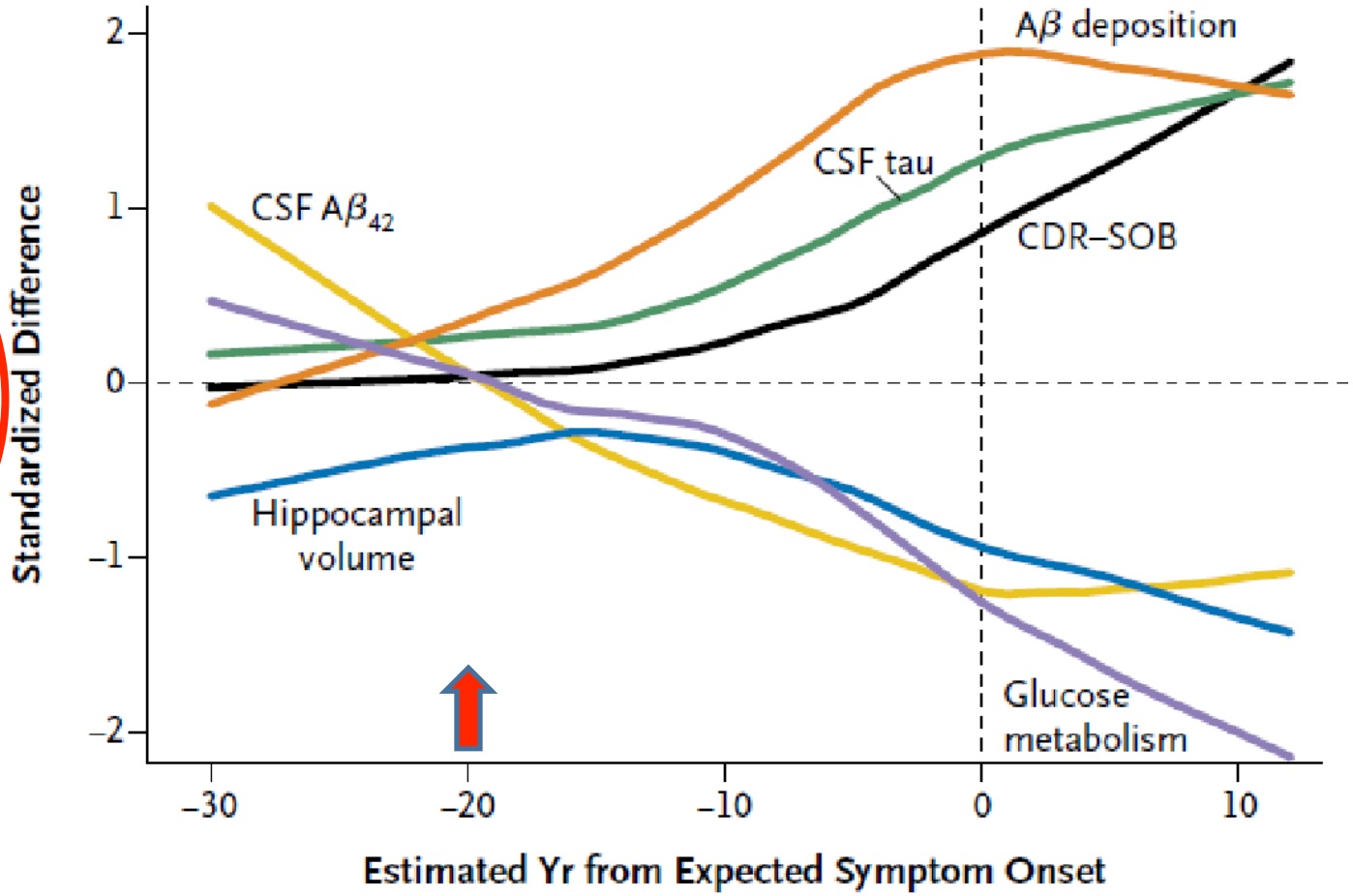
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2012 VOL. 367 NO. 9

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M Krista Moulder, Ph.D., Paul S. Aisen, M.D., Ralph N. Martins, Ph.D., Colin L. M Martin N. Rossor, M.D., Peter R. Schofi and John C. Morris, M.D

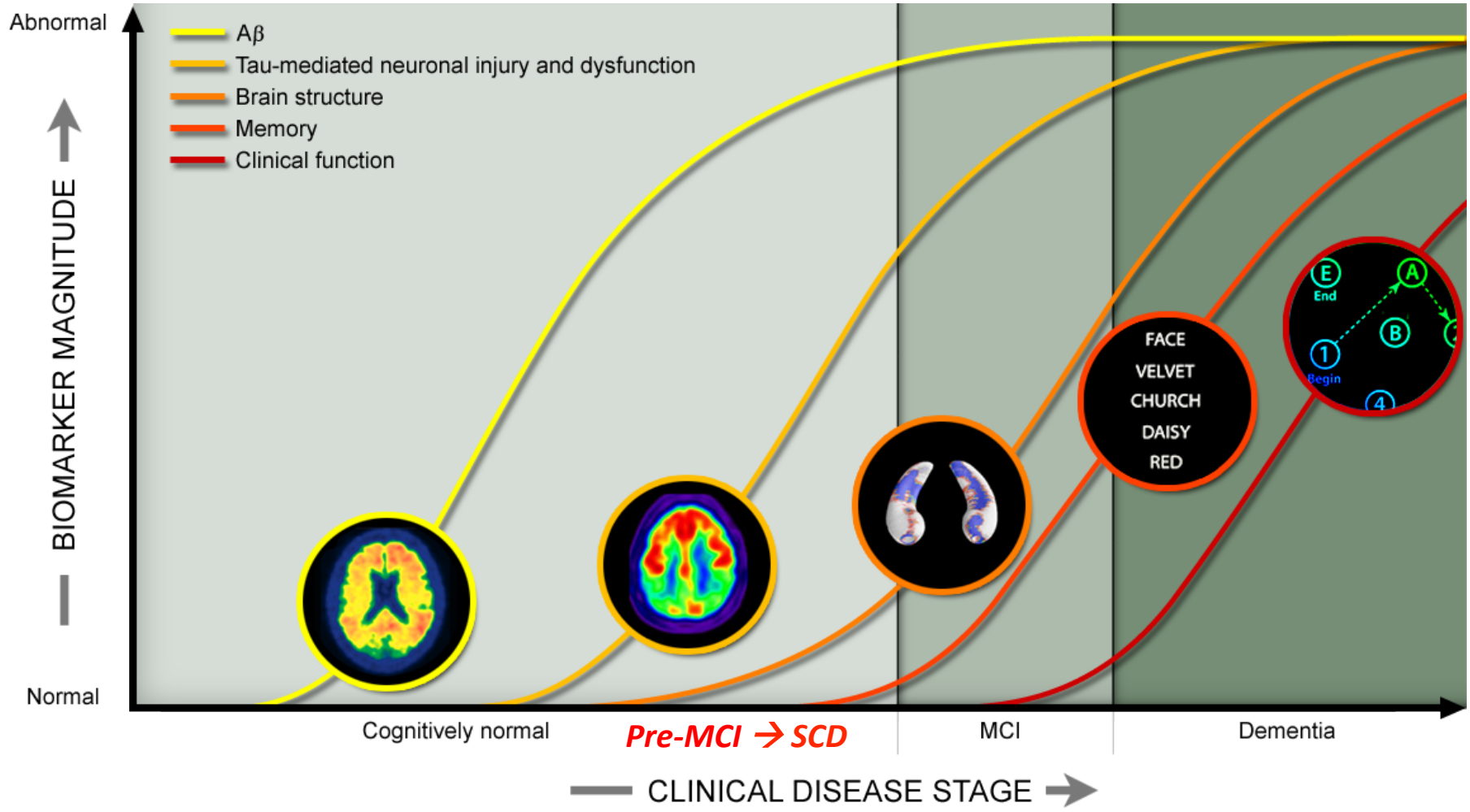
Evidence that AD begins 20 years prior to diagnosis



Bateman et al, NEJM (2012)

Role of Biomarkers

Temporal ordering and time-dependent roles



http://adni.loni.usc.edu/study-design/background-rationale/

Neuroimaging Phenotypes

Subjective Cognitive Decline
Informant Perception

Amyloid PET/CSF
Tau PET/CSF

Cognitive Performance

MRI - structure
MRI - function
Connectome

Lifestyle & environment
- Cognitive stimulation, diet, exercise, sleep

Vascular function & disease

Biomarkers
- CSF, blood, others

Immune System, Inflammation & Oxidative Stress

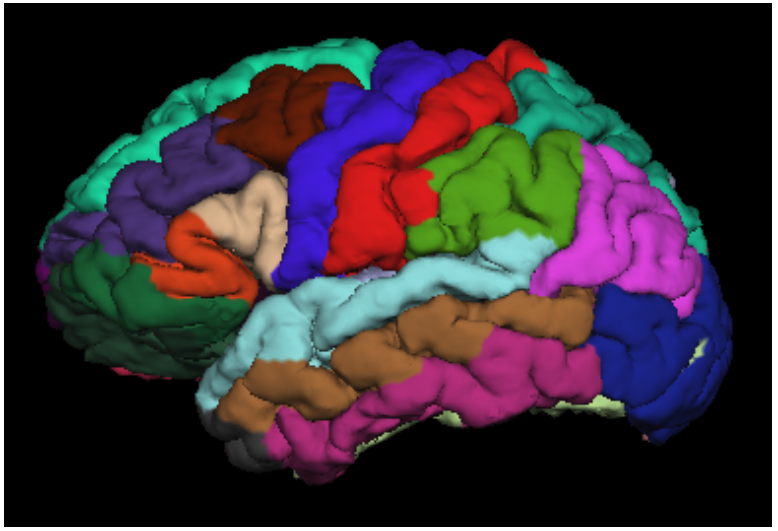
Genomics
- DNA
- RNA
- Epigenetics

Therapeutics & Prevention

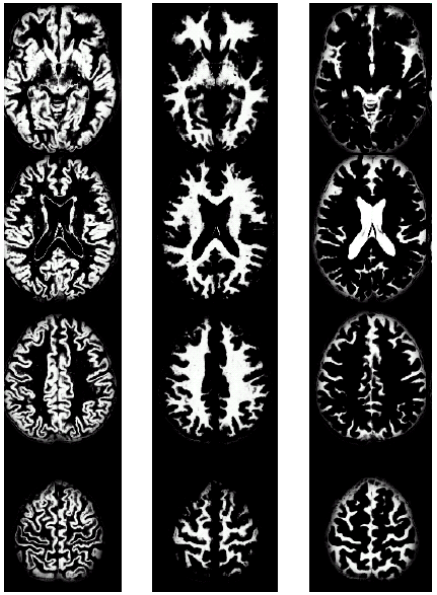
Saykin 2014

Imaging Biomarkers and Phenotypes: Structural Changes

Hippocampus

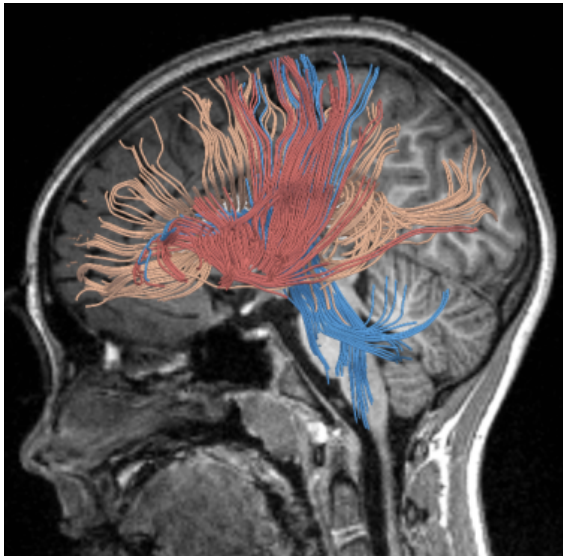


Cortical Atrophy



Voxel-Based Morphometry (VBM)

White Matter: Connectome



Earlier Detection than MCI?
"Pre-MCI" Imaging & Clinical Status

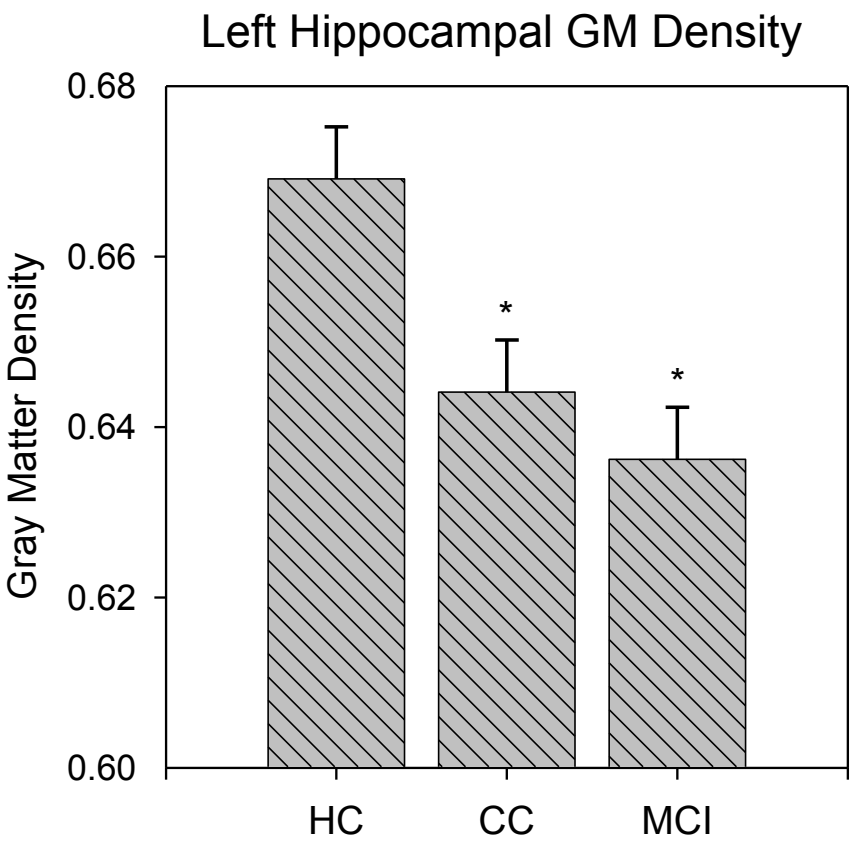
Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI

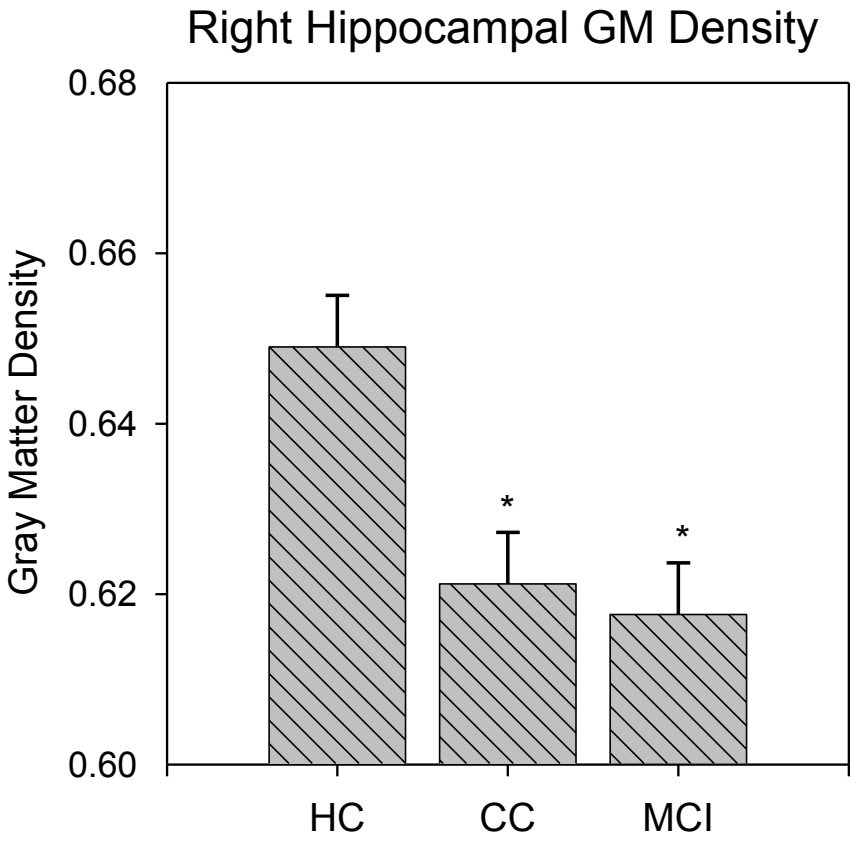
A.J. Saykin, PsyD; H.A. Wishart, PhD; L.A. Rabin, PhD; R.B. Santulli, MD; L.A. Flashman, PhD; J.D. West, MS; T.L. McHugh, MA; and A.C. Mamourian, MD

Abstract—*Objective:* To examine the neural basis of cognitive complaints in healthy older adults in the absence of memory impairment and to determine whether there are medial temporal lobe (MTL) gray matter (GM) changes as reported in Alzheimer disease (AD) and amnestic mild cognitive impairment (MCI). *Methods:* Participants were 40 euthymic individuals with cognitive complaints (CCs) who had normal neuropsychological test performance. The authors compared their structural brain MRI scans to those of 40 patients with amnestic MCI and 40 healthy controls (HCs) using voxel-based morphometry and hippocampal volume analysis. *Results:* The CC and MCI groups showed similar patterns of decreased GM relative to the HC group on whole brain analysis, with differences evident in the MTL, frontotemporal, and other neocortical regions. The degree of GM loss was associated with extent of both memory complaints and performance deficits. Manually segmented hippocampal volumes, adjusted for age and intracranial volume, were significantly reduced only in the MCI group, with the CC group showing an intermediate level. *Conclusions:* Cognitive complaints in older adults may indicate underlying neurodegenerative changes even when unaccompanied by deficits on formal testing. The cognitive complaint group may represent a pre–mild cognitive impairment stage and may provide an earlier therapeutic opportunity than mild cognitive impairment. MRI analysis approaches incorporating signal intensity may have greater sensitivity in early preclinical stages than volumetric methods.

