

Bioinformatics Strategies for Multidimensional Brain Imaging Genetics

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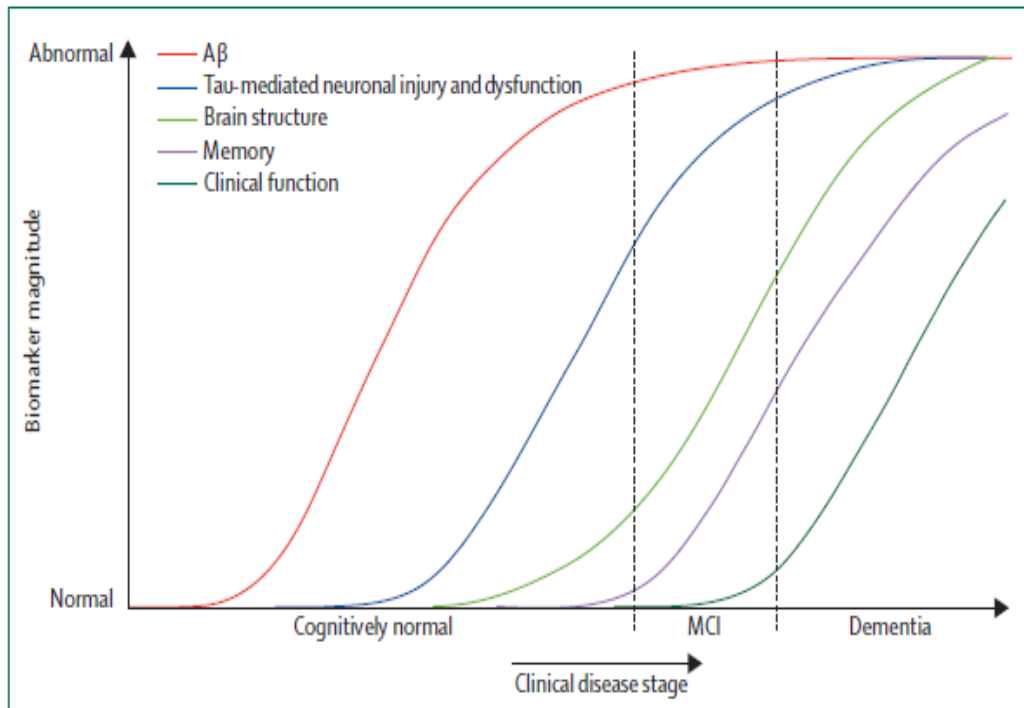
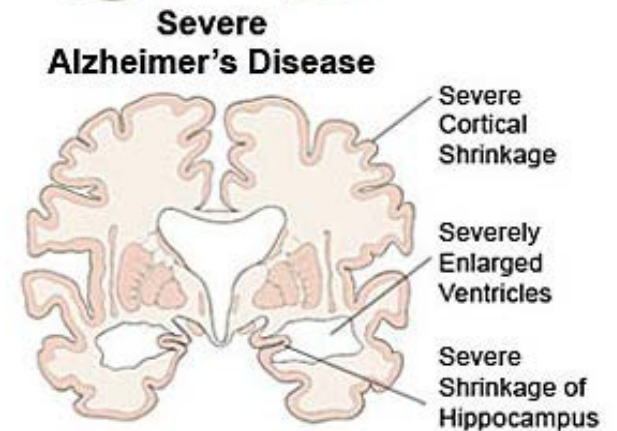
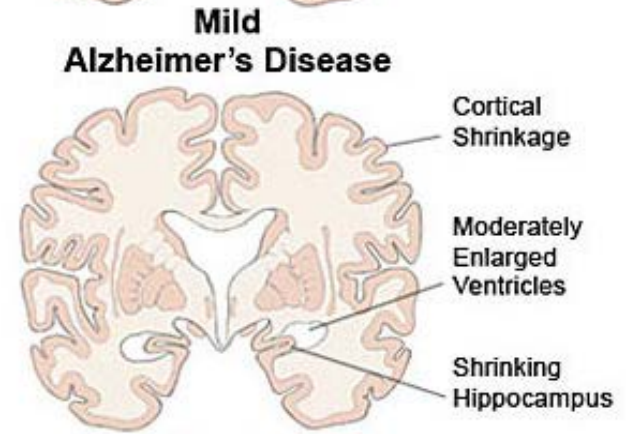
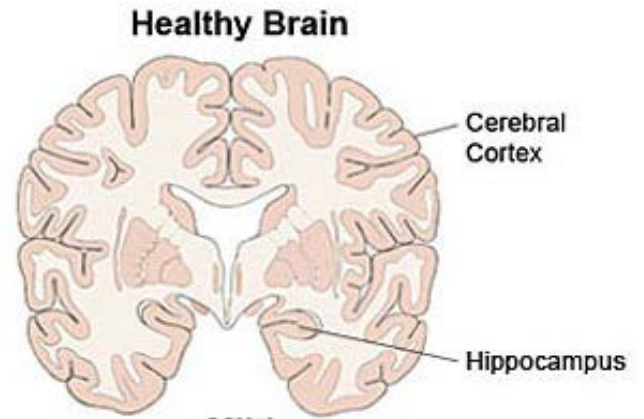
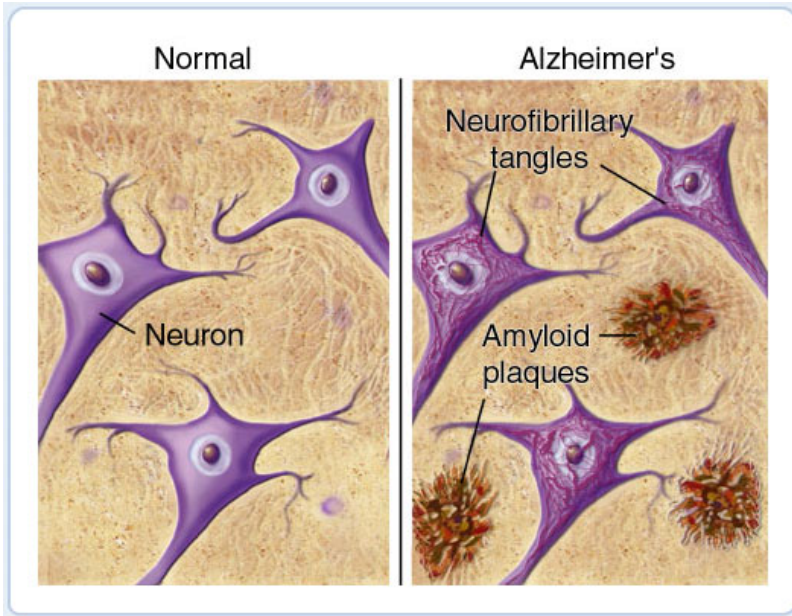
Indiana University School of Medicine



MICGen: MICCAI Workshop on Imaging Genetics, 9/14/2014

Outline

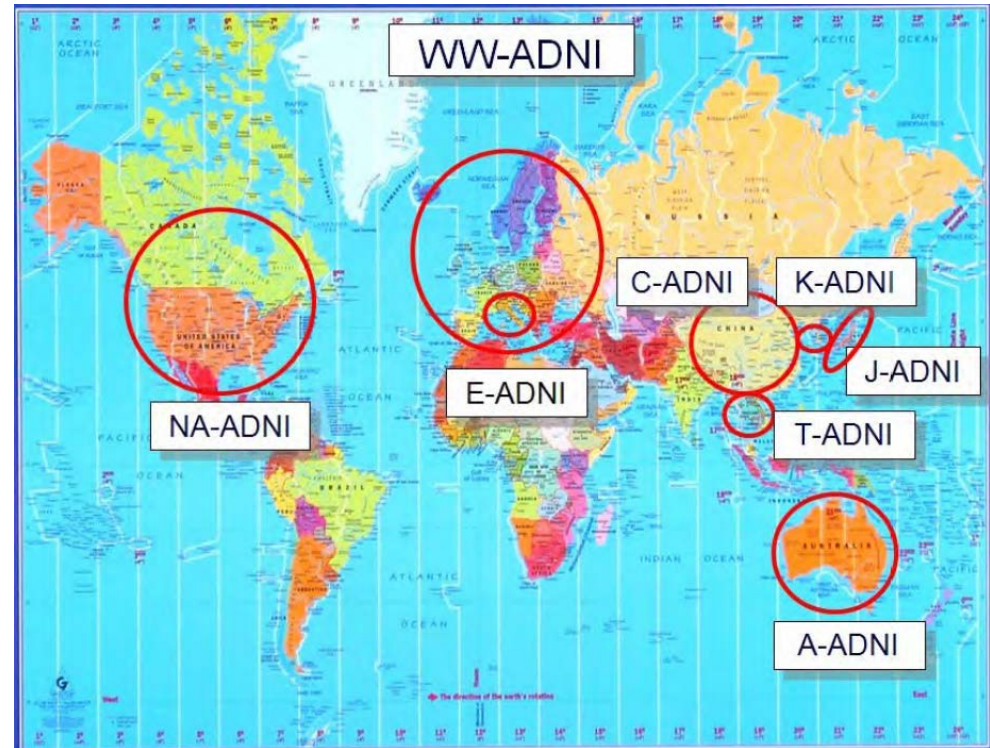
- Neuroimaging Genomics
- ADNI Genetics Review
- Example Study
- Major Findings and Discussion



ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE



CLINICAL DATA	GENETICS DATA
<ul style="list-style-type: none"> Demographics Clinical Assessments Cognitive Assessments 	<ul style="list-style-type: none"> Illumina SNP genotyping
MR IMAGE DATA	PET IMAGE DATA
<ul style="list-style-type: none"> Raw, pre- and post- processed image files fMRI (ADNI GO/ADNI2) DTI (ADNI GO/ADNI2) 	<ul style="list-style-type: none"> Raw, pre- and post- processed image files PIB (ADNI1) FDG (ADNI1/GO/2) Florbetapir (ADNI GO/2)
IMAGE ANALYSIS RESULTS	CHEMICAL BIOMARKER
<ul style="list-style-type: none"> Numeric results derived from image analyses MRI Analysis PET Analysis 	<ul style="list-style-type: none"> Laboratory Results Proteomic Analysis



	Normal	EMCI	MCI	LMCI	AD	MRI	fMRI	DTI	FDG	AV45	PIB	Biosamples
ADNI 1	200	-	400	-	200	✓			✓		✓	✓
ADNI GO	↓	200	↓	-	-	✓	✓	✓	✓	✓		✓
ADNI 2	150	150	↓	150	200	✓	✓	✓	✓	✓		✓



Overview of ADNI Genetics

Alzheimer's
&
Dementia

Alzheimer's & Dementia 6 (2010) 265–273

Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: Genetics core aims, progress, and plans

Andrew J. Saykin^{a,b,*}, Li Shen^{a,c}, Tatiana M. Foroud^b, Steven G. Potkin^d,
Shanker Swaminathan^{a,b}, Sungeun Kim^{a,c}, Shannon L. Risacher^a, Kwangsik Nho^{a,c},
Matthew J. Huentelman^f, David W. Craig^f, Paul M. Thompson^g, Jason L. Stein^g, Jason H. Moore^{h,i},
Lindsay A. Farrer^j, Robert C. Green^j, Lars Bertram^k, Clifford R. Jack, Jr.^l,
Michael W. Weiner^{m,n,o,p}; and the Alzheimer's Disease Neuroimaging Initiative



Saykin et al (2010) Alzheimer's & Dementia

Human Genome and SNP

- ❑ SNP (Single Nucleotide Polymorphism) - single nucleotide site where two or more different nucleotides occur in a large percentage of population.
- ❑ Total number of SNP (09/13/2014): [Entrez SNP](#)

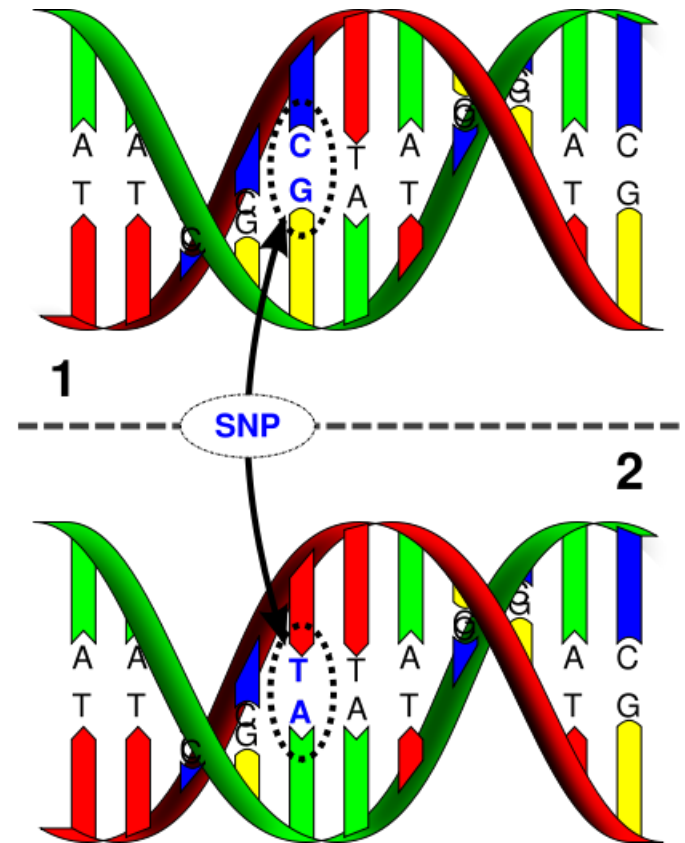
⚠ Limits Activated: homo sapiens, snp [Change](#) | [Remove](#)

Results: 1 to 20 of 61935139

❑ [rs34039386](#) [*Homo sapiens*]

1.

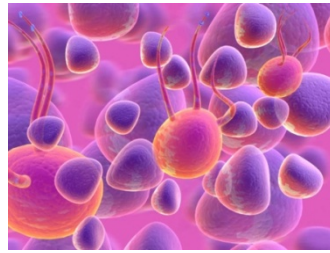
TCTGACCACCTGCAGGAAGGAAGGC [A/G] GTGACCTYRCAZ



Imaging Genetics



Genes

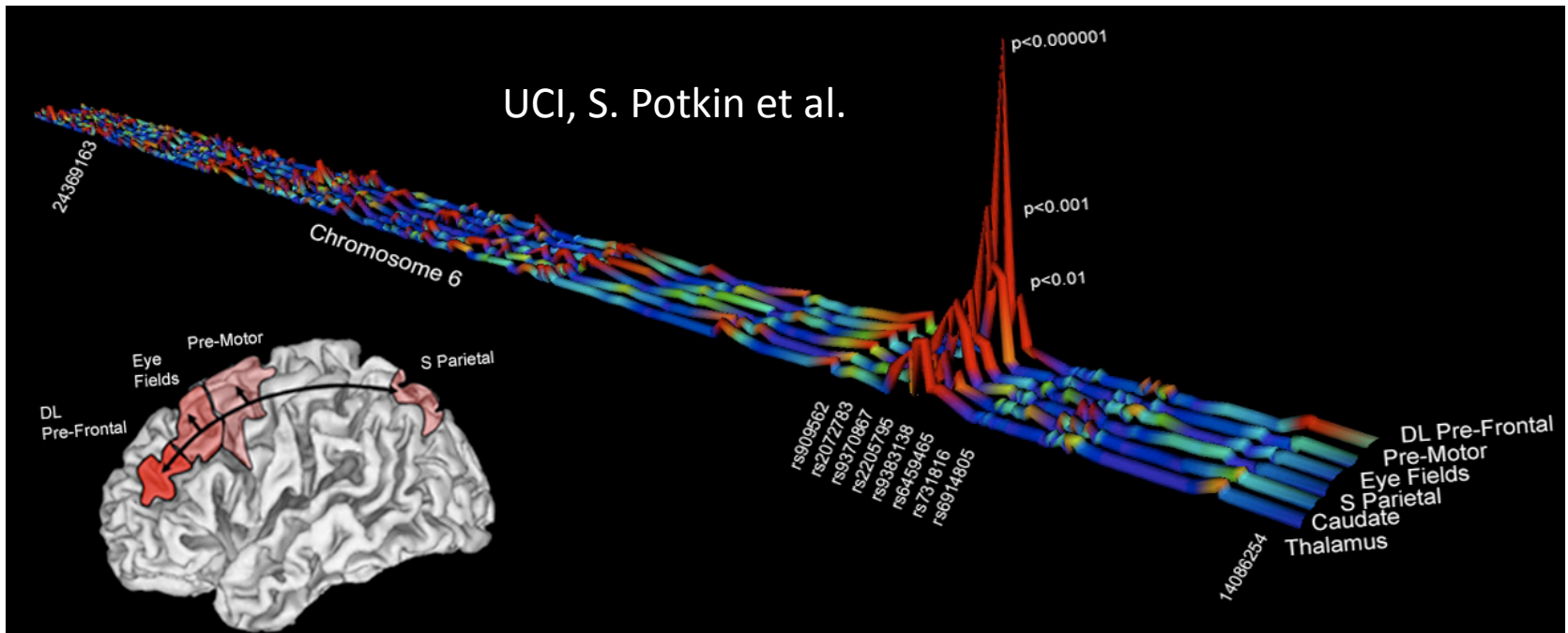


Cells



Systems

Behavior:
Disorders,
Complex
interactions,
phenomena,
diseases.



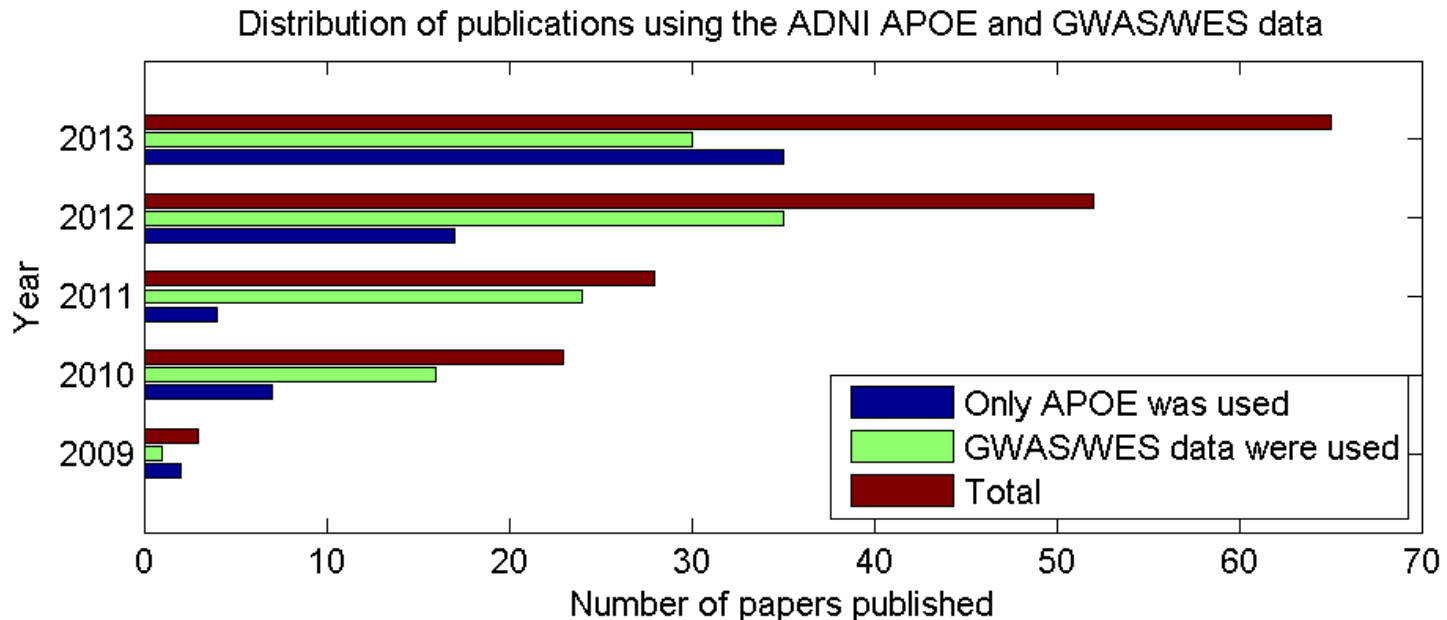
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Publications using ADNI Genetics Data

ADNI Genetics Papers:

$$3 (2009) + 23 (2010) + 28 (2011) + 52 (2012) + 65 (2013) = 171$$



Distribution of publications using the ADNI APOE and GWAS/WES genotyping data between 2009 and 2013: Of the 171 papers, 65 papers used only APOE data, and 106 papers used GWAS data.