NEUROLOGY 2006;67:834–842

Baseline Hippocampal Gray Matter Density in MCI & Cognitive Complaints





N=40,40,40

** MCI < HC, p <.001*

** CC < HC, p <.005*

Saykin et al, NEUROLOGY 2006;67:834-842

Altered Structural Connectivity Pre-MCI

Biochimica et Biophysica Acta 1822 (2012) 423–430

Contents lists available at SciVerse ScienceDirect

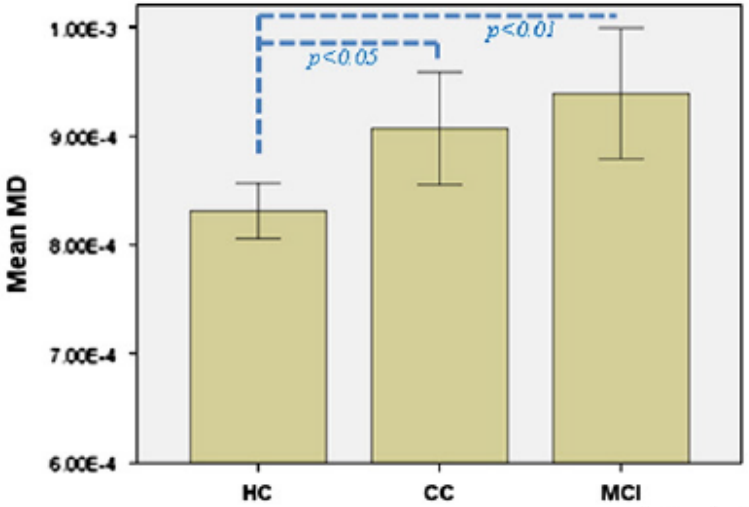
Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Selective changes in white matter integrity in MCI and older adults with cognitive complaints ☆

Yang Wang [a], John D. West [a], Laura A. Flashman [b], Heather A. Wishart [b], Robert B. Santulli [b], Laura A. Rabin [c], Nadia Pare [d], Konstantinos Arfanakis [e], Andrew J. Saykin [a,b,*]

[a] Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA
[b] Brain Imaging Laboratory, Department of Psychiatry, Dartmouth Medical School, Lebanon, NH, USA
[c] Brooklyn College and the Graduate Center of CUNY, Brooklyn, NY, USA
[d] The Nebraska Medical Center, Omaha, NE, USA
[e] Department of Biomedical Engineering, Illinois Institute of Technology, Chicago, IL, US



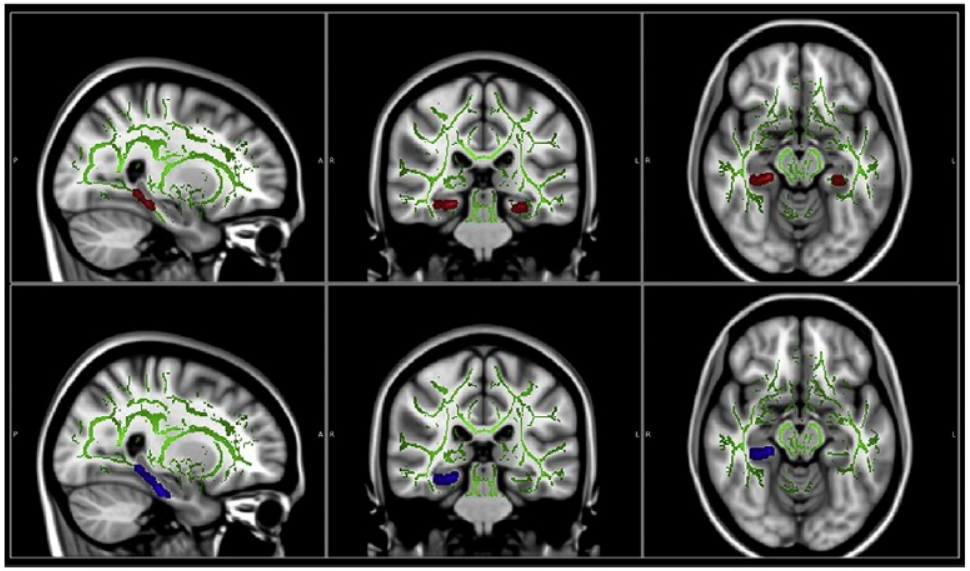


Fig. 1. Voxel-wise DTI comparison using tract-based spatial statistics analysis. The brain images showing underlying standard Montreal Neurological Institute (MNI) atlas MNI152 1-mm brain template and white matter skeleton derived from tract-based spatial statistics (TBSS) analysis (shown in green). Red color indicates tracts with reduced fractional anisotropy (FA) in bilateral parahippocampal white matter in patients with MCI vs. controls; Blue color indicates region with increased radial diffusivity (DR) in right parahippocampal white matter in MCI vs. controls. Only clusters surviving correction for multiple comparisons of voxel-wise whole brain analysis are shown on brain images ($p<0.01$). Statistical maps were dilated from the TBSS skeleton for visualization purposes.

Connectivity (Resting State fMRI)

Journal of Alzheimer's Disease 35 (2013) 751–760
DOI 10.3233/JAD-130080
IOS Press

Altered Default Mode Network Connectivity in Older Adults with Cognitive Complaints and Amnestic Mild Cognitive Impairment

Yang Wang[a], Shannon L. Risacher[a], John D. West[a], Brenna C. McDonald[a,b], Tamiko R. MaGee[a], Martin R. Farlow[b], Sujuan Gao[c], Darren P. O'Neill[a] and Andrew J. Saykin[a,*]
[a]*Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA*
[b]*Department of Neurology, Indiana University School of Medicine, Indianapolis, IN, USA*
[c]*Department of Biostatistics, Indiana University School of Medicine, Indianapolis, IN, USA*

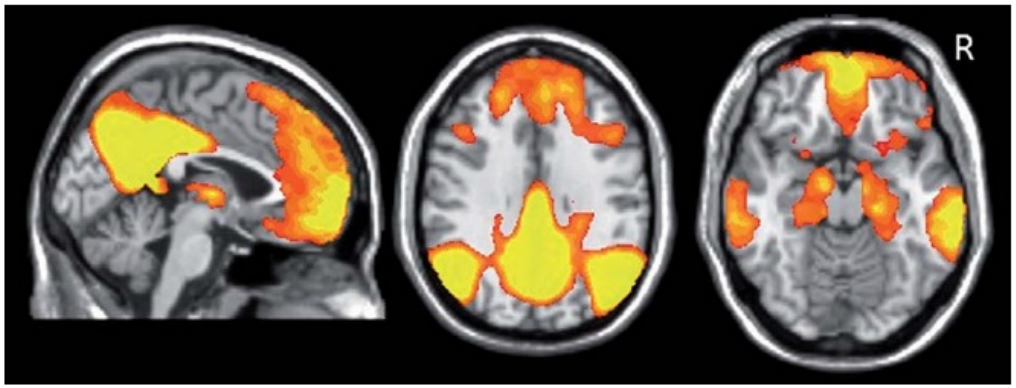


Fig. 1. Illustration of default model network (DMN) regions derived from group independent component analysis (ICA). The DMN component identified by meta-ICA analysis included the posterior cingulate cortex, precuneus, medial prefrontal cortex, lateral parietal regions, lateral temporal regions, and bilateral medial temporal regions ($p < 10^{-4}$).

Decreased Right Hippocampal Connectivity in Cognitive Complaint Group

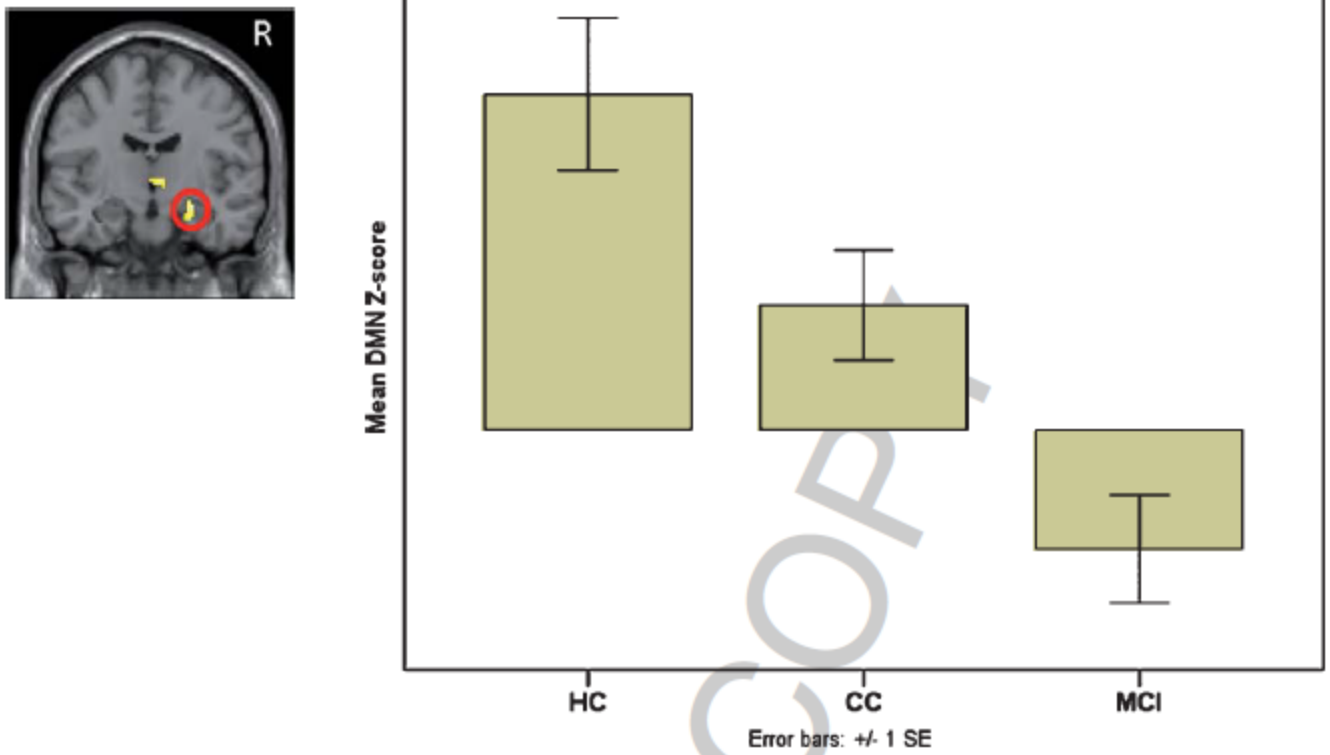
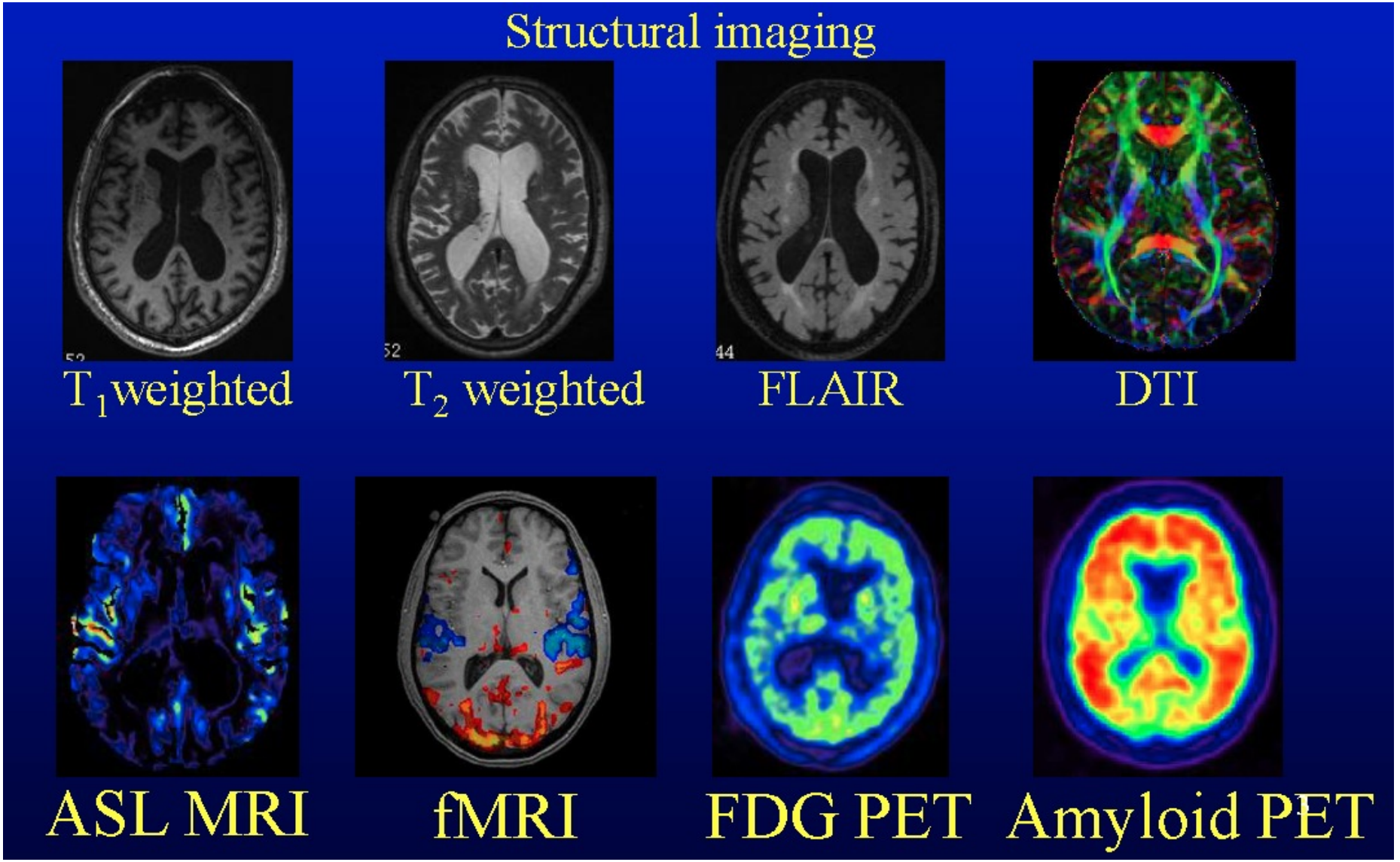


Fig. 3. Region of interest analysis of default mode network (DMN) connectivity in the right hippocampus showed significant differences in DMN Z-scores (±SE) between groups (HC > CC > MCI; $p < 0.02$), covaried for age, years of education, and gender.