Classification by Genotype (2013 Papers)

Genotype	#	Example Paper	
APOE alone	35	Risacher, Kim, et al. 2013, Front Aging Neurosci	The role of apolipoprotein E (APOE) genotype in early mild cognitive impairment (E-MCI)
CNVs	1	Guffanti, Torri, et al. 2013, Genomics	Increased CNV-Region deletions in mild cognitive impairment (MCI) and Alzheimer's disease (AD) subjects in the ADNI sample
SNPs	13	Kim, Swaminathan, et al. 2013, PLoS One	Influence of genetic variation on plasma protein levels in older adults using a multi-analyte Panel
Gene/Pathways	10	Kohannim, Hua, et al. 2013, Neuroimage Clin	Multilocus genetic profiling to empower drug trials and predict brain atrophy
GWAS	9	Sherva, Tripodis, et al. 2013, Alzheimers Dement	Genome-wide association study of the rate of cognitive decline in Alzheimer's disease
Sequencing	2	Nho, Kim, et al. 2013, Mol Psychiatry	Whole-exome sequencing and imaging genetics identify functional variants for rate of change in hippocampal volume in mild cognitive impairment

Classification by Phenotype (2013 Papers)

Phenotype	#	Example Paper	
Case Control	4	Boada, Antunez, et al. 2013, Mol Psychiatry	ATP5H/KCTD2 locus is associated with Alzheimer's disease risk
Structural Imaging (sMRI, dMRI)	27	Hibar, Stein, et al. 2013, Brain Imaging Behav	Genome-wide association identifies genetic variants associated with lentiform nucleus volume in N=1345 young and elderly subjects
Functional Imaging (fMRI, PET)	14	Swaminathan, Risacher, et al. 2013, Alzheimers Dement	Association of plasma and cortical amyloid beta is modulated by APOE ε4 status
Fluid (CSF, Blood)	14	Cruchaga, Kauwe, et al. 2013, Neuron	GWAS of Cerebrospinal Fluid Tau Levels Identifies Risk Variants for Alzheimer's Disease
Neuropsychological Assessments	19	Chang, Fennema-Notestine, et al. 2013, Alzheimers Dement	APOE interacts with age to modify rate of decline in cognitive and brain changes in Alzheimer's disease

Classification by Method (2013 Papers)

Method	#	Example Paper	
Univariate Analysis	19	Benitez, Karch, et al. 2013, PLoS Genet	The PSEN1, p.E318G Variant Increases the Risk of Alzheimer's Disease in APOE-e4 Carriers
Multivariate Analysis	19	Bryant, Giovanello, et al. 2013, PLoS One	Mapping the Genetic Variation of Regional Brain Volumes as Explained by All Common SNPs from the ADNI Study
Meta Analysis	6	Lambert, Ibrahim-Verbaas, et al. 2013, Nat Genet	Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease
Pathway Analysis	4	Mukherjee, Kim, et al. 2013, Brain Imaging Behav	Gene-based GWAS and biological pathway analysis of the resilience of executive functioning
Interaction and Network Analysis	2	Meda, Koran, et al. 2013, Neurobiol Aging	Genetic interactions associated with 12-month atrophy in hippocampus and entorhinal cortex in Alzheimer's Disease Neuroimaging Initiative
Prediction and Progression	22	Gray, Aljabar, et al. 2013, Neuroimage	Random forest-based similarity measures for multi-modal classification of Alzheimer's disease

Reviews (2013 Papers)

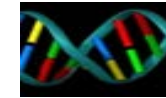
Review	#	Example Paper	
ADNI Findings	2	Weiner, Veitch, et al. 2013, Alzheimers Dement	The Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception
ADNI Genetics Findings		Shen, Thompson, et al. 2013, Brain Imaging Behav	Genetic analysis of quantitative phenotypes in AD and MCI: imaging, cognition and biomarkers

Brain-Genome Association Strategies

Candidate Gene/SNP

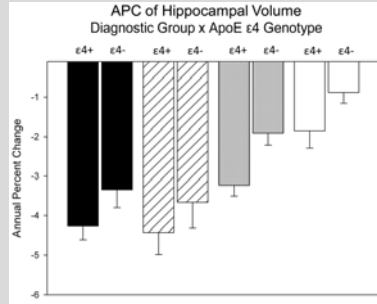


Biological Pathway/Network



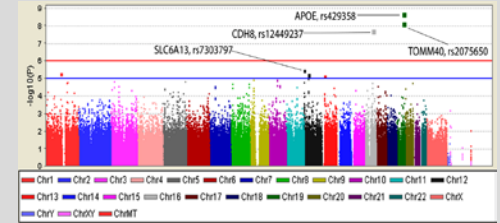
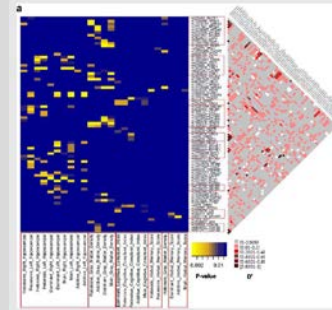
Genome-wide Analysis

ROI



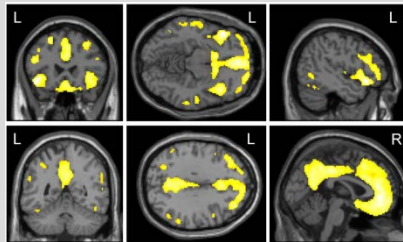
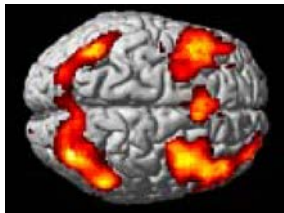
Risacher et al 2010

Sloan et al 2010

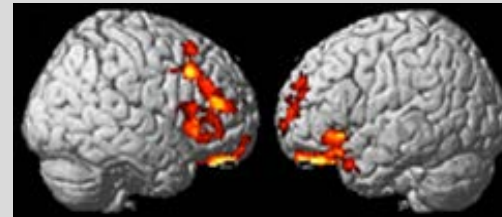


Potkin et al 2009;
Saykin et al 2010

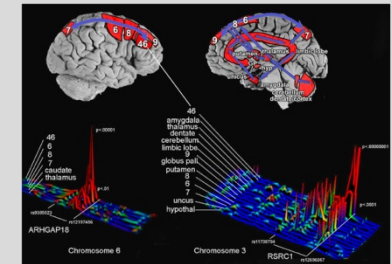
Circuit



Risacher et al 2013
AV45 ROIs & APOE

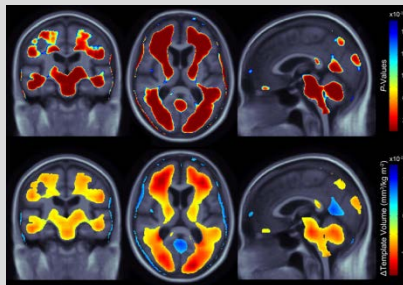
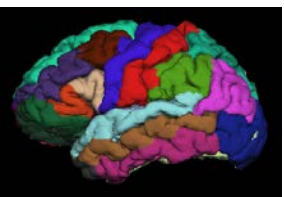


Swaminathan et al 2012 PiB
ROIs & amyloid pathway

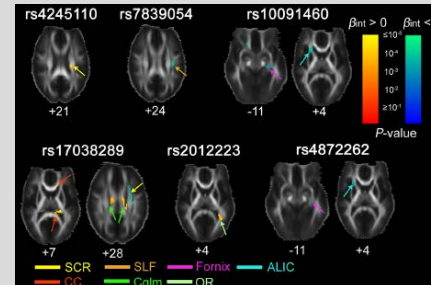


Potkin et al 2009 Mol Psych
schizophrenia study

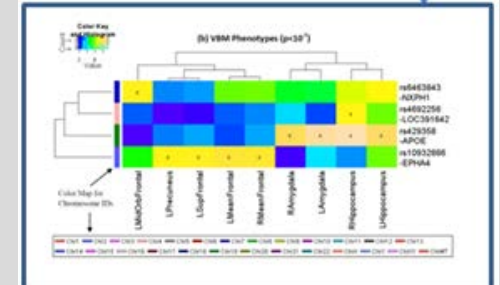
Whole Brain



Ho et al 2010 FTO;
Reiman et al PNAS 2009



Chiang et al 2012 SNP/Gene
networks & WM integrity



Shen et al 2010 ROIs;
Stein et al 2010 voxels

Outline

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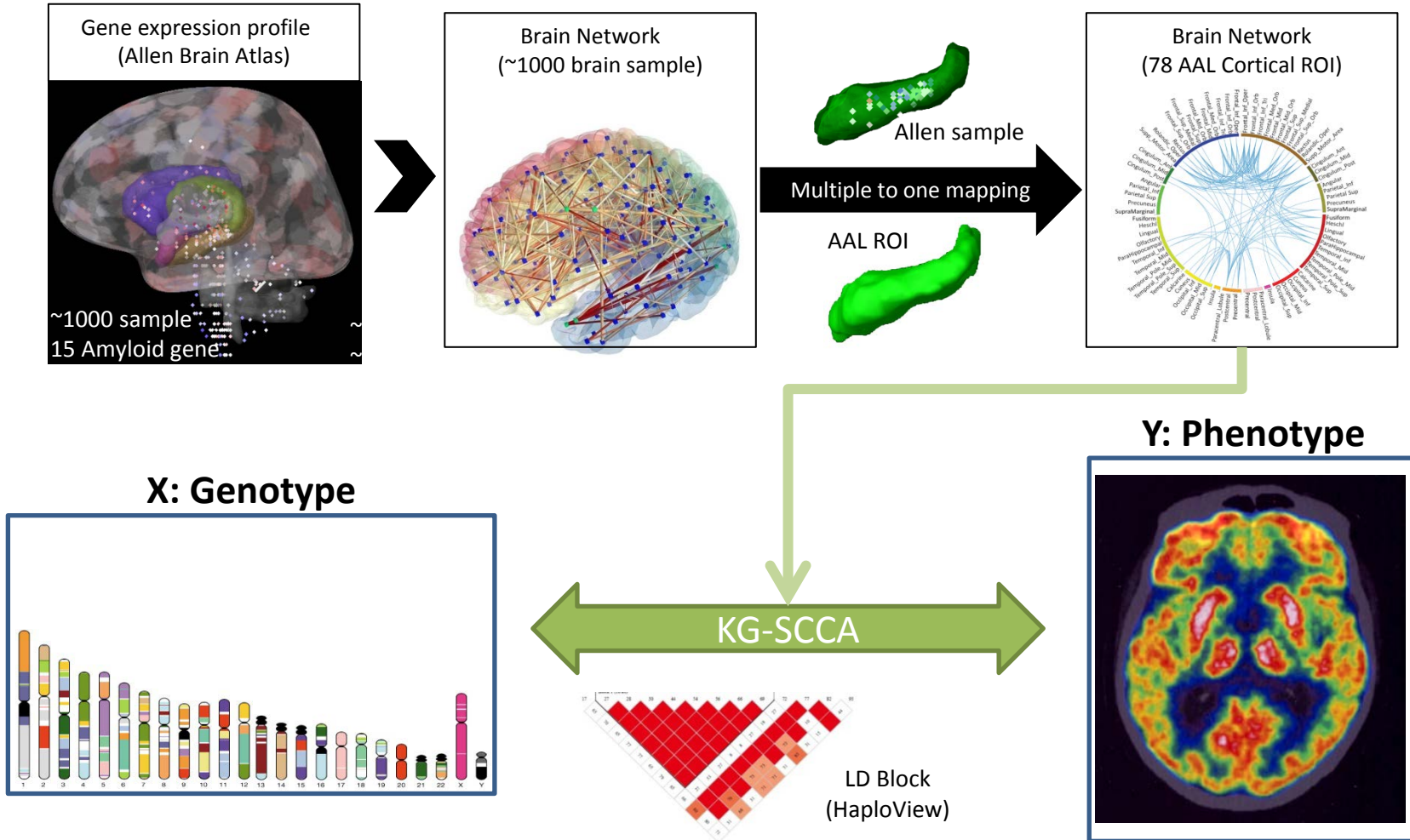
Transcriptome-Guided Amyloid Imaging Genetic Analysis via A Novel Structured Sparse Learning Algorithm