Wang et al JAD 2013

Multimodal Imaging in ADNI-2

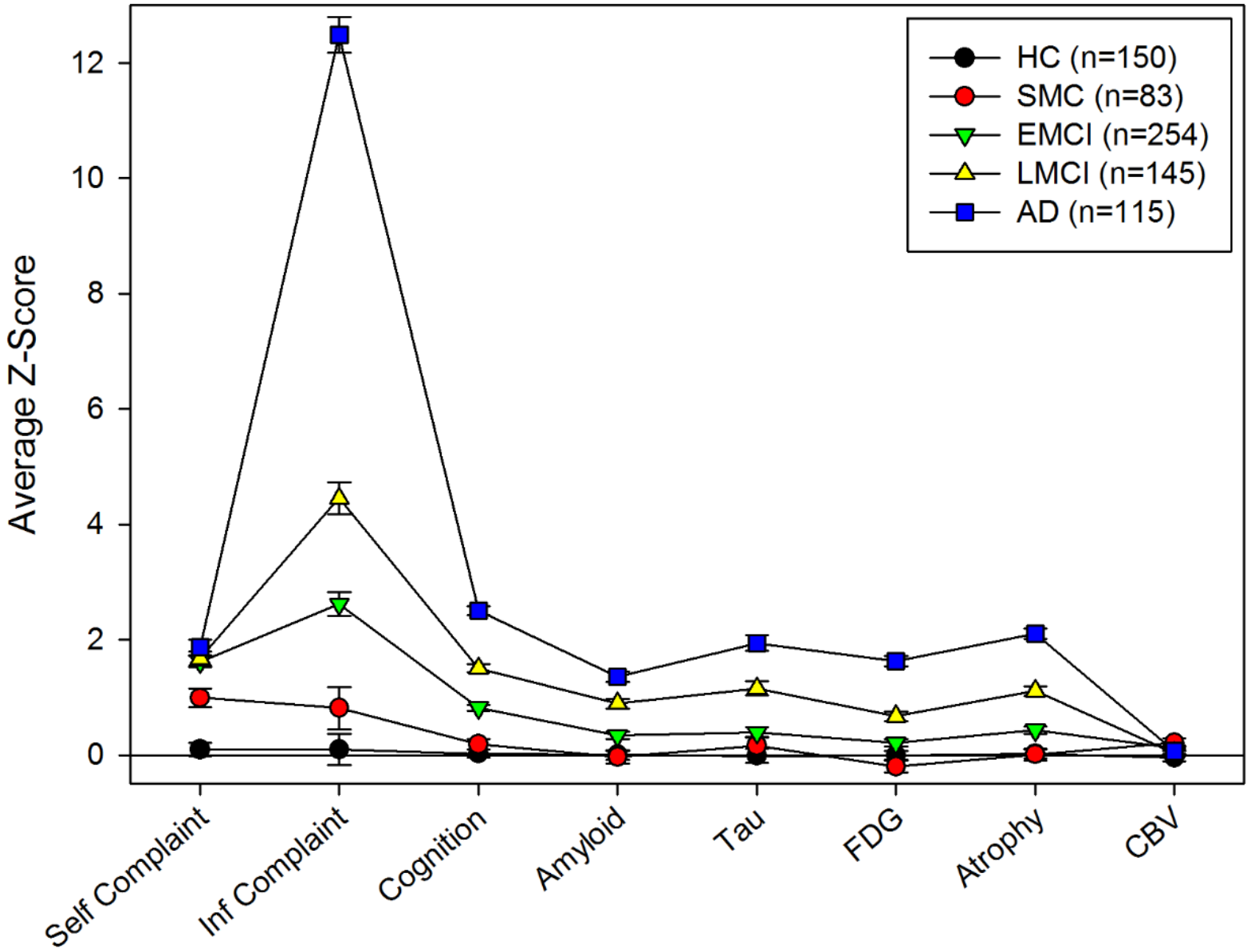


Courtesy of M. Weiner, WW-ADNI, July 2014

Alzheimer's Disease: Network Perspectives

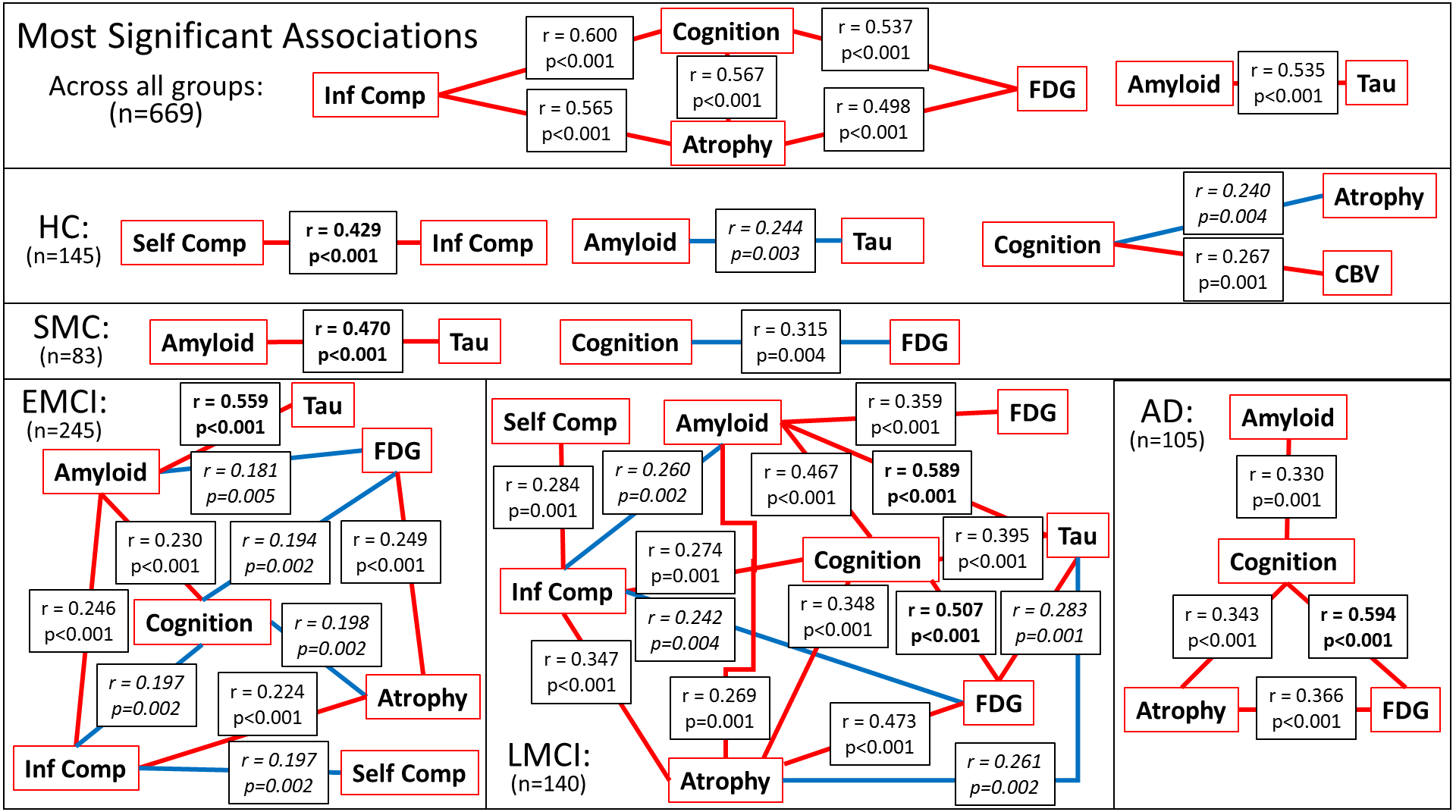
- Alzheimer's Disease
  - A complex disorder: Snapshot of the science
  - Prodromal stages: Subjective Cognitive Decline & Mild Cognitive Impairment
- Brain Networks – The Connectome
- **Biomarker Networks (phenotype clusters)**
- Gene Pathways, Networks & Systems Biology
- Social Networks
  - Families, Communities, Healthcare systems, Provider networks, Social media, Science of Science, ELSI issues

The AD Phenome: Phenotype Profiling Project



Saykin & Risacher, Unpublished data, 2014

The AD Phenome: Phenotype Profiling Project



Saykin & Risacher, Unpublished data, 2014

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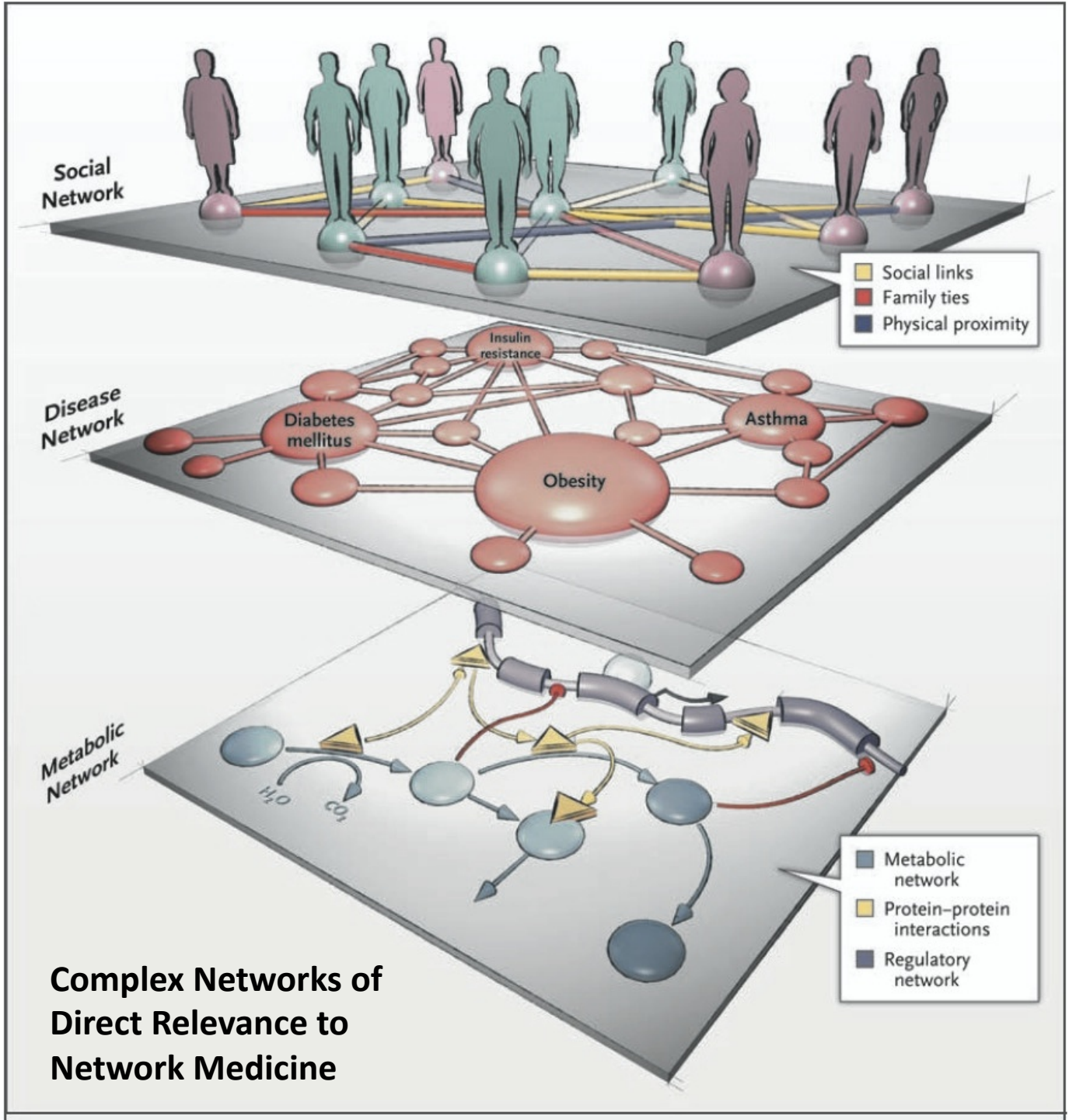
Systems Biology & The Diseasome

Network Medicine — From Obesity to the "Diseasome"
Albert-László Barabási

NEJM; 357(4)
July 26, 2007
www.nejm.406 org



Complex Networks of Direct Relevance to Network Medicine

IGAP Meta-Analysis: Now a "Top 20" AD Genes (2013)

Lambert et al Nature Genetics (2013)* LETTERS

nature genetics

Largest AD GWAS

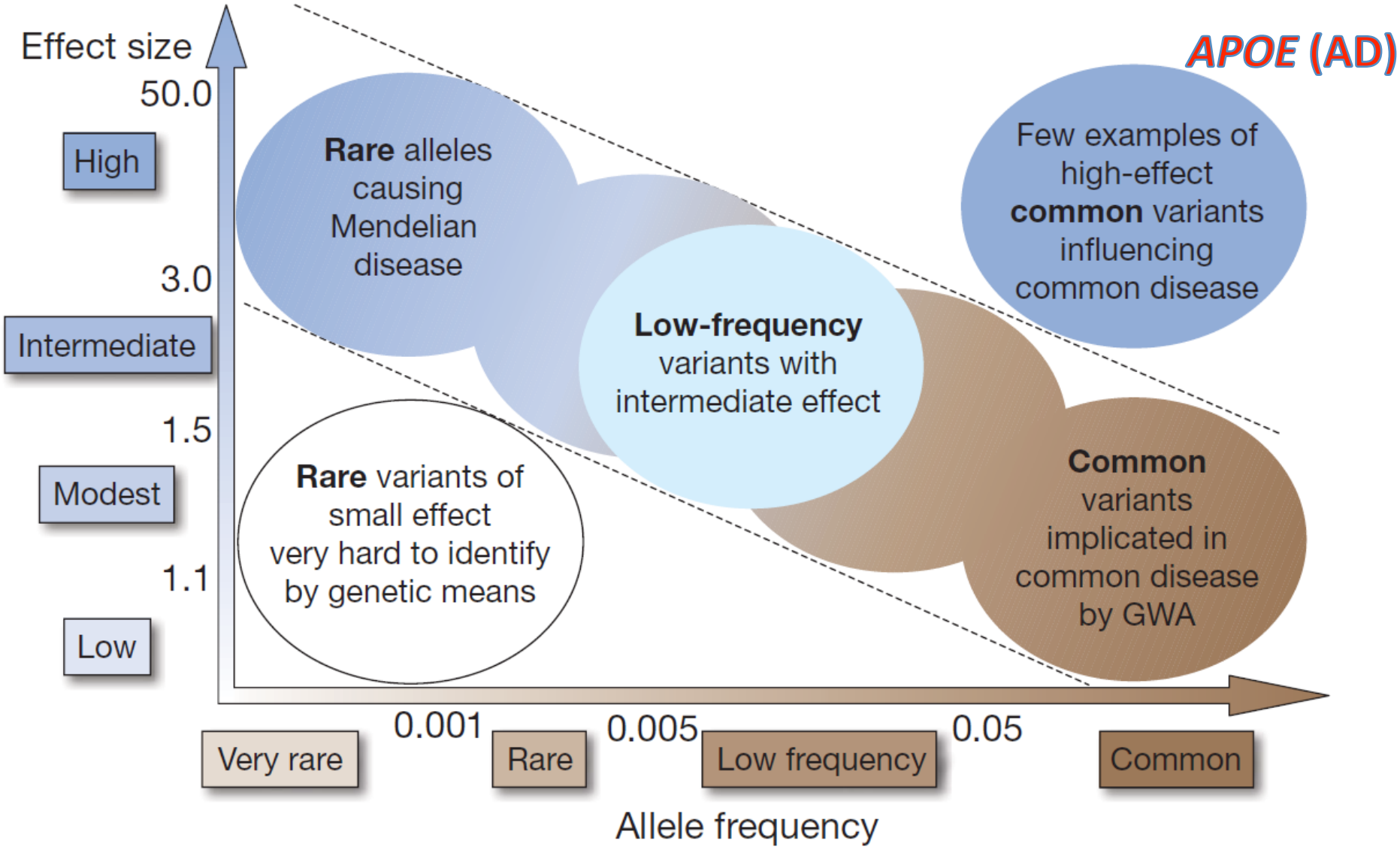
Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease

Eleven susceptibility loci for late-onset Alzheimer's disease (LOAD) were identified by previous studies; however, a large portion of the genetic risk for this disease remains unexplained. We conducted a large, two-stage meta-analysis of genome-wide association studies (GWAS) in individuals of European ancestry. In stage 1, we used genotyped and imputed data (7,055,881 SNPs) to perform meta-analysis on 4 previously published GWAS data sets consisting of 17,008 Alzheimer's disease cases and 37,154 controls. In stage 2, 11,632 SNPs were genotyped and tested for association in an independent set of 8,572 Alzheimer's disease cases and 11,312 controls. In addition to the *APOE* locus (encoding apolipoprotein E), 19 loci reached genome-wide significance ($P < 5 \times 10^{-8}$) in the combined stage 1 and stage 2 analysis, of which 11 are newly associated with Alzheimer's disease.

"In addition to the *APOE* locus, 14 genomic regions had associations that reached genome-wide significance. 9 had been previously identified by GWAS as genetic susceptibility factors, and 5 (HLA-DRB5–HLA-DRB1, PTK2B, SORL1, SLC24A4-RIN3 and DSG2) represent newly associated loci."

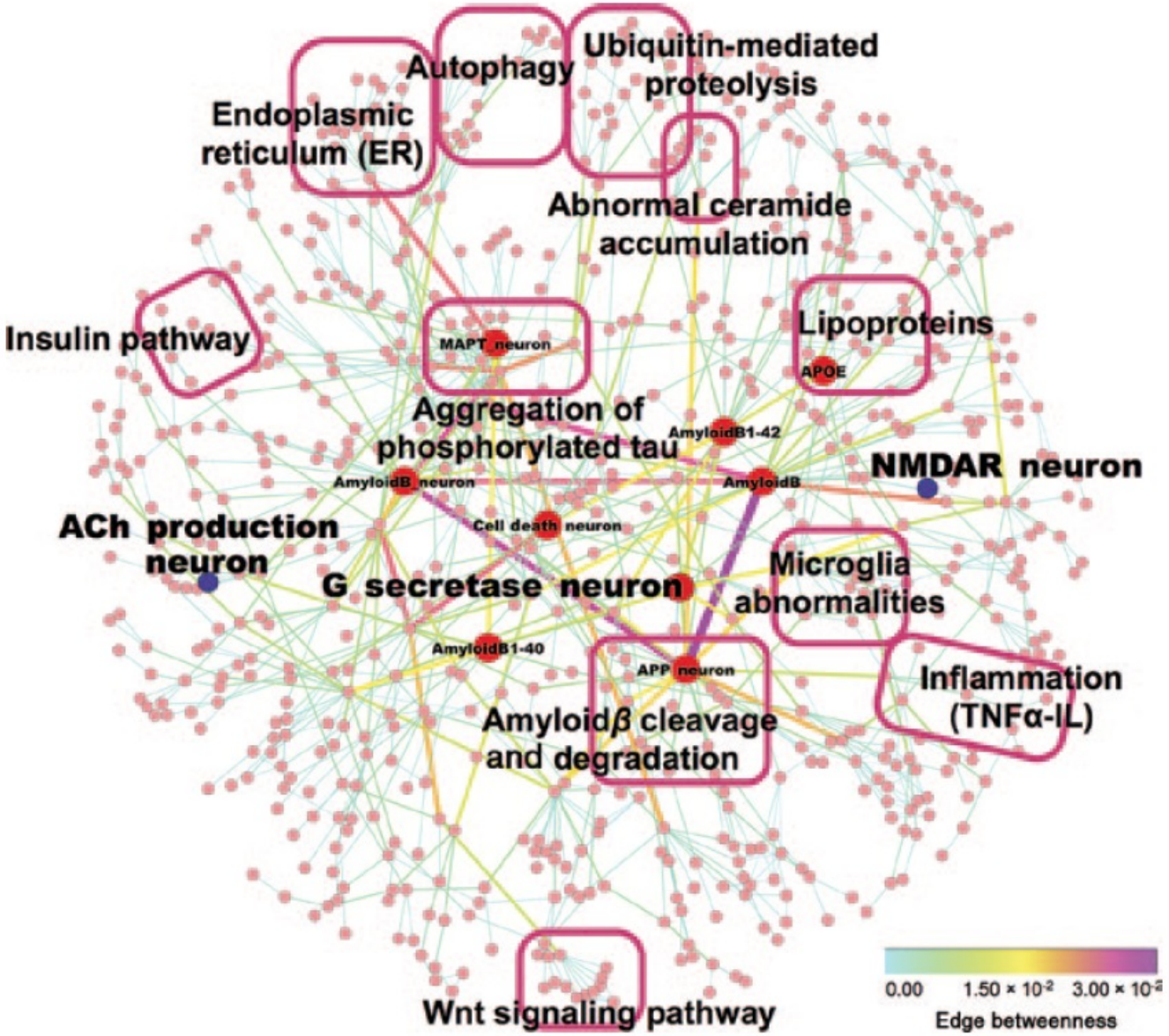
* ADNI data included as part of the ADGC

Genomic Landscape of Association Studies



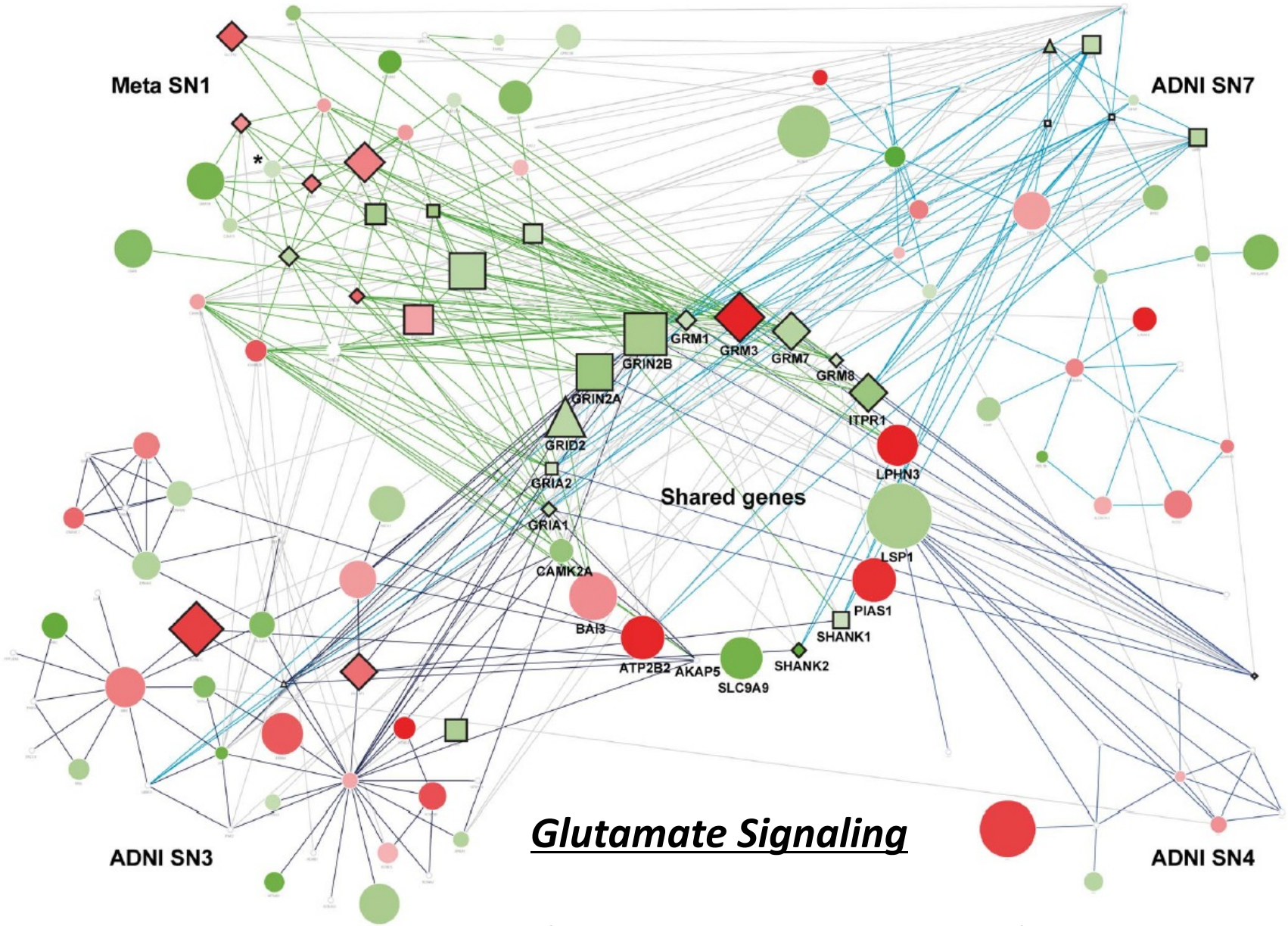
Manolio, Collins et al, *Nature* (2009); adapted from *McCarthy et al, Nature Reviews Genetics (2008)*

Key molecules in AlzPathway



Ogishima et al, *Clin Pharmacol Ther*, 2013; 93(5)

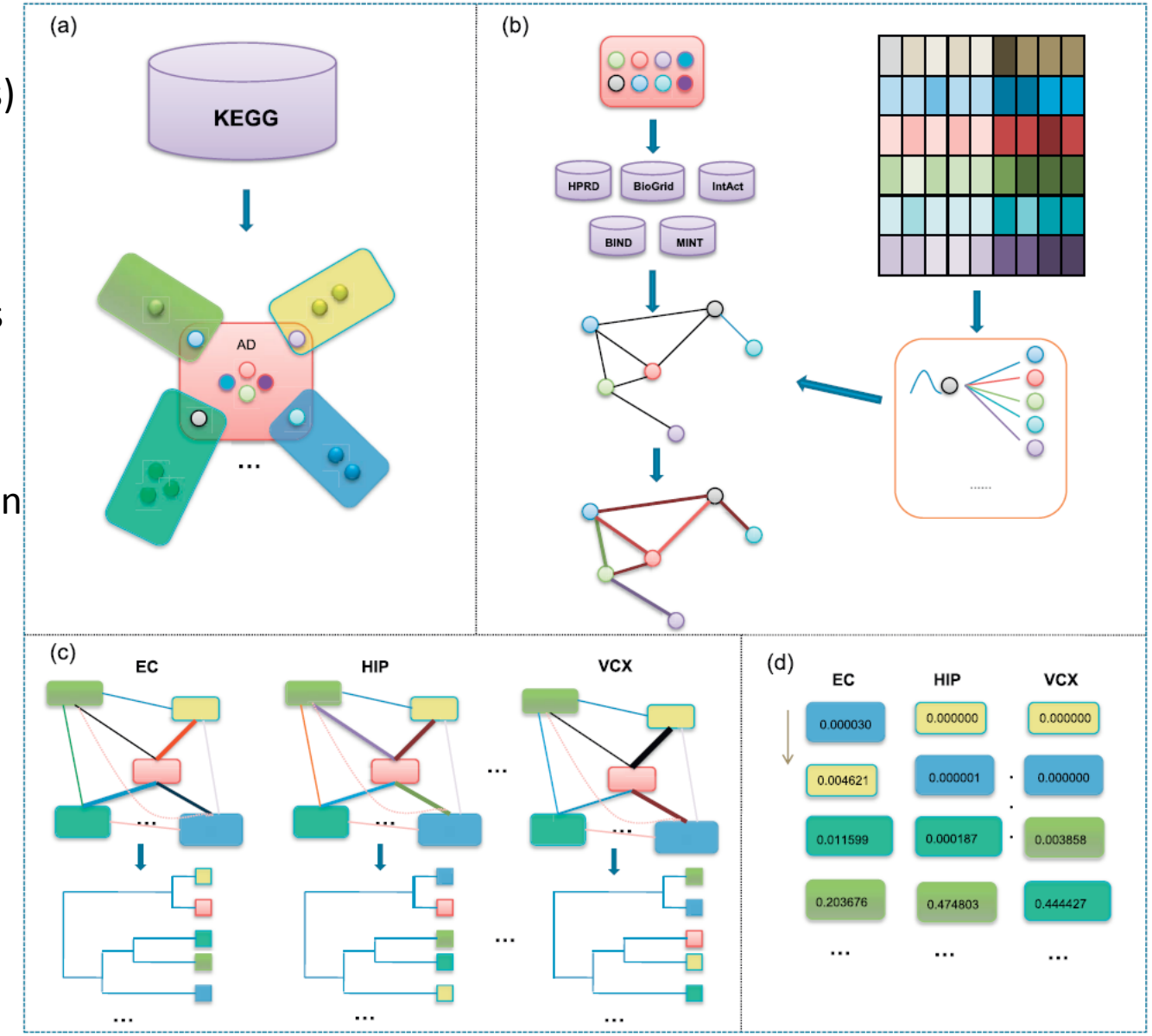
Network enrichment meta-analysis using ADNI data



Perez-Palma et al, *Overrepresentation of glutamate signaling in Alzheimer's disease: network-based pathway enrichment using meta-analysis of genome-wide association studies.* PLoS One, 2014; 9(4).