Jingwen Yan, Lei Du, Sungeun Kim, Shannon L. Risacher, Heng Huang, Jason H. Moore, Andrew J. Saykin, Li Shen, and for the Alzheimer's Disease Neuroimaging Initiative

Introduction

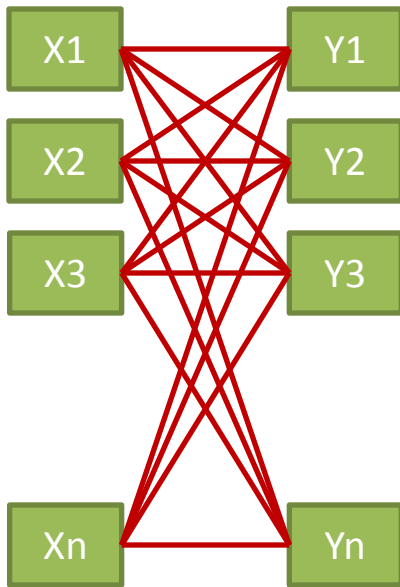
- Bi-multivariate associations
 - Genotype: APOE SNPs
 - Phenotype: Amyloid imaging
- Prior knowledge
 - LD structures in the genome
 - Network structure in the brain
 - Whole brain transcriptomics
- Knowledge-guided SCCA

Overview



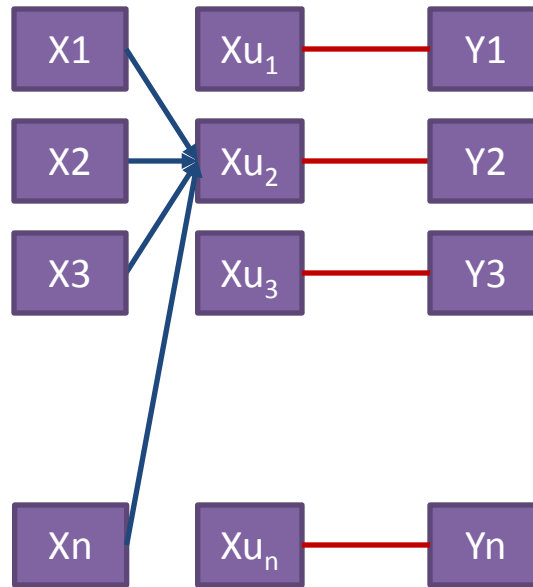
Imaging Genetics Strategies

Univariate



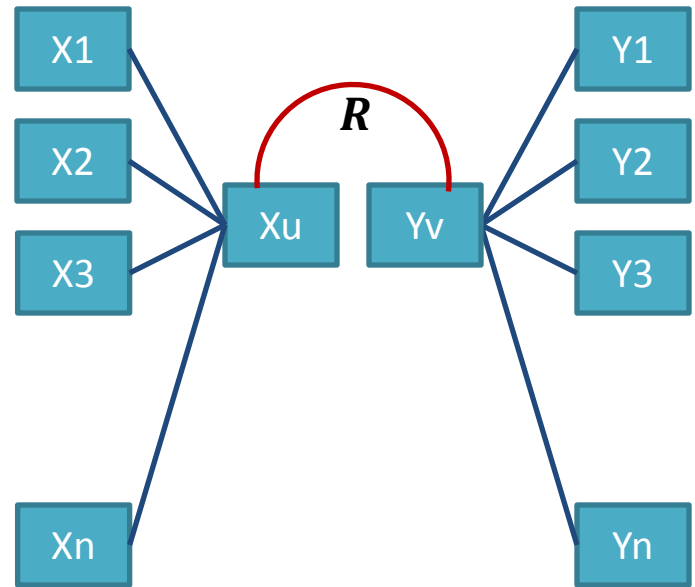
Pairwise Analysis

Multivariate



Multiple Regression

Bi-multivariate



Canonical Correlation Analysis

Sparse CCA

- Sparse canonical correlation analysis (SCCA)
 - R package: Penalized Multivariate Analysis (PMA)
(*Witten, et al, 2009*)

$$\max_{\mathbf{u}, \mathbf{v}} \mathbf{u}^T \mathbf{X}^T \mathbf{Y} \mathbf{v}$$

$$\text{subject to } \mathbf{u}^T \mathbf{X}^T \mathbf{X} \mathbf{u} = 1, \mathbf{v}^T \mathbf{Y}^T \mathbf{Y} \mathbf{v} = 1$$
$$P_1(\mathbf{u}) \leq c_1, P_2(\mathbf{v}) \leq c_2$$

- X, Y : imaging and genetics data respectively
- $P_1(\mathbf{u}), P_2(\mathbf{v})$: sparse penalties, mostly L_1 norm
- For simplicity, assuming $\mathbf{X}^T \mathbf{X} = \mathbf{I}$ and $\mathbf{Y}^T \mathbf{Y} = \mathbf{I}$
- Bi-convex and non differentiable problem
- Iterative solution

Sparse CCA

- Sparse canonical correlation analysis (SCCA)
 - Problem

$$\max_{\mathbf{u}, \mathbf{v}} \mathbf{u}^T \mathbf{X}^T \mathbf{Y} \mathbf{v}$$

$$\text{subject to } \mathbf{u}^T \mathbf{u} = 1, \mathbf{v}^T \mathbf{v} = 1, \|\mathbf{u}\|_1 \leq c_1, \|\mathbf{v}\|_1 \leq c_2$$

- Iterative solution

$$1. \mathbf{u} \leftarrow \arg \max_{\mathbf{u}} \mathbf{u}^T \mathbf{X}^T \mathbf{Y} \mathbf{v},$$
$$\text{subject to } \mathbf{u}^T \mathbf{u} = 1, \|\mathbf{u}\|_1 \leq c_1$$

$$2. \mathbf{v} \leftarrow \arg \max_{\mathbf{v}} \mathbf{u}^T \mathbf{X}^T \mathbf{Y} \mathbf{v},$$
$$\text{subject to } \mathbf{v}^T \mathbf{v} = 1, \|\mathbf{v}\|_1 \leq c_2$$

Assumption:
Independence
among data
features

- $\mathbf{u} \leftarrow \frac{\mathcal{S}(\mathbf{X}^T \mathbf{Y} \mathbf{v}, \Delta)}{\|\mathcal{S}(\mathbf{X}^T \mathbf{Y} \mathbf{v}, \Delta)\|_2}$, $\mathcal{S}(\mathbf{X}^T \mathbf{Y} \mathbf{v}, \Delta)$ is the **soft thresholding operator** and $\Delta \geq 0$ is chosen so that $\|\mathbf{u}\|_1 \leq c_1$

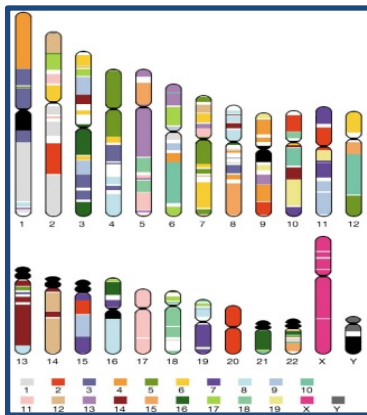
KG-SCCA

- Knowledge-guided Sparse canonical correlation analysis (KG-SCCA)

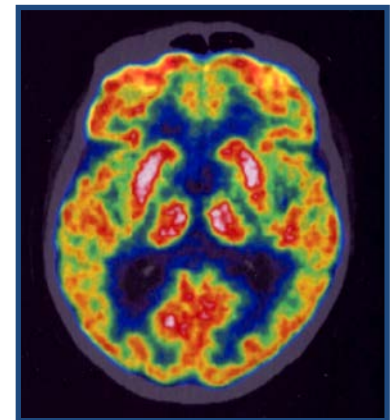
$$\max_{\mathbf{u}, \mathbf{v}} \mathbf{u}^T \mathbf{X}^T \mathbf{Y} \mathbf{v}$$

$$\text{subject to } \mathbf{u}^T \mathbf{X}^T \mathbf{X} \mathbf{u} = 1, \mathbf{v}^T \mathbf{Y}^T \mathbf{Y} \mathbf{v} = 1$$
$$P_1(\mathbf{u}) \leq c_1, P_2(\mathbf{v}) \leq c_2$$

X: Genotype

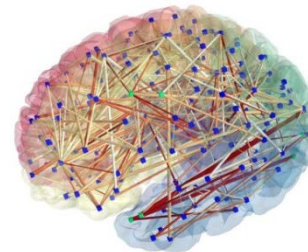
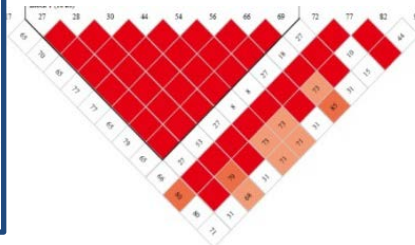