“Crosstalk” of dysfunctional pathways for AD brain regions

- A: Gene sets from KEGG (AD & neighbor pathways)
- B: PPI networks from 5 databases
- C: Clustering PPI networks by 6 AD brain regions
- D: Ranked pathways by dysfunction score based on activation during AD progression (apoptosis, notch & wnt signaling, cytokine interactions, etc)

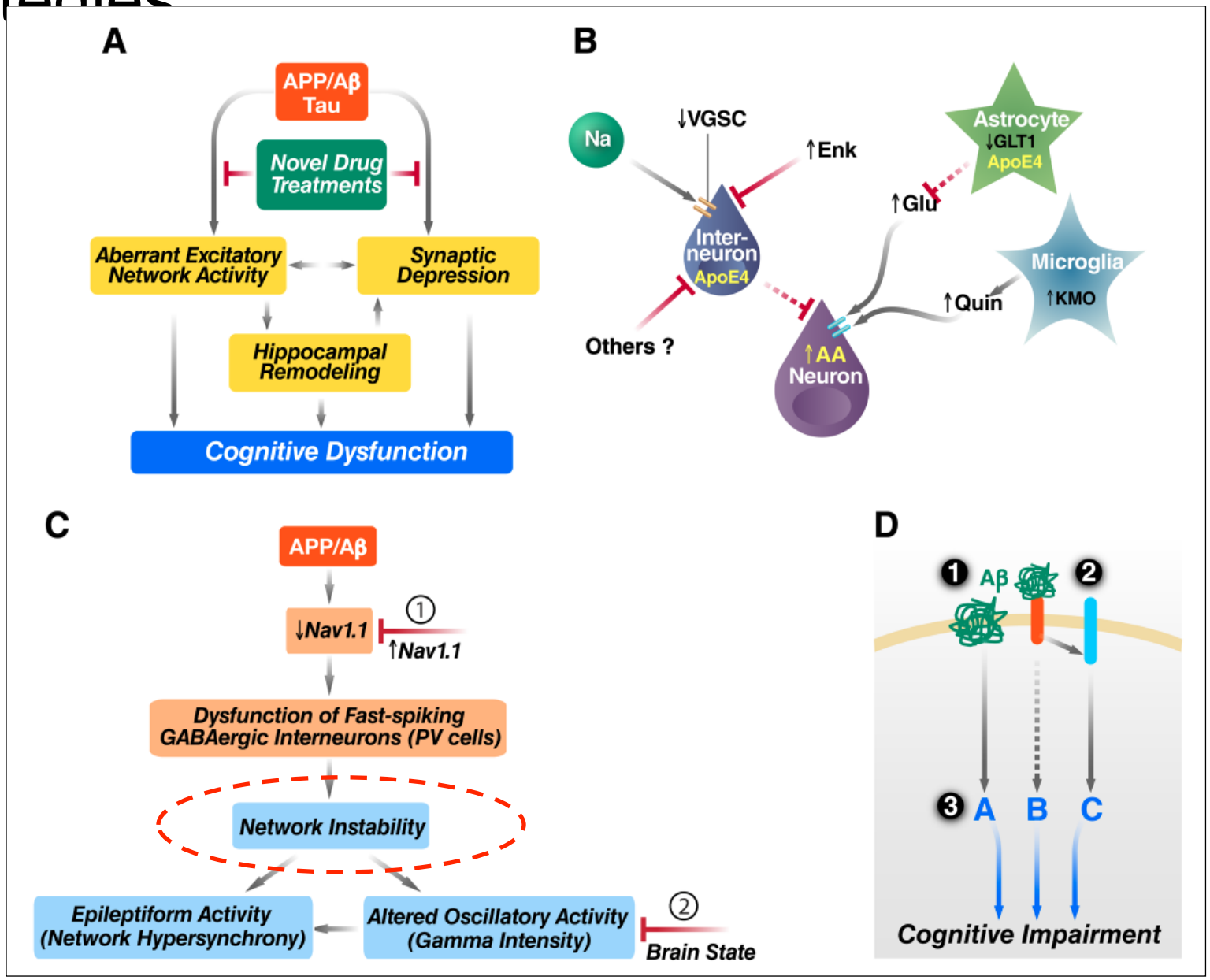


Liu et al (2010)

BMC Systems Biology, 4(S2)

http://www.biomedcentral.com/1752-0509/4?issue=S2/S11

Aβ, Network Instability & Therapeutic Strategies

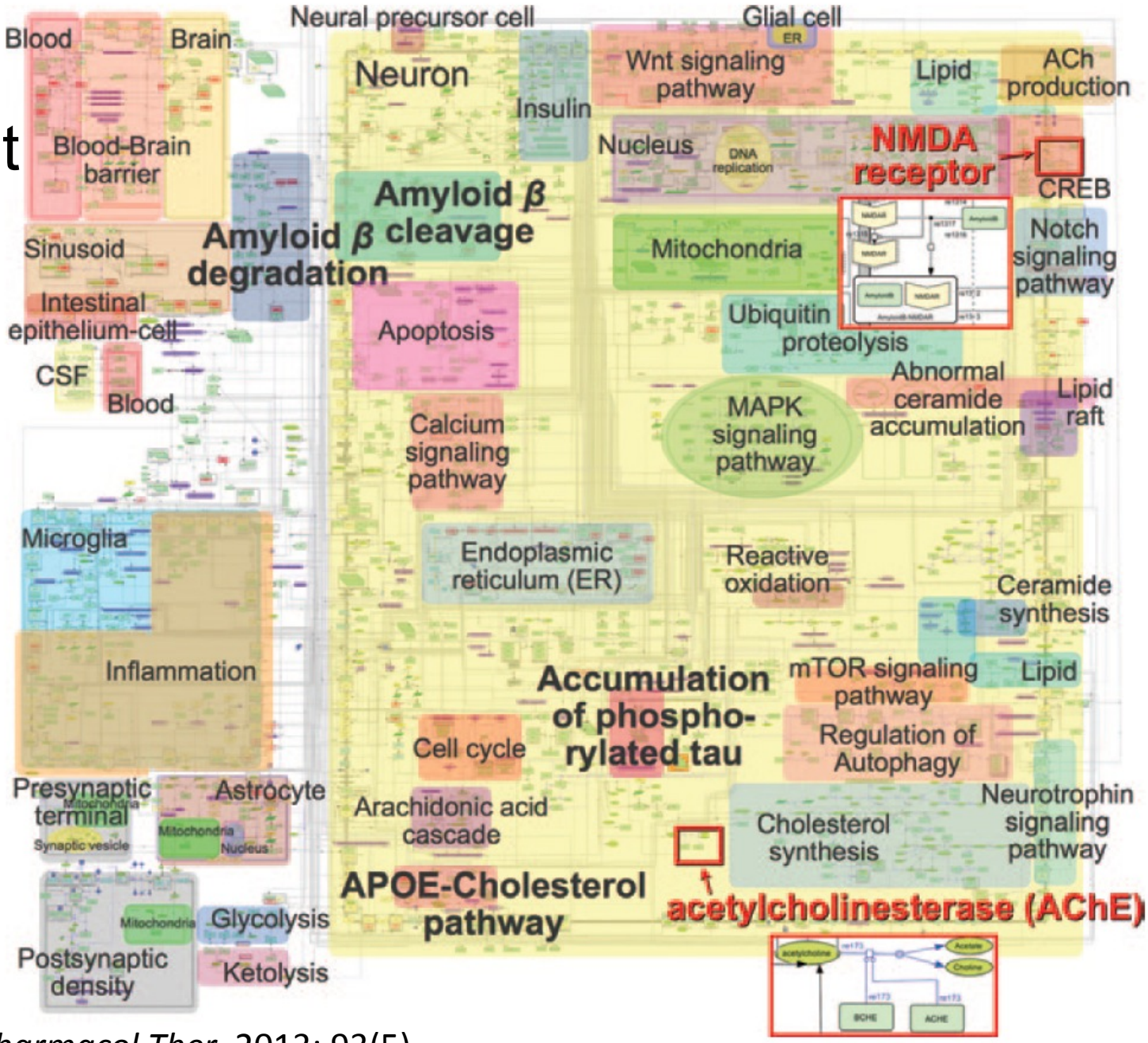


Huang & Mucke, *Cell*, 2012:148(6)

Drug Development Networks

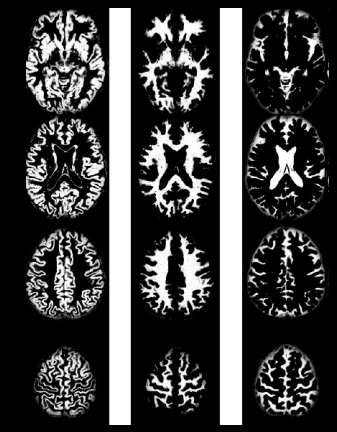
Alzheimer's Pathways and Therapeutic Targets

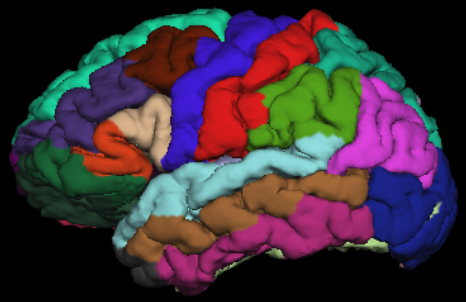
(Existing FDA-Approved Agents)

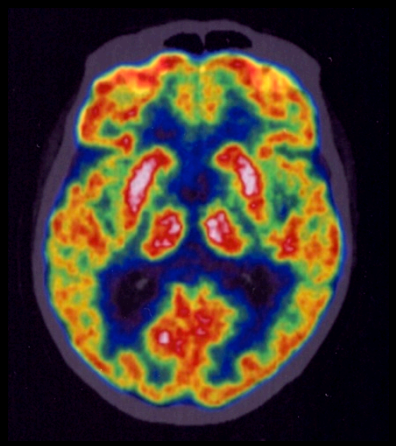


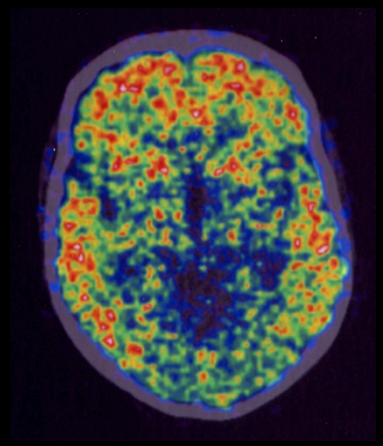
Ogishima et al, *Clin Pharmacol Ther*, 2013; 93(5)

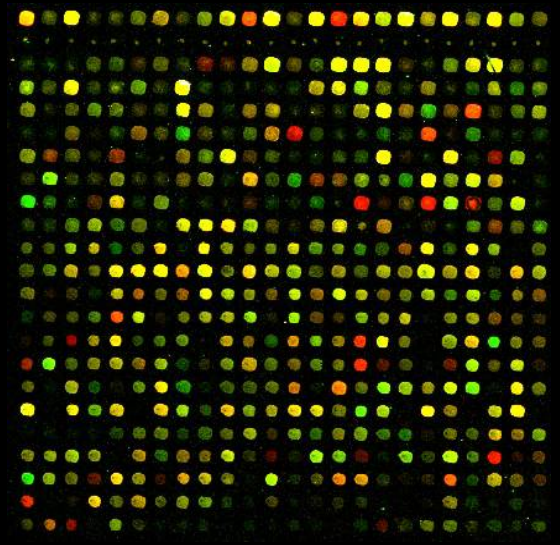
Imaging Genetics: Relating Imaging, Genes & Clinical Information is a BIG DATA Challenge







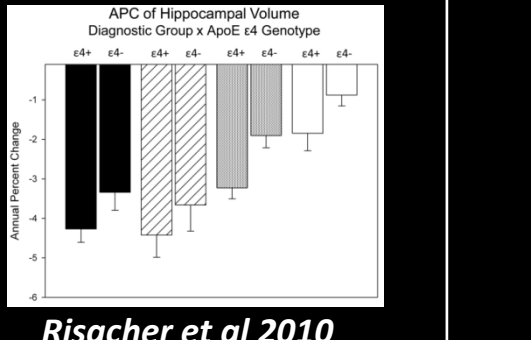
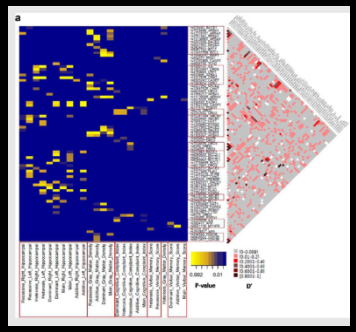
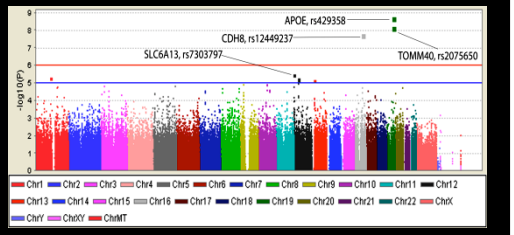
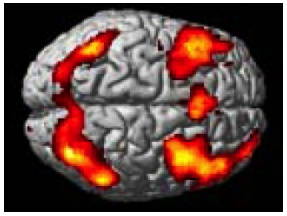
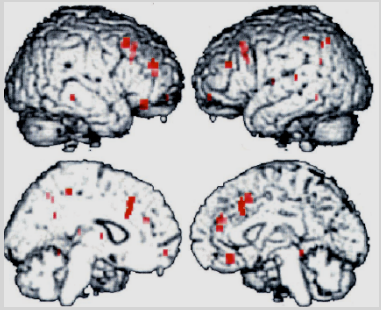
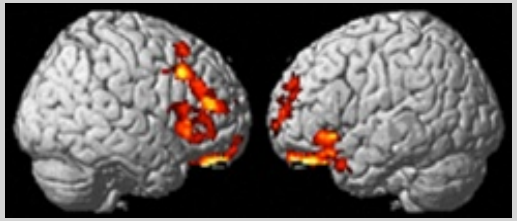
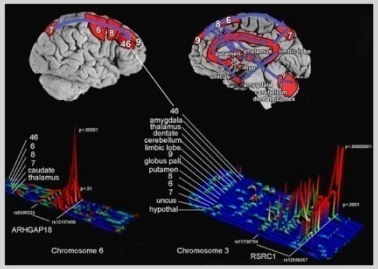
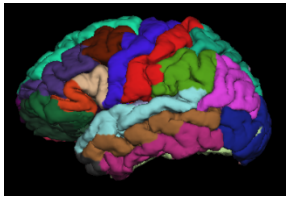
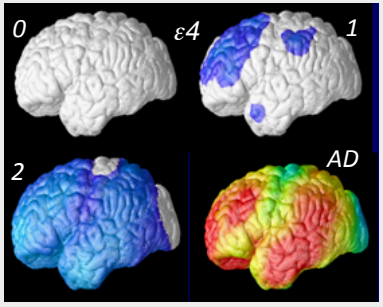
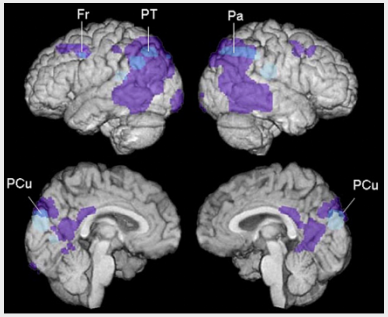
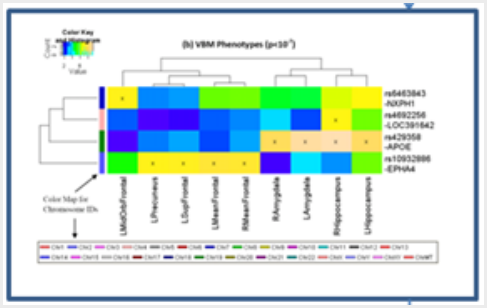




Gene“Chip”

- Multiple testing problem
- Non-independence due to LD and spatial autocorrelation

Brain-Genome Association Strategies

	Candidate Gene/SNP	Biological Pathway	Genome-wide Analysis
ROI		 *Risacher et al 2010*		
Circuit		 *Egan et al 2001 COMT*	 *Swaminathan et al 2010 PiB ROIs & amyloid pathway*	 *Potkin et al 2009 Mol Psych schizophrenia study*
Whole Brain		 *Reiman et al PNAS 2009; Also Ho et al 2010 FTO*	 *Reiman et al 2008 cholesterol pathway genes*	 *Shen et al 2010 ROIs; Stein et al 2010 voxels*

Saykin, 2011

Connectome as GWAS Phenotype: *SPON1* Gene

chromosome 11 (11p15.2)

PNAS

Genome-wide scan of healthy human connectome discovers *SPON1* gene variant influencing dementia severity

Neda Jahanshad[a], Priya Rajagopalan[a], Xue Hua[a], Derrek P. Hibar[a], Talia M. Nir[a], Arthur W. Toga[a], Clifford R. Jack, Jr.[b], Andrew J. Saykin[c], Robert C. Green[d], Michael W. Weiner[e,f], Sarah E. Medland[g], Grant W. Montgomery[g], Narelle K. Hansell[g], Katie L. McMahon[h], Greig I. de Zubicaray[i], Nicholas G. Martin[g], Margaret J. Wright[g], Paul M. Thompson[a,1], and the Alzheimer's Disease Neuroimaging Initiative[2]

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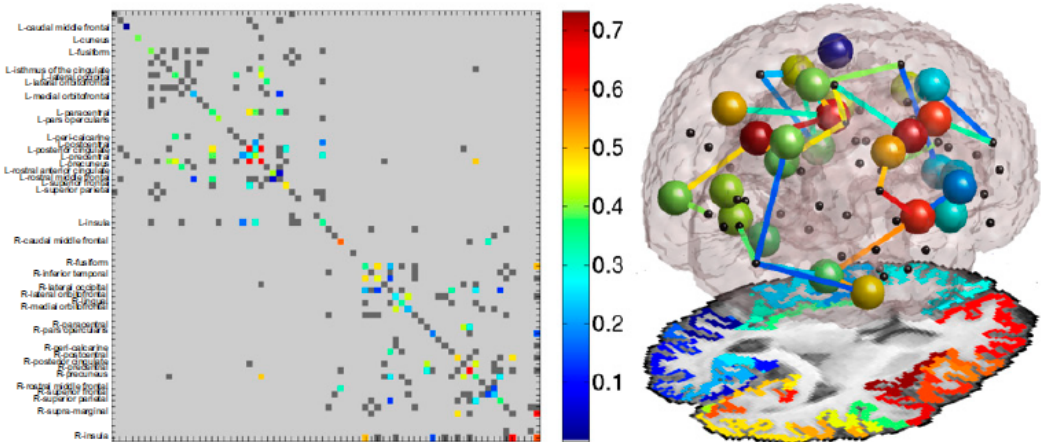
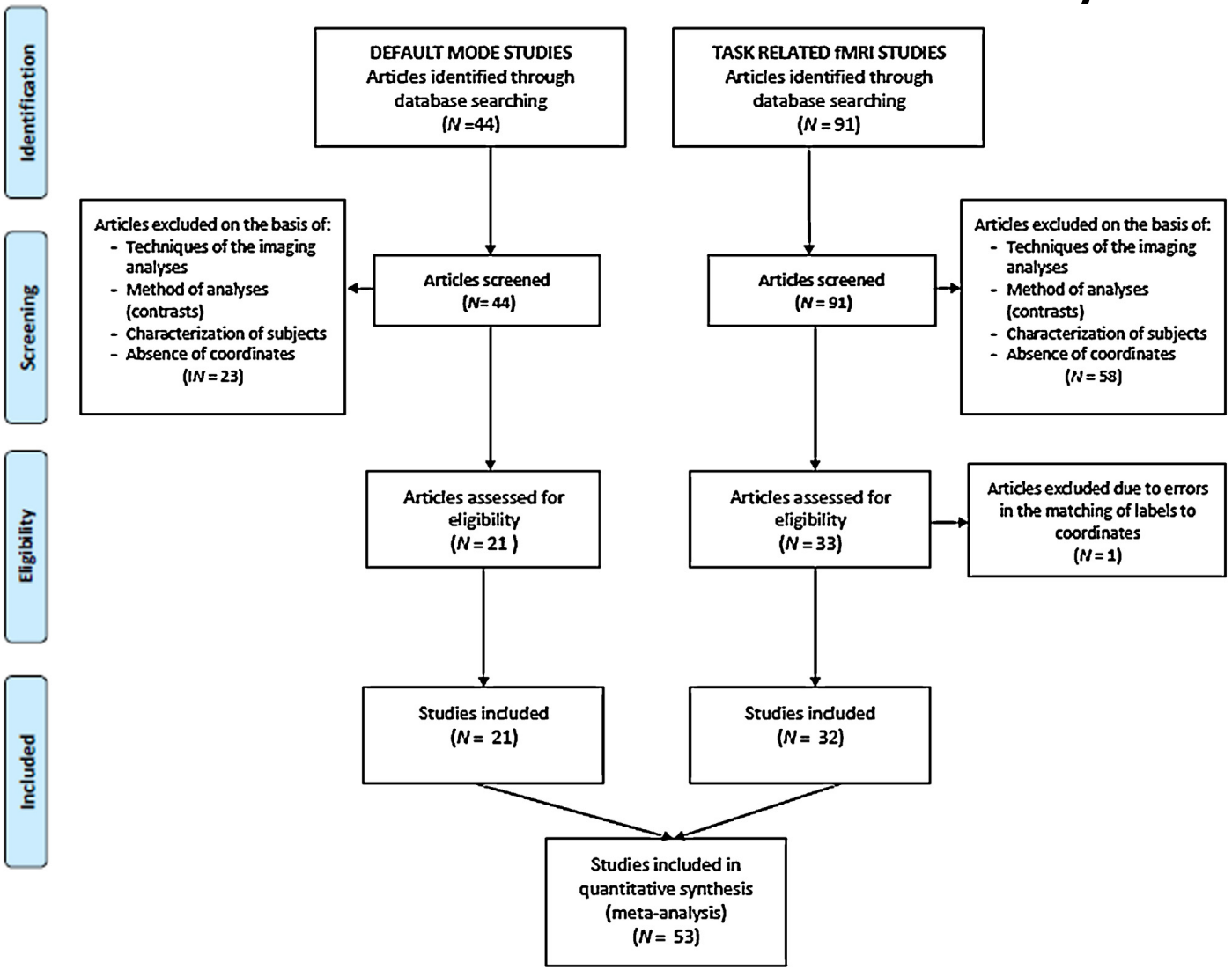
Edited by Marcus E. Raichle, Washington University, St. Louis, MO, and approved January 29, 2013 (received for review September 19, 2012)

PNAS

Fig. 1. Heritable brain connections. Quantitative genetic analysis of brain connectivity matrices in 46 MZ and 64 DZ twin pairs based on the A/E model of genetic influence. This model breaks down the observed variance in neural connectivity into components attributable to additive genetic (A) vs. unique environmental effects (E). For all nodes where the A/E model was fitted to the data, the additive genetic component is shown. Regions are displayed only if the additive genetic term exceeded 1% and the model was fitted to the data (χ^2 goodness-of-fit test, $P > 0.05$, denoted a good fit). Adding a shared environmental term did not significantly improve the fit of this model of the factors affecting brain connectivity. Regions listed on the matrix *x* and *y*



Altered Brain Networks in AD: Disordered Connectome and Connectivity



Jacobs et al, *Meta-analysis of functional network alterations in Alzheimer's disease: toward a network biomarker.* Neurosci Biobehav Rev, 2013. 37(5):753-65.

Meta-Analysis: Altered Default Mode Network and Task-Based Networks

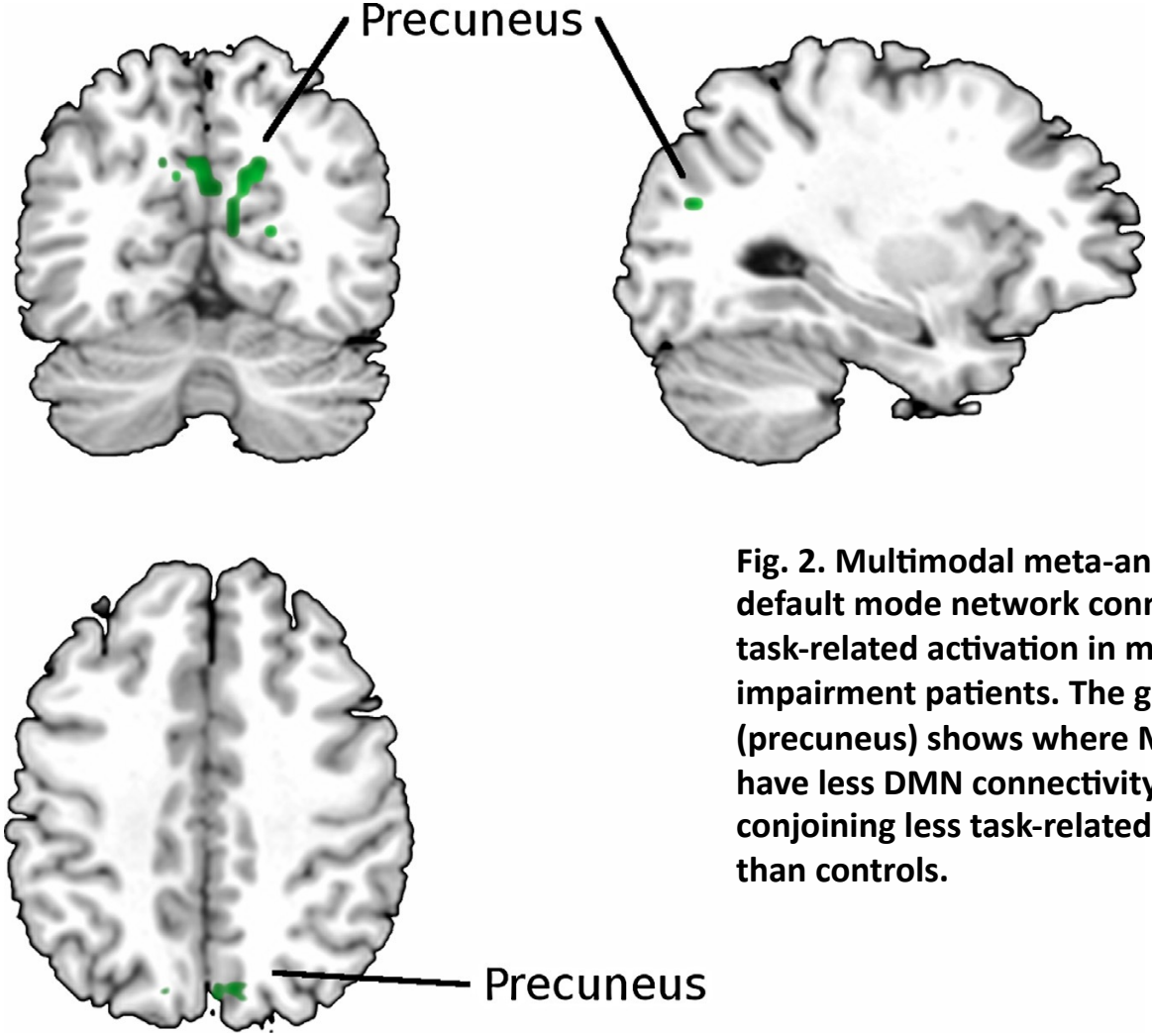
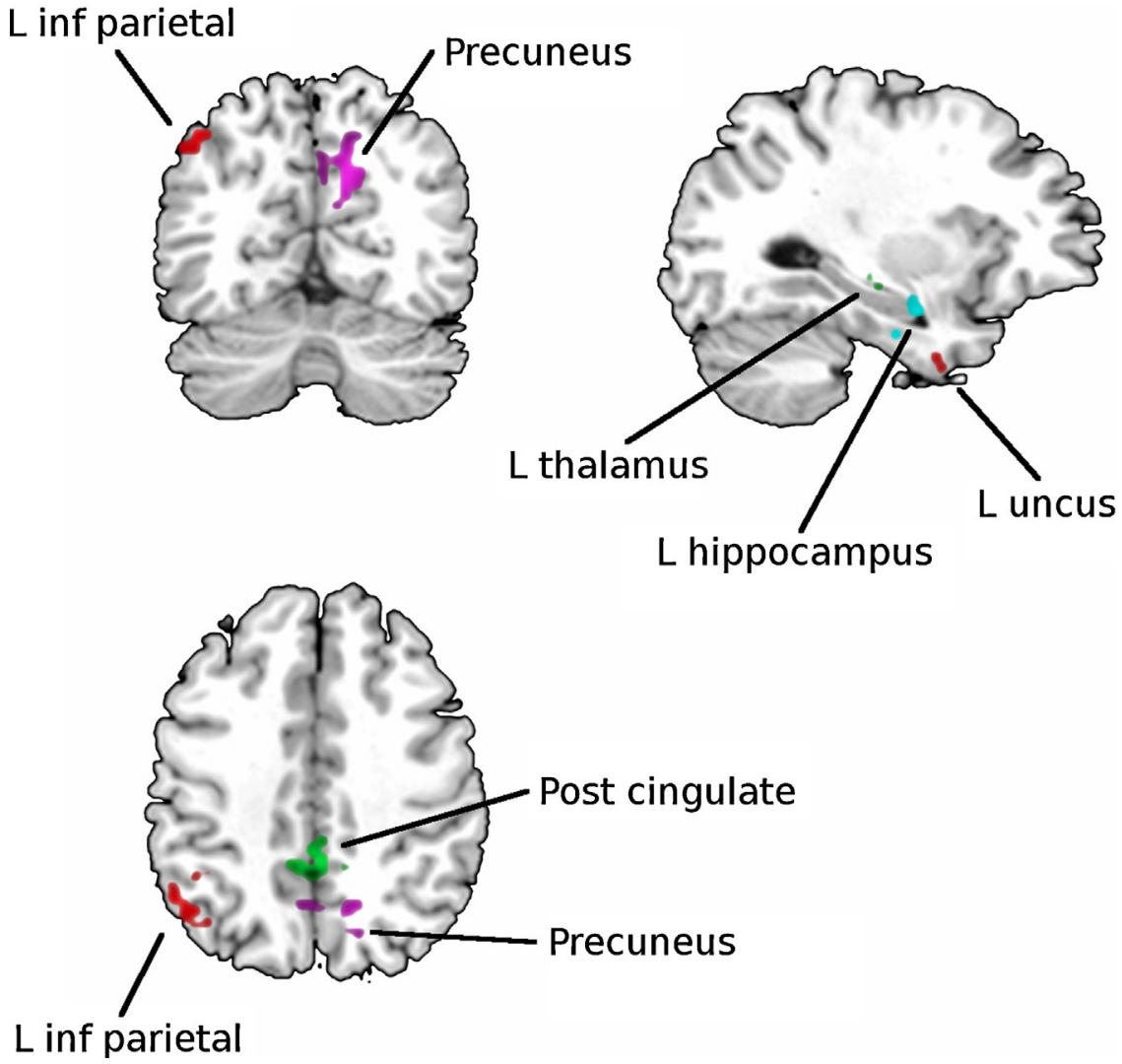


Fig. 2. Multimodal meta-analysis of default mode network connectivity and task-related activation in mild cognitive impairment patients. The green area (precuneus) shows where MCI patients have less DMN connectivity with conjoining less task-related activation than controls.

Jacobs et al, *Meta-analysis of functional network alterations in Alzheimer's disease: toward a network biomarker.* Neurosci Biobehav Rev, 2013. 37(5):753-65.

Meta-Analysis: Altered Default Mode Network and Task-Based Networks



Jacobs et al, Neurosci Biobehav Rev, 2013. 37(5):753-65.

Fig. 3. Multimodal meta-analysis of DMN connectivity and task-related activation in AD.

- The green area (posterior cingulate gyrus and thalamus) shows where AD patients have less DMN connectivity with conjoining less task-related activation.

- Red areas (inferior parietal lobule and uncus) show where AD patients have more DMN connectivity and more task-related activation compared to controls.

- Regions colored in cyan are regions where AD patients have more DMN connectivity (hippocampus), but less task-related activation compared to controls.

- Violet regions show areas (precuneus) where AD patients have less DMN connectivity but more task-related activation than controls.