Y: Phenotype

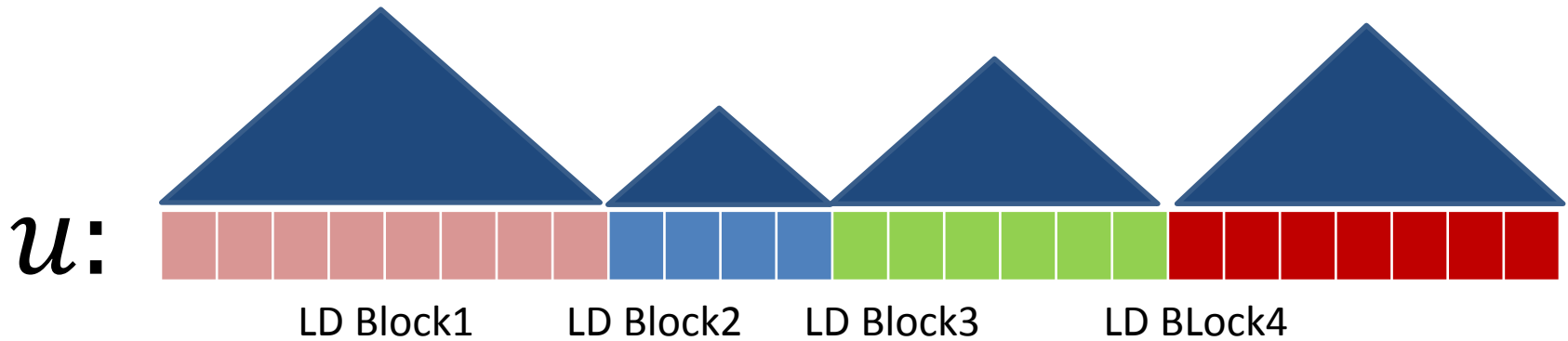


$P_1(\mathbf{u})$

$P_2(\mathbf{v})$

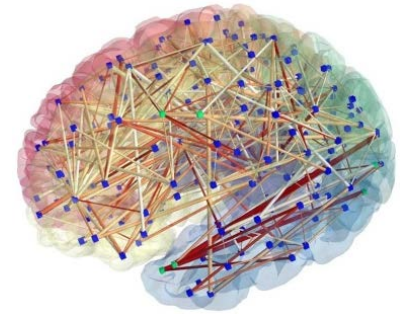


Group Structure



$$\begin{aligned} P_1 = \|\mathbf{u}\|_G &= \beta_1 \sum_{k_1=1}^{K_1} \sqrt{\sum_{i \in \pi_{k_1}} u_i^2} + \theta_1 \|\mathbf{u}\|_1 \\ &= \beta_1 \sum_{k_1=1}^{K_1} \|\mathbf{u}^{k_1}\|_2 + \theta_1 \|\mathbf{u}\|_1, \end{aligned}$$

Network Structure



\mathbf{v} :

	1	2	3	4	5
1	1	-0.4	0.2	0.8	0.1
2	-0.4	1	0.2	0.9	-0.3
3	0.2	0.2	1	0.3	0.5
4	0.8	0.9	0.3	1	0.7
5	0.1	-0.3	0.5	0.7	1

Connection Matrix



0	0.9	0	-0.9	0
0.4	0.4	0	0	0
...				
0	0.3	0	0	0.3
0	0.2	-0.2	0	0

Neighboring Matrix: \mathbf{C}

$$P_2 = \|\mathbf{v}\|_N = \beta_2 \|\mathbf{C}\mathbf{v}\|_2^2 + \theta_2 \|\mathbf{v}\|_1.$$

Iterative Algorithm

- Let $\mathbf{B}_1 = \frac{1}{\gamma_1} \mathbf{Y}\mathbf{v}$ and $\mathbf{B}_2 = \frac{1}{\gamma_2} \mathbf{X}\mathbf{u}$

$$\min_{\mathbf{u}} \frac{1}{2} \|\mathbf{X}\mathbf{u} - \mathbf{B}_1\|_2^2 + \frac{\beta_1}{\gamma_1} \sum_{k_1=1}^{K_1} \|\mathbf{u}^{k_1}\|_2 + \frac{\theta_1}{\gamma_1} \|\mathbf{u}\|_1$$



$$\min_{\mathbf{v}} \frac{1}{2} \|\mathbf{Y}\mathbf{v} - \mathbf{B}_2\|_2^2 + \frac{\beta_2}{2\gamma_2} \|\mathbf{C}\mathbf{v}\|_2^2 + \frac{\theta_2}{\gamma_2} \|\mathbf{v}\|_1$$

- \mathbf{u} : G-SMuRFS
 - (Wang et al., Bioinformatics, 28(2):229-237, 2012)
- \mathbf{v} : Network-guided $L_{2,1}$
 - (Yan et al., pp. 1202-1205, ISBI 2014)

Simulated Data

- Simulated Data

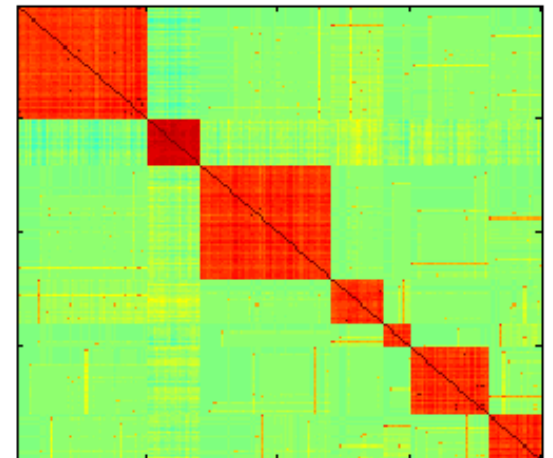
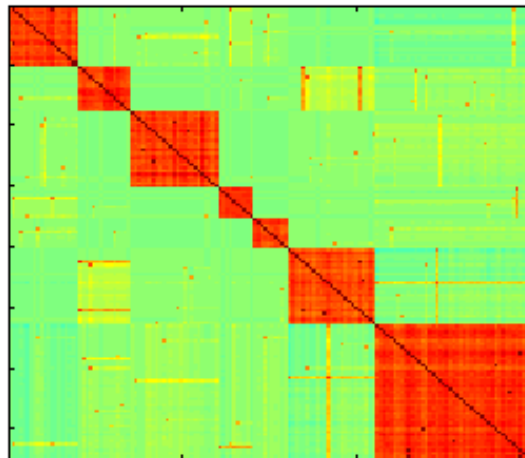
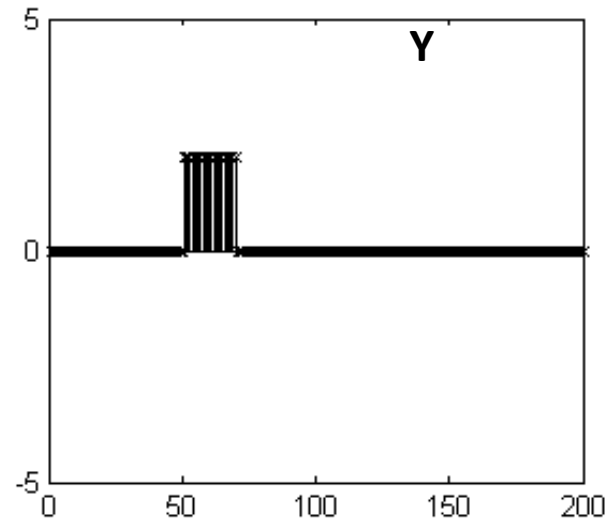
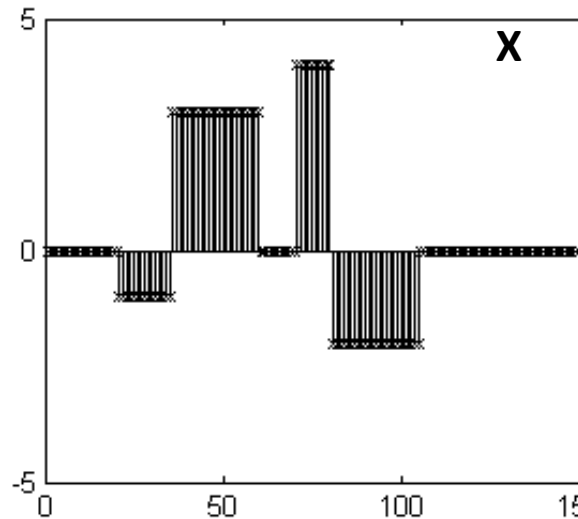
- Subj.: $n=200$
- GT: $p=200$
- PT: $q=150$

- 7 data sets

- Correlations

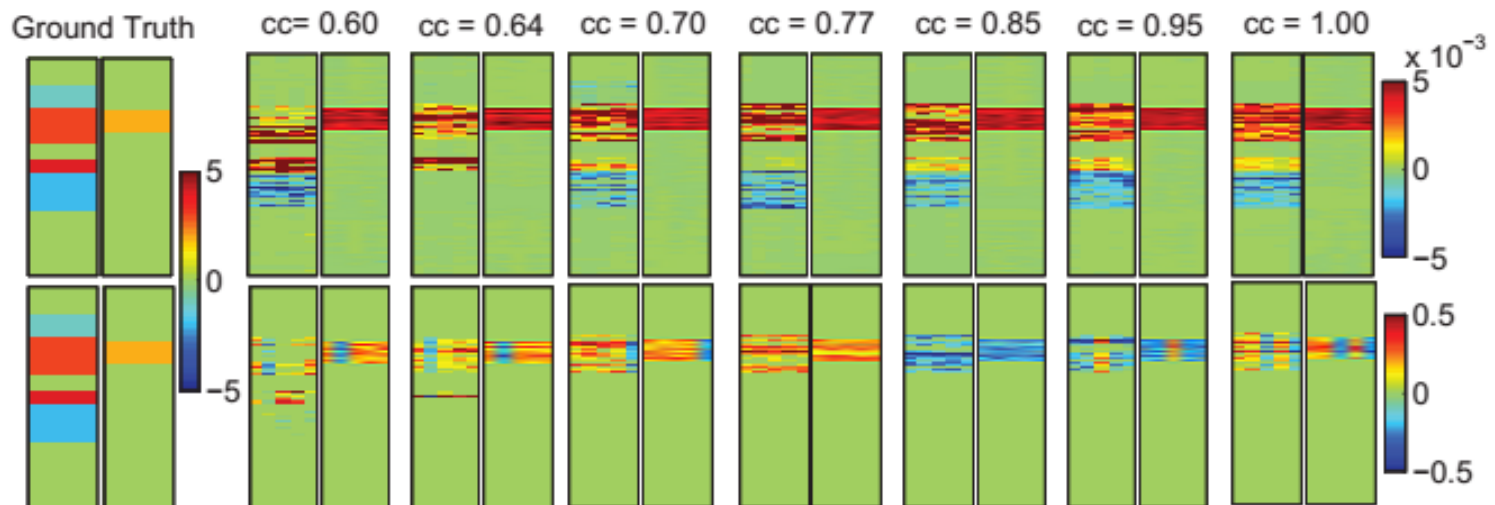
- $0.6 \sim 1.0$

- *The canonical loadings and group structure remained the same across all the datasets.*



Results: Synthetic Data

True CC	Correlation Coefficients (CC)			Area under ROC (AUC)				
	KG-SCCA	PMA	p	KG-SCCA:u	PMA:u	p	KG-SCCA:v	PMA:v
0.60	0.56±0.12	0.31±0.14	2.19E-03	0.83±0.08	0.64±0.02	3.36E-03	1.0±0.00	1.0±0.00
0.64	0.56±0.1	0.51±0.12	2.32E-02	0.96±0.04	0.65±0.01	2.20E-05	1.0±0.00	1.0±0.00
0.70	0.64±0.1	0.53±0.1	1.27E-05	0.99±0.01	0.62±0.	6.21E-08	1.0±0.00	1.0±0.00
0.77	0.7±0.14	0.6±0.14	6.62E-03	0.99±0.01	0.62±0.	9.67E-09	1.0±0.00	1.0±0.00
0.85	0.76±0.08	0.65±0.1	1.02E-04	0.98±0.03	0.63±0.01	4.57E-06	1.0±0.00	1.0±0.00
0.95	0.87±0.04	0.67±0.09	1.19E-03	1.00±0.00	0.63±0.01	1.39E-08	1.0±0.00	1.0±0.00
1.00	0.92±0.04	0.71±0.06	2.46E-04	1.00±0.00	0.64±0.01	4.02E-08	1.0±0.00	1.0±0.00



ADNI Imaging Data

- Alzheimer's disease Neuroimaging Initiative (ADNI)
- AV45 amyloid imaging data
- 39 pairs of bilateral cortical ROIs (78 in total)
- **Covariates:** baseline age, gender, education, and handedness.

	AD	MCI	HC
Number	28	343	196
Gender(M/F)	18/10	203/140	102/94
Handedness(R/L)	23/5	309/34	178/18
Age(mean \pm std)	75.23 \pm 10.66	71.92 \pm 7.47	74.77 \pm 5.39
Education(mean \pm std)	15.61 \pm 2.74	15.99 \pm 2.75	16.46 \pm 2.65

ADNI Genetics Data

- Alzheimer's disease Neuroimaging Initiative (ADNI)
- All the APOE SNPs extracted based on the quality controlled and imputed data combining two phases together
 - Including only SNPs available in both Illumina 610Quad and/or OmniExpress
- 58 SNPs located within 10 LD blocks computed using HaploView
- **Covariates:** baseline age, gender, education, and handedness.

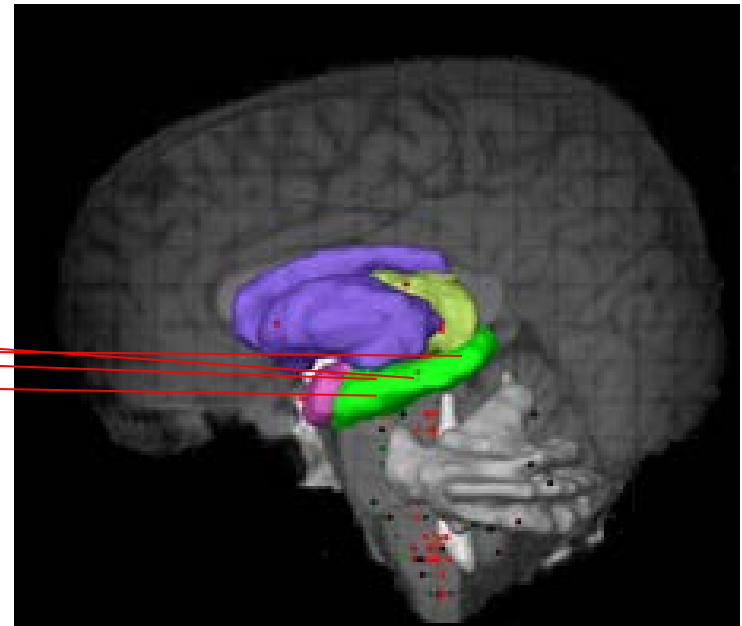
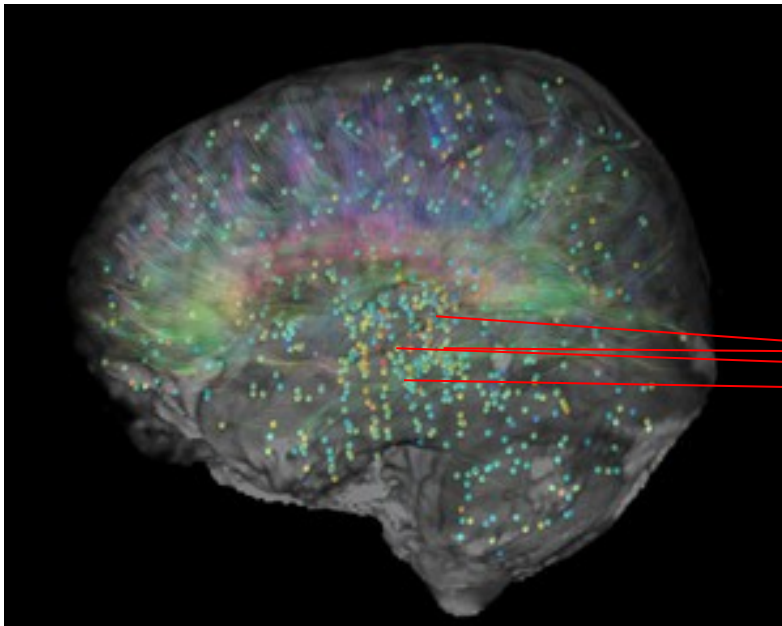
Brain Network

- Amyloid pathway-based gene co-expression network
- Allen Human Brain Atlas (AHBA)
- 15 candidate genes from amyloid pathways studied in (*Swaminathan et al., 2012*)

	LOC_1	LOC_2	LOC_3	LOC_4	LOC_5
Gene_1	10.7	12.5	10.2	9.4	6.54
Gene_2	9.36	8.23	10.2	9.4	12.5
Gene_3	23.67	12.5	9.36	12.5	3.22
Gene_4	10.7	9.36	12.5	9.4	15.96
Gene_5	10.34	9.4	19.22	12.5	12.5
Gene_6	19.7	12.5	10.2	9.4	8.2

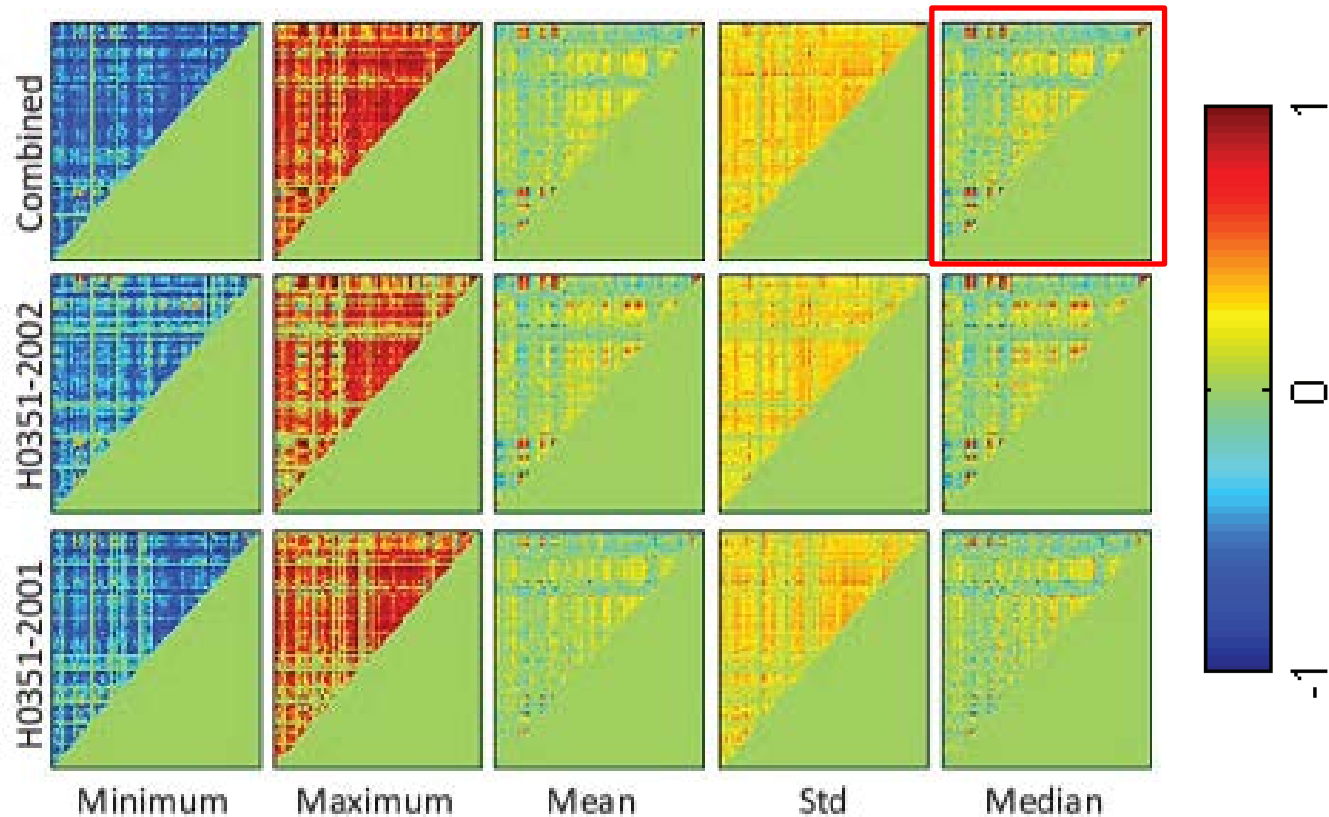
Brain Network

- Allen Human Brain Atlas (AHBA)
- Two Full brain sample
- AHBA space -> MarsBAR AAL space