Meta-Analysis: Altered Default Mode Network and Task-Based Networks

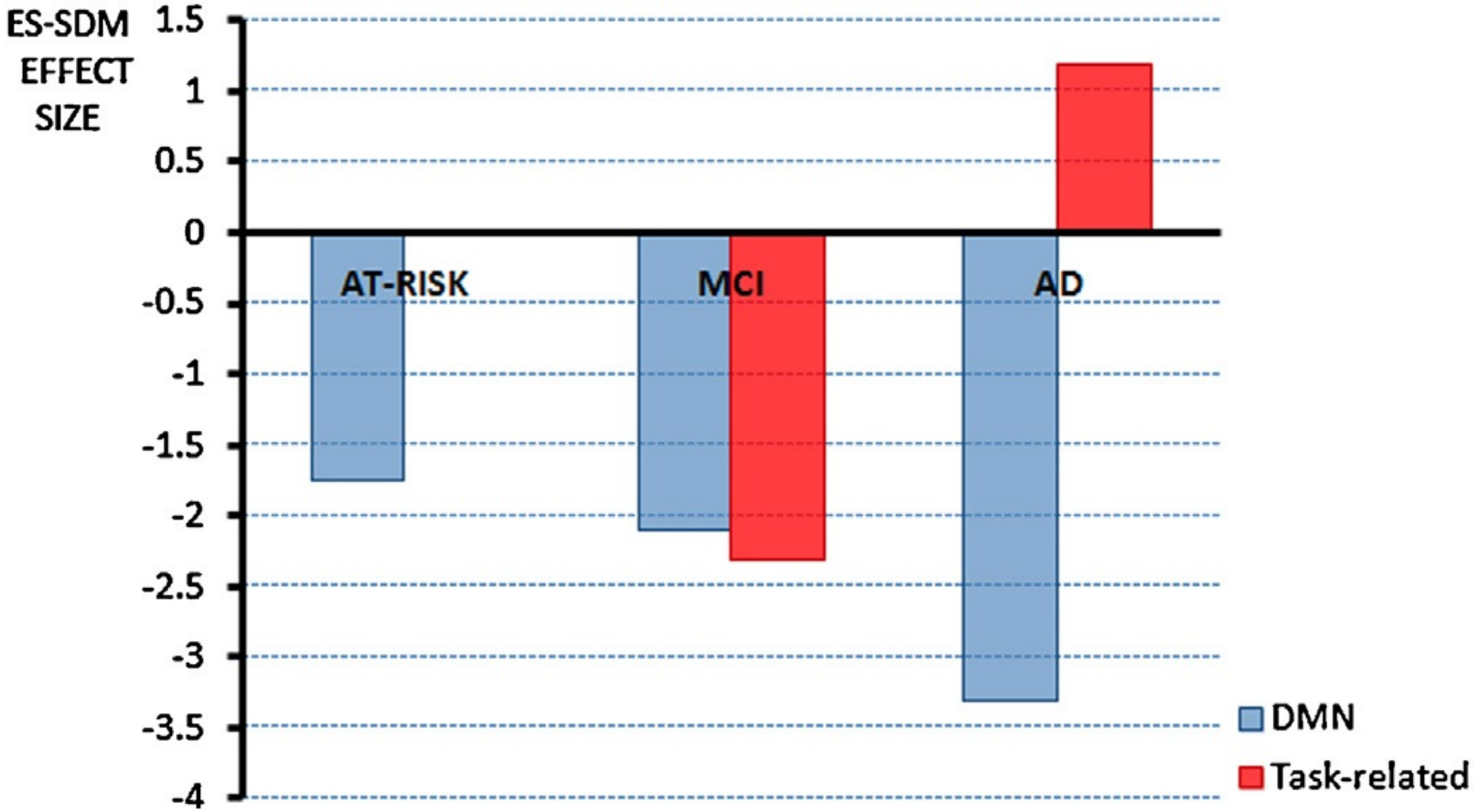
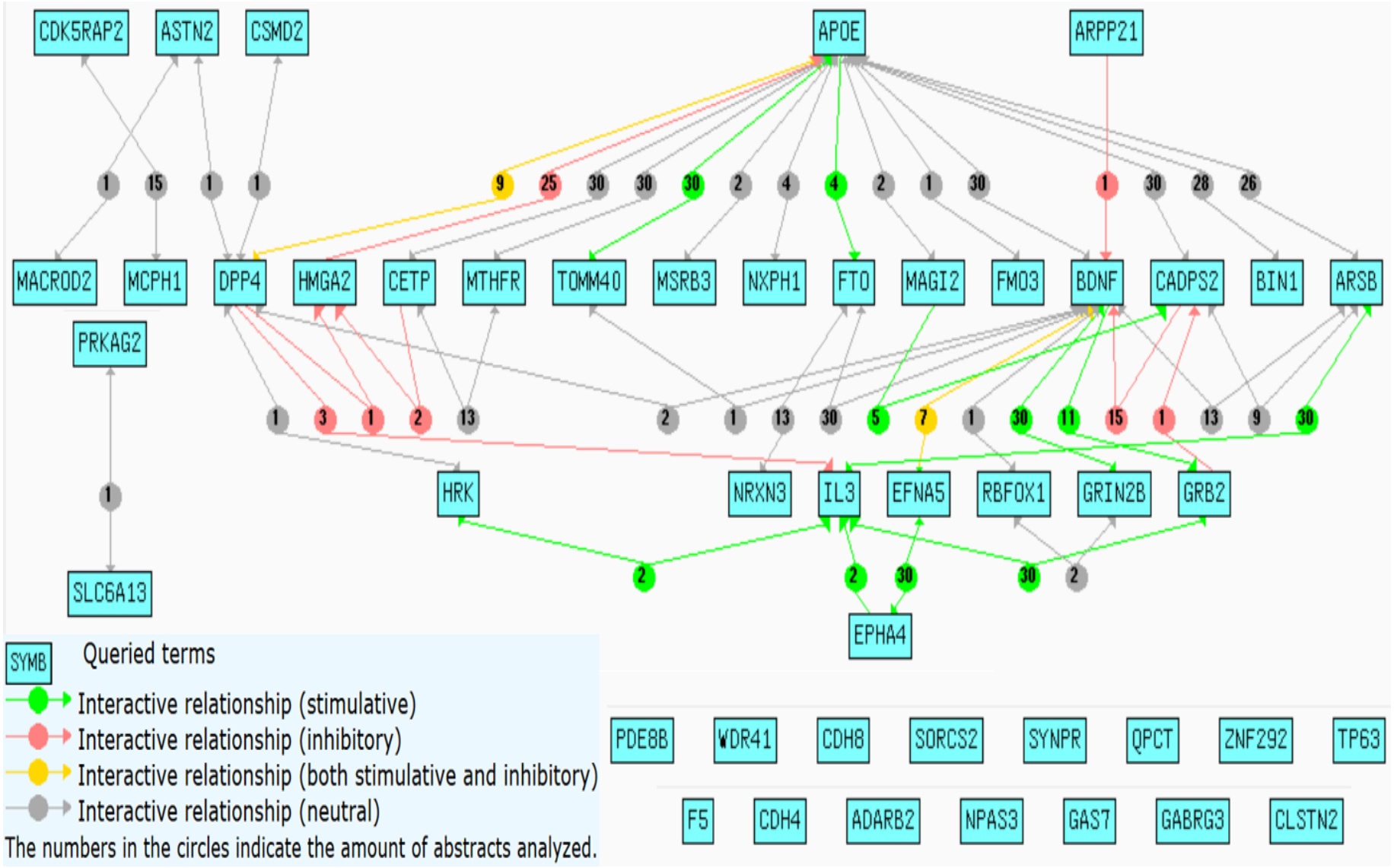


Fig. 4. Effect-size of the modulation between DMN connectivity and task-related activation in the medial parietal areas (posterior cingulate cortex/precuneus) vs controls. Blue: DMN connectivity; Red: task related activation (NS).

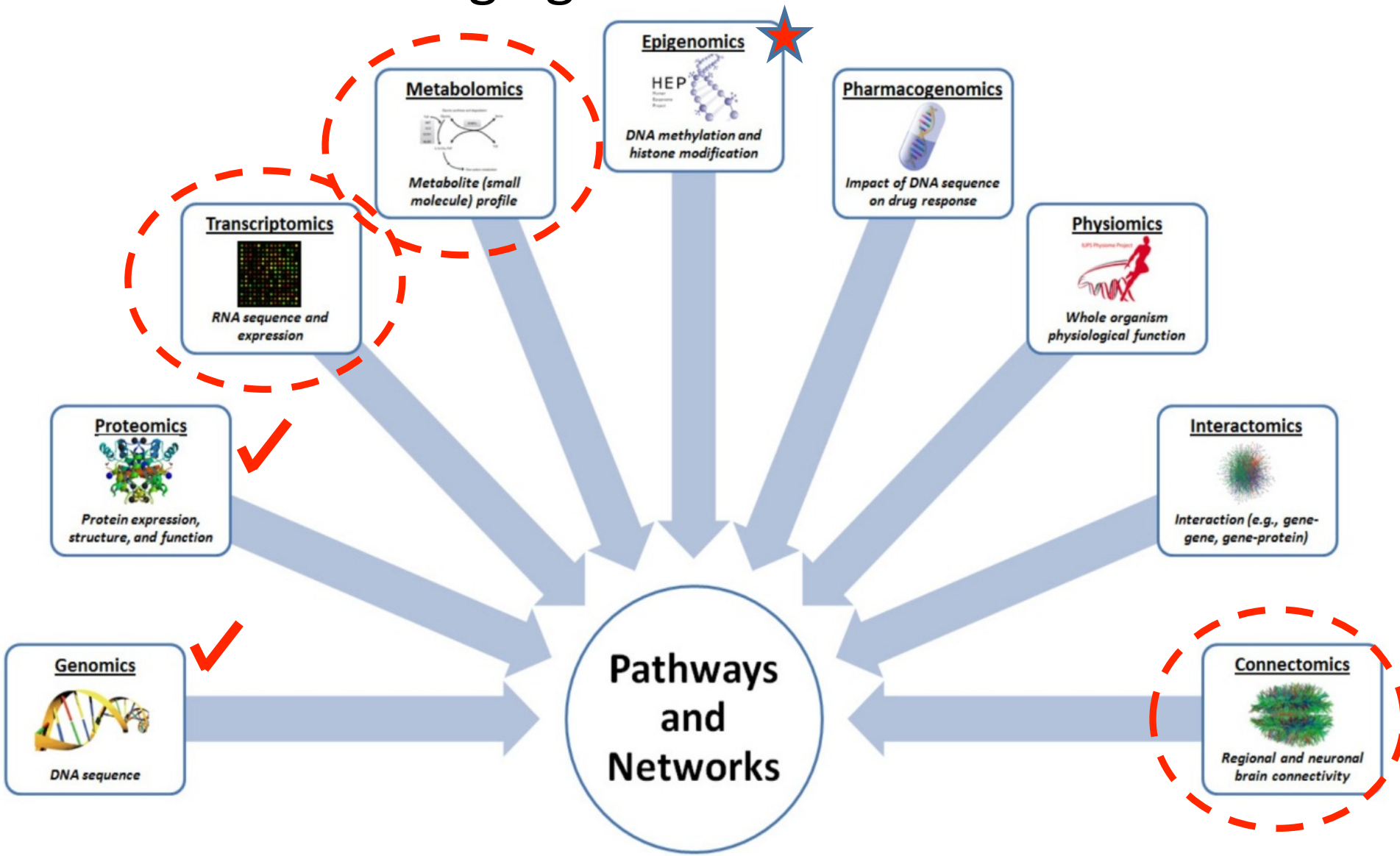
Jacobs et al, Neurosci Biobehav Rev, 2013. 37(5):753-65.

Gene Network Analysis: ADNI Phenotypes



Shen et al *Brain Imaging and Behavior* (2013): Review of Published Genetic Studies using ADNI Multimodality Quantitative Phenotypes: MRI, PET, Fluid Biomarkers, Cognition, and Clinical Status

Converging -*omics* in AD Research



Ramanan & Saykin, Pathways to Neurodegeneration…, AJND (2013);
Adapted from Ramanan et al, Trends in Genetics, 28(7):323-332.

Alzheimer's Disease: Network Perspectives

- Alzheimer's Disease
  - A complex disorder: Snapshot of the science
  - Prodromal stages: Subjective Cognitive Decline & Mild Cognitive Impairment
- Brain Networks – The Connectome
- Biomarker Networks (phenotype clusters)
- Gene Pathways, Networks & Systems Biology
- **Social Networks**
  - Families, Communities, Healthcare systems, Provider networks, Social media, Science of Science, ELSI issues

Social Networks, Alzheimer's Disease & Aging

- Families & Caregivers
- Healthcare systems and Provider networks
- Communities
- Economy
- Social media
- Science of Science
- Ethical, legal & social issues
  - Return of results from genetic and imaging tests
  - End of life care and decisions

Healthcare Provider Networks

IDND
FROM DISCOVERY TO DELIVERY.

Indianapolis Discovery Network for Dementia

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Cognitive Assessment to Be Included in the Medicare Annual Wellness Exam

An assessment of cognitive impairment will be a mandatory part of the annual wellness visit for Medicare beneficiaries beginning January 2011, as part of passage of comprehensive health care reform legislation known as the Patient Protection and Affordable Care Act.

In October 2007, IDND launched the RAPID-PC tools – Recognizing and Assessing the Progression of Cognitive Impairment and Dementia in Primary Care with a summit meeting for researchers, clinicians, nurses, nurse practitioners and physician assistants to share experiences and progress.

RAPID-PC TOOLS

1 2 3 4

CALENDAR OF EVENTS

OCTOBER 2014

S	M	T	W	T	F	S
28	29	30	1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31	1
2	3	4	5	6	7	8

No Events are scheduled for this Month!

More...

LAST MONTH NEXT MONTH

GOAL #1
Build a local, diverse, and sustainable "Think-Tank" of health care providers, clinical researchers, and community advocates.

GOAL #2
To become an international authority in unifying clinical care and clinical research in dementia.

GOAL #3
Create an environment that facilitates information exchange among diverse, autonomous, and collaborative individuals.

GOAL #4
Enhance the quality of life and care of individuals with Dementia.

MAILING LIST

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NEWS
(Click Links to visit Pages)

Registration open for the upcoming Memory University 2014

Registration open for Indiana Alzheimer Disease Center symposium

Developed by Malaz Boustani MD and Colleagues

Social Networks, Cognition & AD Pathology

The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study

David A Bennett, Julie A Schneider, Yuxiao Tang, Steven E Arnold, Robert S Wilson

Lancet Neurol 2006; 5: 406–12

Published Online
April 4, 2006
DOI:10.1016/S1474-4422(06)
70417-3

Rush Alzheimer's Disease Center (D A Bennett MD, J A Schneider MD, R S Wilson PhD), **Department of Neurological Sciences** (D A Bennett, J A Schneider, R S Wilson), **Department of Pathology** (J A Schneider), **Department of Behavioral Science** (R S Wilson), **and Rush Institute for Healthy Aging and Department of Internal Medicine** (Y Tang PhD), **Rush University Medical Center, Chicago, IL, USA; and Center for Neurobiology and Behavior, University of Pennsylvania, Philadelphia, PA, USA** (S E Arnold MD)

Correspondence to:
Dr David A Bennett, Rush Alzheimer's Disease Center, Rush University Medical Center, 600 S

Summary

Background Few data are available about how social networks reduce the risk of cognitive impairment in old age. We aimed to measure this effect using data from a large, longitudinal, epidemiological clinicopathological study.

Methods 89 elderly people without known dementia participating in the Rush Memory and Aging Project underwent annual clinical evaluation. Brain autopsy was done at the time of death. Social network data were obtained by structured interview. Cognitive function tests were Z scored and averaged to yield a global and specific measure of cognitive function. Alzheimer's disease pathology was quantified as a global measure based on modified Bielschowsky silver stain. Amyloid load and the density of paired helical filament tau tangles were also quantified with antibody-specific immunostains. We used linear regression to examine the relation of disease pathology scores and social networks to level of cognitive function.

Findings Cognitive function was inversely related to all measures of disease pathology, indicating lower function at more severe levels of pathology. Social network size modified the association between pathology and cognitive function (parameter estimate 0·097, SE 0·039, p=0·016, R^2=0·295). Even at more severe levels of global disease pathology, cognitive function remained higher for participants with larger network sizes. A similar modifying association was observed with tangles (parameter estimate 0·011, SE 0·003, p=0·001, R^2=0·454). These modifying effects were most pronounced for semantic memory and working memory. Amyloid load did not modify the relation between pathology and network size. The results were unchanged after controlling for cognitive, physical, and social activities, depressive symptoms, or number of chronic diseases.

Interpretation These findings suggest that social networks modify the relation of some measures of Alzheimer's disease pathology to level of cognitive function.

Bennett et al, *The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study.* Lancet Neurol, 2006;5(5):406-12.