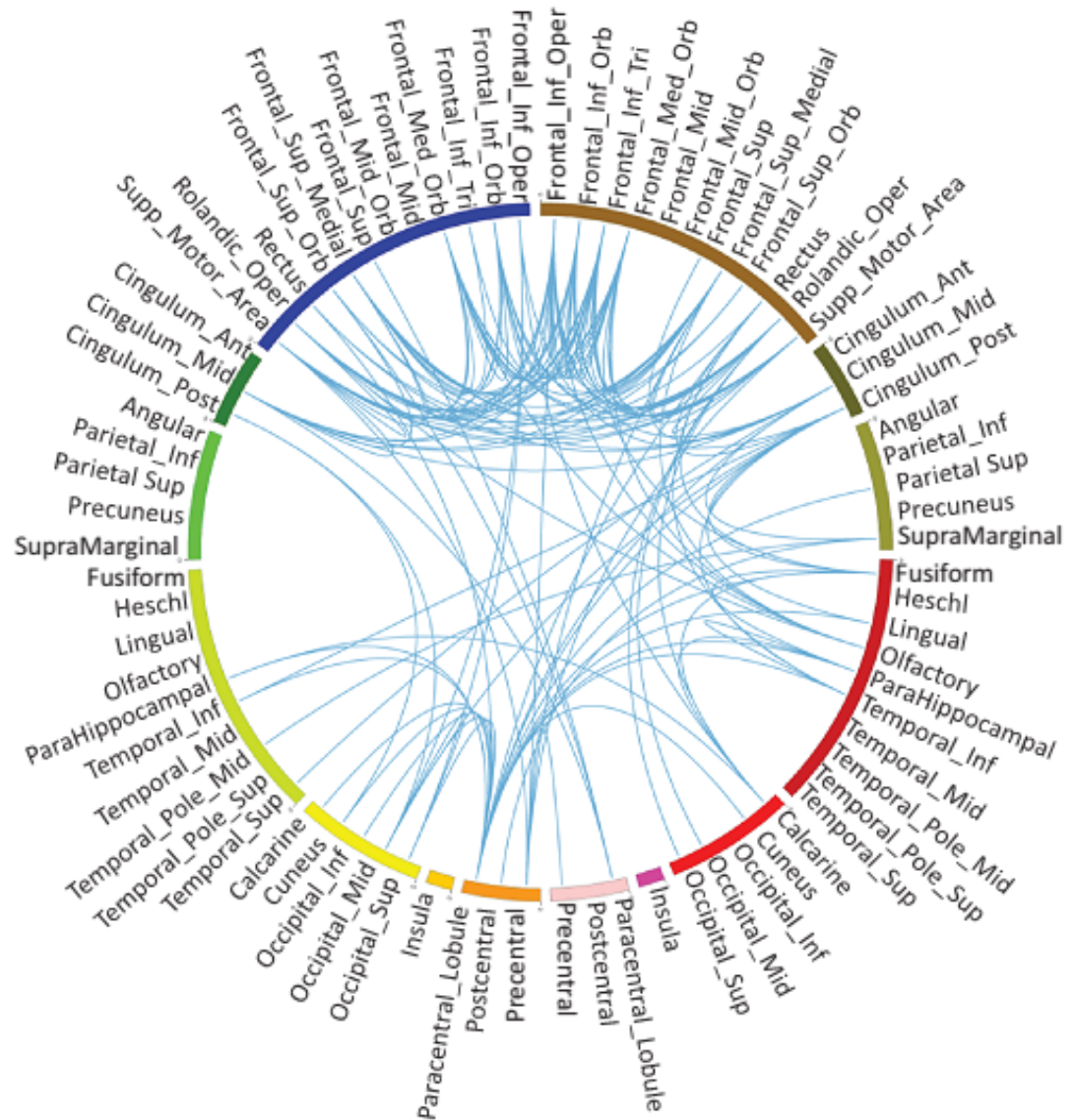
Brain Network

- Allen Human Brain Atlas (AHBA)
- Two Full brain sample



Brain Network

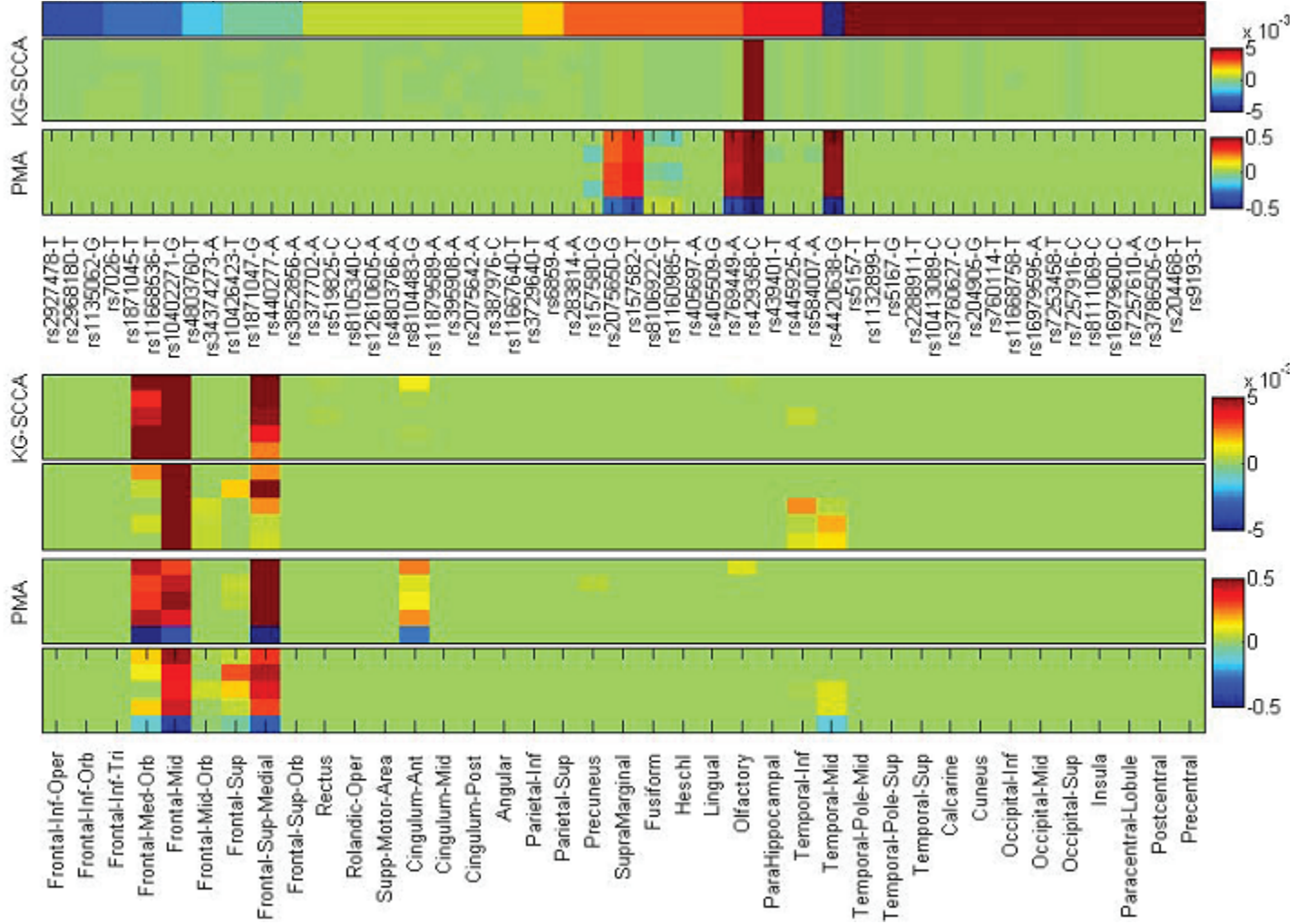
- Network visualization by correlation
 - ≥ 0.5 or ≤ -0.5
- Symmetric
 - left / right brain
- From top to bottom: frontal lobe, cingulate, parietal lobe, temporal lobe, occipital lobe, insula, and sensory-motor cortex.



Results: Real Data

		Train					Test							
		f1	f2	f3	f4	f5	mean	f1	f2	f3	f4	f5	mean	
KG-SCCA	exp1	0.471	0.448	0.475	0.451	0.46	0.461	0.431	0.515	0.401	0.417	0.459	0.445	
	exp2	0.476	0.453	0.454	0.476	0.461	0.464	0.402	0.505	0.503	0.401	0.458	0.454	
	exp3	0.476	0.474	0.474	0.468	0.402	0.459	0.408	0.393	0.413	0.435	0.565	0.443	
	exp4	0.468	0.466	0.459	0.46	0.466	0.464	0.441	0.409	0.47	0.476	0.445	0.448	
	exp5	0.49	0.502	0.434	0.449	0.447	0.464	0.35	0.297	0.584	0.527	0.528	0.457	
PMA	exp1	0.439	0.418	0.438	0.438	0.426	0.432	0.368	0.45	0.398	0.379	0.439	0.407	
	exp2	0.444	0.416	0.425	0.436	0.432	0.431	0.354	0.463	0.449	0.399	0.416	0.416	
	exp3	0.442	0.445	0.439	0.427	0.398	0.43	0.382	0.341	0.382	0.432	0.544	0.416	
	exp4	0.434	0.44	0.425	0.427	0.431	0.432	0.414	0.363	0.445	0.438	0.415	0.415	
	exp5	0.459	0.462	0.406	0.416	0.411	0.431	0.288	0.287	0.517	0.486	0.501	0.416	
						pvalue						3.08E-6		
												pvalue	8.07E-5	

Results: Real Data



Conclusion

- Brain imaging genetics study between brain-wide amyloid accumulation and genetic variations in the APOE gene
- Proposed a novel knowledge-guided sparse canonical correlation analysis (KG-SCCA) algorithm
 - not only removes the independence assumption, but also models both the group-like and network-like prior knowledge
 - Better performance in both synthetic data and real data
- **Limitation:** Scalability remains a problem when considering genome-wide study.