Social Networks, Cognition & AD Pathology

The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study

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Rush Alzheimer's Disease Center (D A Bennett MD, J A Schneider MD, R S Wilson PhD), Department of Neurological Sciences (D A Bennett, J A Schneider, R S Wilson), Department of Pathology (J A Schneider), Department of Behavioral Science (R S Wilson), and Rush Institute for Healthy Aging and Department of Internal Medicine (Y Tang PhD), Rush University Medical Center, Chicago, IL, USA; and Center for Neurobiology and Behavior, University of Pennsylvania, Philadelphia, PA, USA (S E Arnold MD)

Correspondence to: Dr David A Bennett, Rush Alzheimer's Disease Center, Rush University Medical Center, 600 S

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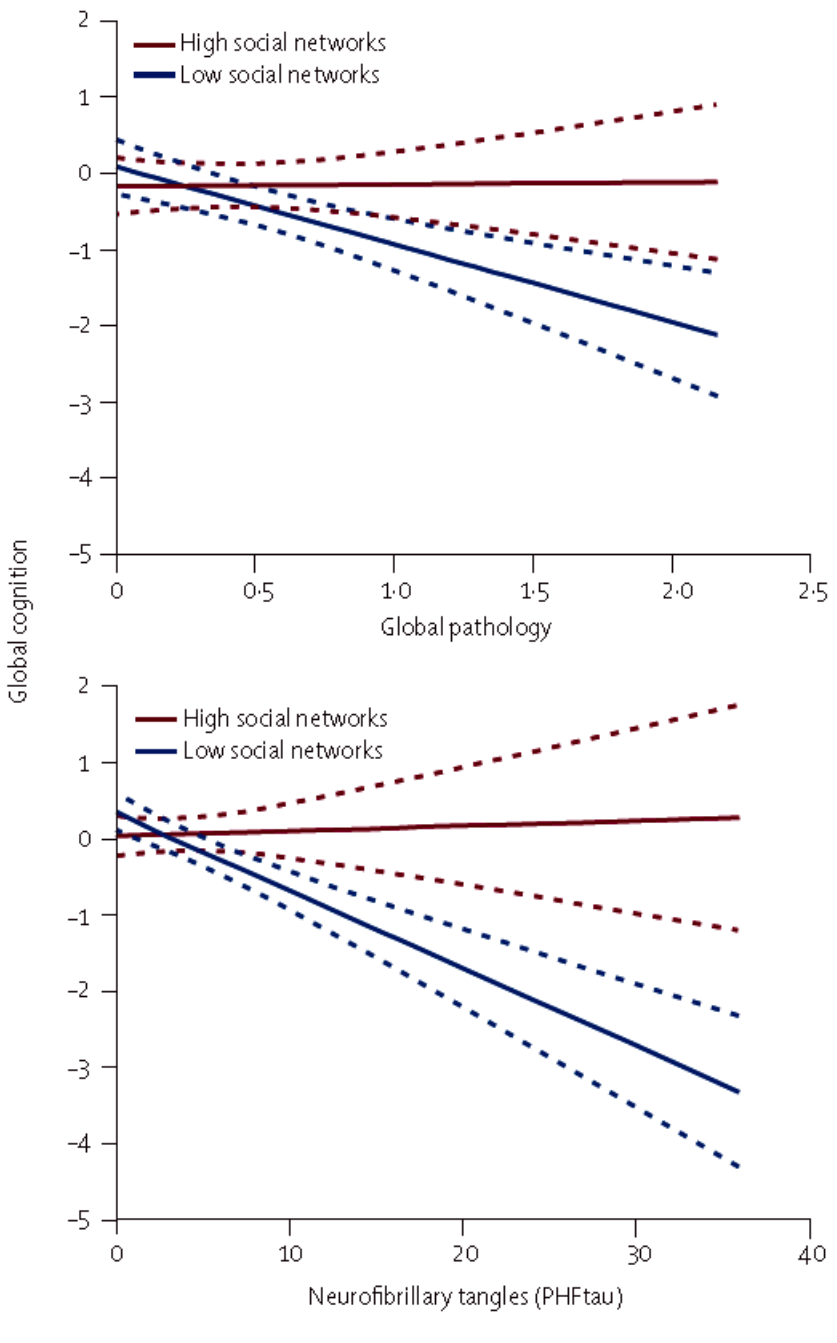

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Science of Science

Original Investigation

The Growth and Impact of Alzheimer Disease Centers as Measured by Social Network Analysis

Michael E. Hughes, PhD; John Peeler, BA; John B. Hogenesch, PhD; John Q. Trojanowski, MD, PhD

IMPORTANCE Alzheimer disease (AD) is a neurodegenerative disorder with no effective therapies. In 1984, the National Institute on Aging created the first 5 AD centers (ADCs) in an effort to coordinate research efforts into the pathology and treatment of the disease. Since that time, the ADC program has expanded to include 27 centers in major medical schools throughout the United States. A major aim of ADCs is to develop shared resources, such as tissue samples and patient populations, and thereby promote large-scale, high-impact studies that go beyond the capabilities of any single investigator or institution working in isolation.

OBJECTIVE To quantitatively evaluate the performance of the ADC program over the past 25 years.

DESIGN AND SETTING We systematically harvested every article published by ADC investigators and used social network analysis to analyze copublication networks.

RESULTS A total of 12 170 ADC papers were published from 1985 through 2012. The frequency of collaborations has increased greatly from the time that the ADCs were started until the present, even after the expansion of ADCs and the recruitment of new investigators plateaued. Moreover, the collaborations established within the context of the ADC program are increasingly interinstitutional, consistent with the overall goal of the program to catalyze multicenter research teams. Most important, we determined that collaborative multi-ADC research articles are consistently of higher impact than AD articles as a whole.

CONCLUSIONS AND RELEVANCE The ADC program has successfully fostered high-impact, multiuniversity collaborations; we suggest that its structural and administrative features could be replicated in other fields of patient-oriented research.

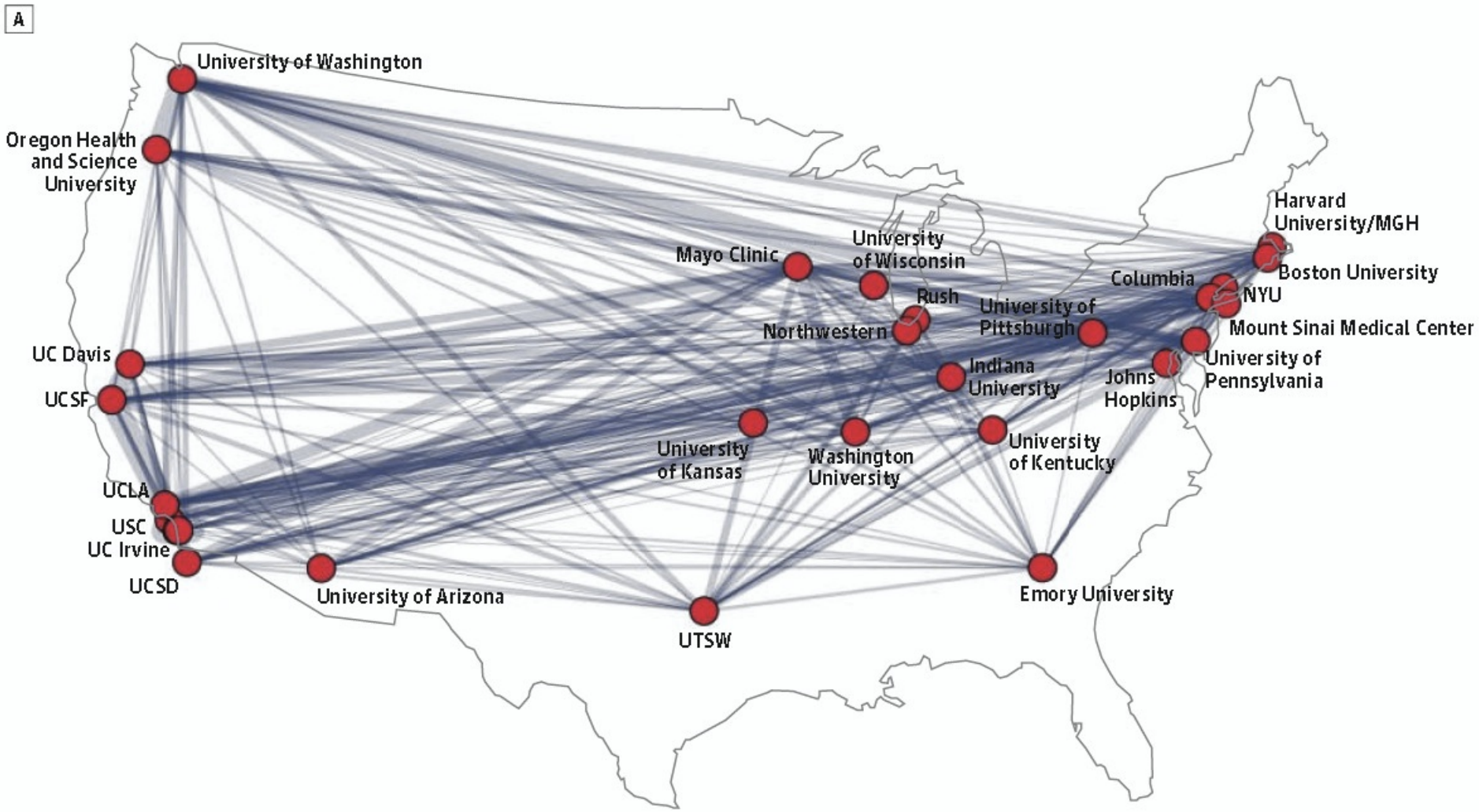
JAMA Neurol. 2014;71(4):412-420. doi:10.1001/jamaneurol.2013.6225
Published online February 10, 2014.

Author Affiliations: Institute for Translational Medicine and Therapeutics, University of Pennsylvania School of Medicine, Philadelphia (Hughes, Peeler, Hogenesch); Department of Biology, University of Missouri–St Louis (Hughes); Department of Pharmacology, University of Pennsylvania School of Medicine, Philadelphia (Hogenesch); Center for Neurodegenerative Disease Research, Philadelphia, Pennsylvania (Trojanowski); Department of Pathology and Laboratory Medicine, Institute on Aging, University of Pennsylvania School of Medicine, Philadelphia (Trojanowski).

Corresponding Author: Michael E. Hughes, PhD, Department of Biology, University of Missouri–St Louis, One University Blvd, Research 223, St Louis, MO 63121

Scientific Impact of NIA AD Centers

Figure 3. Interaction Networks Between Different Alzheimer Disease Centers (ADCs)



Hughes et al, *JAMA Neurology* April 2014 Volume 71, Number 4

Conclusions & Future Directions

- Network concepts and methods has great applicability for Alzheimer's research
- Potential contributions in many areas:
  - Gene pathways and networks
    - NGS, transcriptome, proteome, metabolome, methylome and beyond
    - The diseasome – commonalities and specificity across complex disorders
  - Target identification for drug discovery
  - Structural and functional brain networks
    - Connectome biomarkers – need to be robust & reproducible on an individual vs group basis
  - Social networks of all kinds
- Major challenges for network approaches:
  - Improve early detection/diagnosis?
  - Discover novel agents for therapeutics & prevention?
  - Elucidate broader scientific relationships across domains of biological, brain and social networks?

Network Approach vs 1 Piece at a Time?

Subjective Cognitive Decline
Informant Perception

Amyloid PET/CSF
Tau PET/CSF

Cognitive Performance

MRI - structure
MRI - function
Connectome

Lifestyle & environment
- Cognitive stimulation, diet, exercise, sleep, social networks

Vascular function & disease

Biomarkers
- CSF, blood, others

Immune System, Inflammation & Oxidative Stress

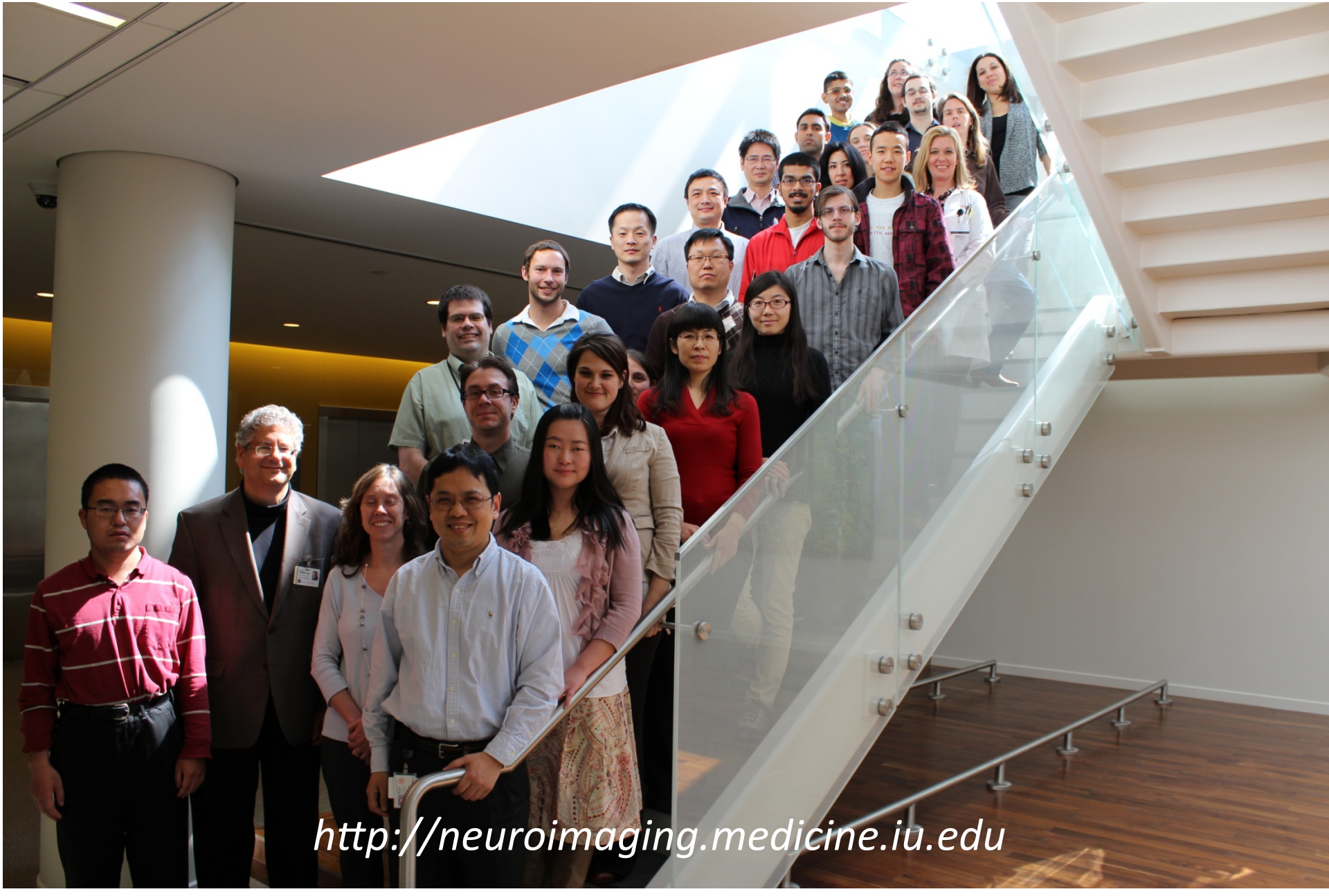
Genomics
- DNA
- RNA
- Epigenetics

Therapeutics & Prevention

Saykin 2014

Indiana Alzheimer Disease Center

IU Center for Neuroimaging



http://neuroimaging.medicine.iu.edu

Genetics Core/Working Group

Indiana University

- Imaging Genomics Lab
  - Andrew Saykin (Leader)
  - Li Shen (co-Leader)
  - Sungeun Kim
  - Kwangsik Nho
  - Shannon Risacher
  - Vijay Ramanan
  - Priya Rajagopalan
- National Cell Repository for AD
  - Tatiana Foroud (co-Leader)
  - Kelley Faber

PPSB Working Group Members

- Xiaolan Hu (BMS)
- Enchi Liu (Janssen)
- Leanne Munsie (Lilly) *
- Qingqin Li (J&J)
- Nadeem Sarwar (Eisai) *
- Adam Schwarz (Lilly)
- Holly Soares (BMS)
- Dave Stone (Merck)
- Erika Tarver (FNIH)

* Genetics Core Liaisons

- Core Collaborators/Consultants
  - Steven Potkin (UCI; co-Leader)
  - Lars Bertram (Max Planck)
  - Lindsay Farrer (BU)
  - Robert Green (BWH)
  - Matt Huentelman (TGen)
  - Jason Moore (Dartmouth)
  - Paul Thompson (USC)
- Other Collaborators – RNA and NGS Projects:
  - Liana Apostolova (UCLA)
  - Nilufer Ertekin-Taner (Mayo Clinic)
  - Keoni Kauwe (BYU)
  - Yunlong Liu (Indiana)
  - Fabio Macciardi (UC Irvine)

2014

IU Health Neuroscience Center