Outline

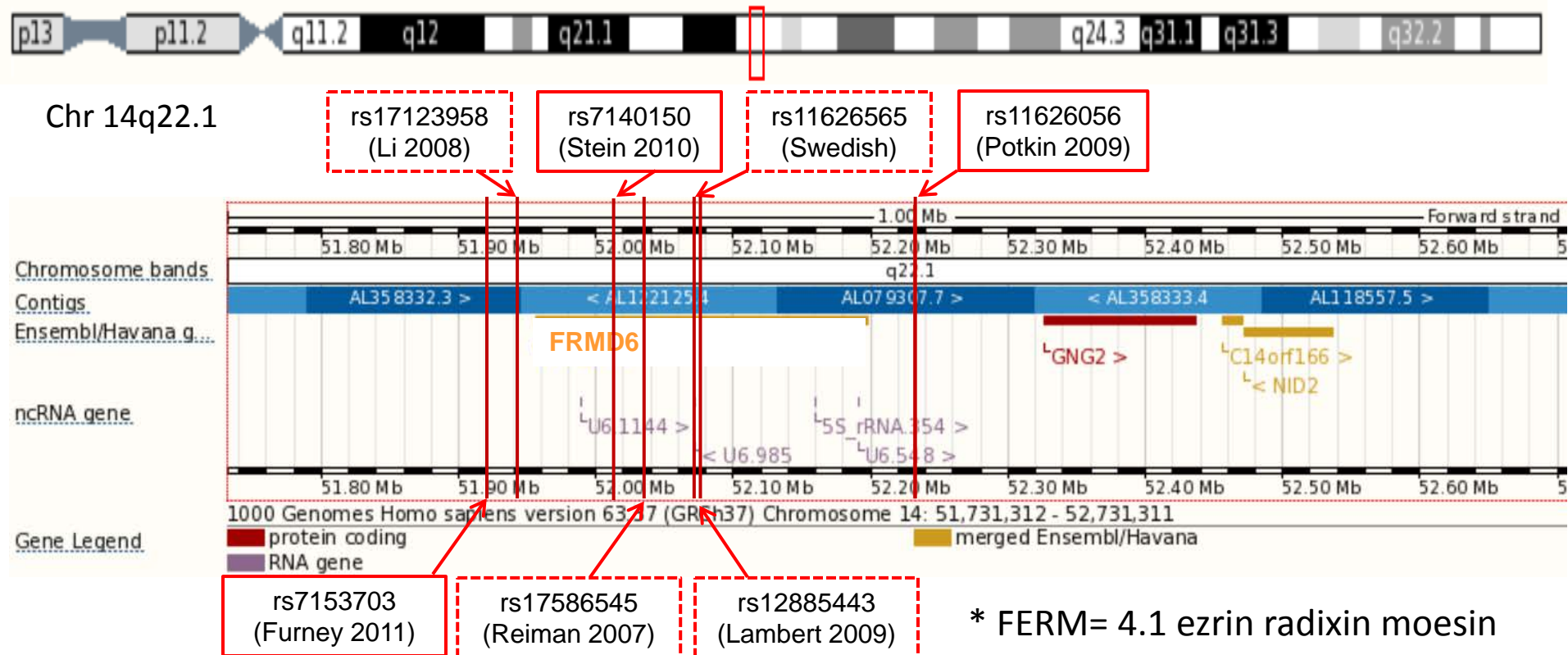
- Neuroimaging Genomics
- ADNI Genetics Review
- Example Study
- Major Findings and Discussion

Major Findings (As of 12/31/2012)

- Top 10 AD genes
 - *APOE, BIN1, CLU, ABCA7, CR1, PICALM, MS4A6A, CD33, MS4A4E, CD2AP*
- Top 10 AD genes associated with QTs
 - *APOE, BIN1, CLU, CR1, PICALM*
- Replicated by ≥ 2 groups
 - *APOC1, APOE, BIN1, CD2AP, CLU, CR1, EPHA1, FTO, GRIN2B, MAGI2, MS4A4A, PICALM, TOMM40*
- Power of quantitative traits
 - *FRMD6*

FRMD6: FERM domain-containing protein 6

Detected in 3 imaging genetics studies (2 ADNI; 1 ADNI/ANM) and validated by case/control GWAS



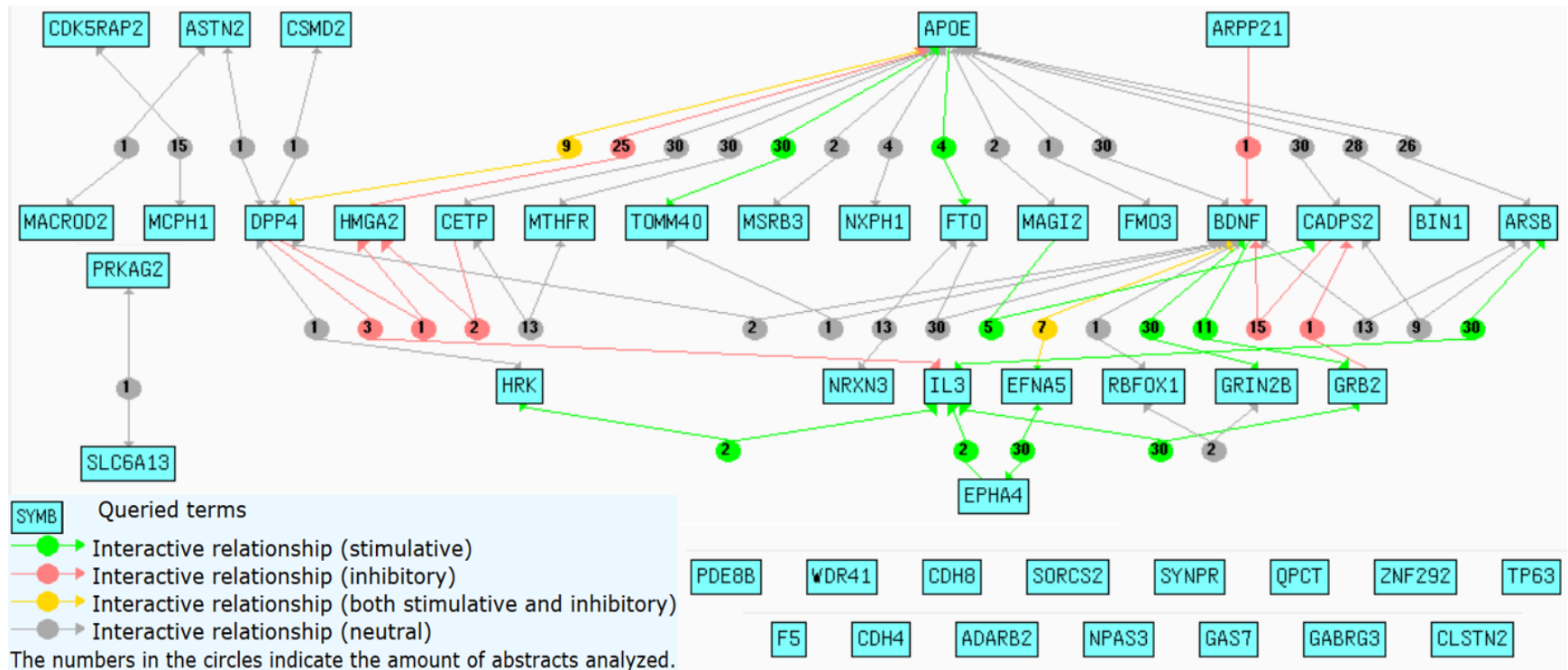
Hong et al, Genome-wide and gene-based association implicates FRMD6 in Alzheimer disease. Hum Mutat. 2012. 33(3):521-9.

Across the four combined GWAS samples, FRMD6 showed the highest non-APOE signal: $p = 2.6 \times 10^{-14}$.

Saykin et al, AAC 2012

Source	SNP	Position	MAF	p-value	OR (95%CI)
Stein 2010	rs7140150	52010799	0.4566	4.77×10^{-7}	<i>n/a - Imaging QTL</i>
Potkin 2009	rs11626056	52233276	0.3295	1.18×10^{-6}	<i>n/a - Imaging QTL</i>
Furney 2011	rs7153703	51919822	0.2130	3.38×10^{-6}	<i>n/a - Imaging QTL</i>
Swedish	rs11626565	52075152	0.0599	2.45×10^{-5}	1.69; 1.34-2.13
Reiman 2007	rs17586545	52035018	0.0334	4.18×10^{-5}	1.86; 1.36-2.54
Li 2008	rs17123958	51942124	0.1040	7.59×10^{-5}	2.12; 1.38-3.24
Lambert 2009	rs12885443	52075653	0.1769	5.34×10^{-4}	1.16; 1.07-1.25

Chilibot Network Analysis



Chilibot analysis on 51 genes discovered from ADNI structural MRI genetic studies. Chilibot (<http://www.chilibot.net/>) searches PubMed abstracts and constructs content-rich relationship networks among biological concepts, genes, proteins, or drugs.

Metacore Pathway Enrichment Analysis

(a) Enrichment by Pathway Maps: Results with FDR $p \leq 0.05$ are shown.

#	Pathway Maps	pValue	FDR p	Hit Genes	Total Genes
1	Cell adhesion Ephrin signaling	8.0E-05	0.018	4	45
2	Neurophysiological process nNOS signaling in neuronal synapses	4.3E-04	0.048	3	29
3	Neurophysiological process NMDA-dependent postsynaptic long-term potentiation in CA1 hippocampal neurons	7.5E-04	0.050	4	80
4	Immune response Alternative complement pathway	1.0E-03	0.050	3	39
5	Development Neurotrophin family signaling	1.1E-03	0.050	3	40

(b) Enrichment by Process Networks: Results with FDR $p \leq 0.05$ are shown.

#	Process Networks	pValue	FDR p	Hit Genes	Total Genes
1	Development Neurogenesis Axonal guidance	2.3E-04	0.020	8	230
2	Cell adhesion Synaptic contact	3.4E-04	0.020	7	184
3	Development Regulation of angiogenesis	1.1E-03	0.041	7	223
4	Cell adhesion Attractive and repulsive receptors	1.6E-03	0.042	6	175
5	Development Neurogenesis Synaptogenesis	1.8E-03	0.042	6	180

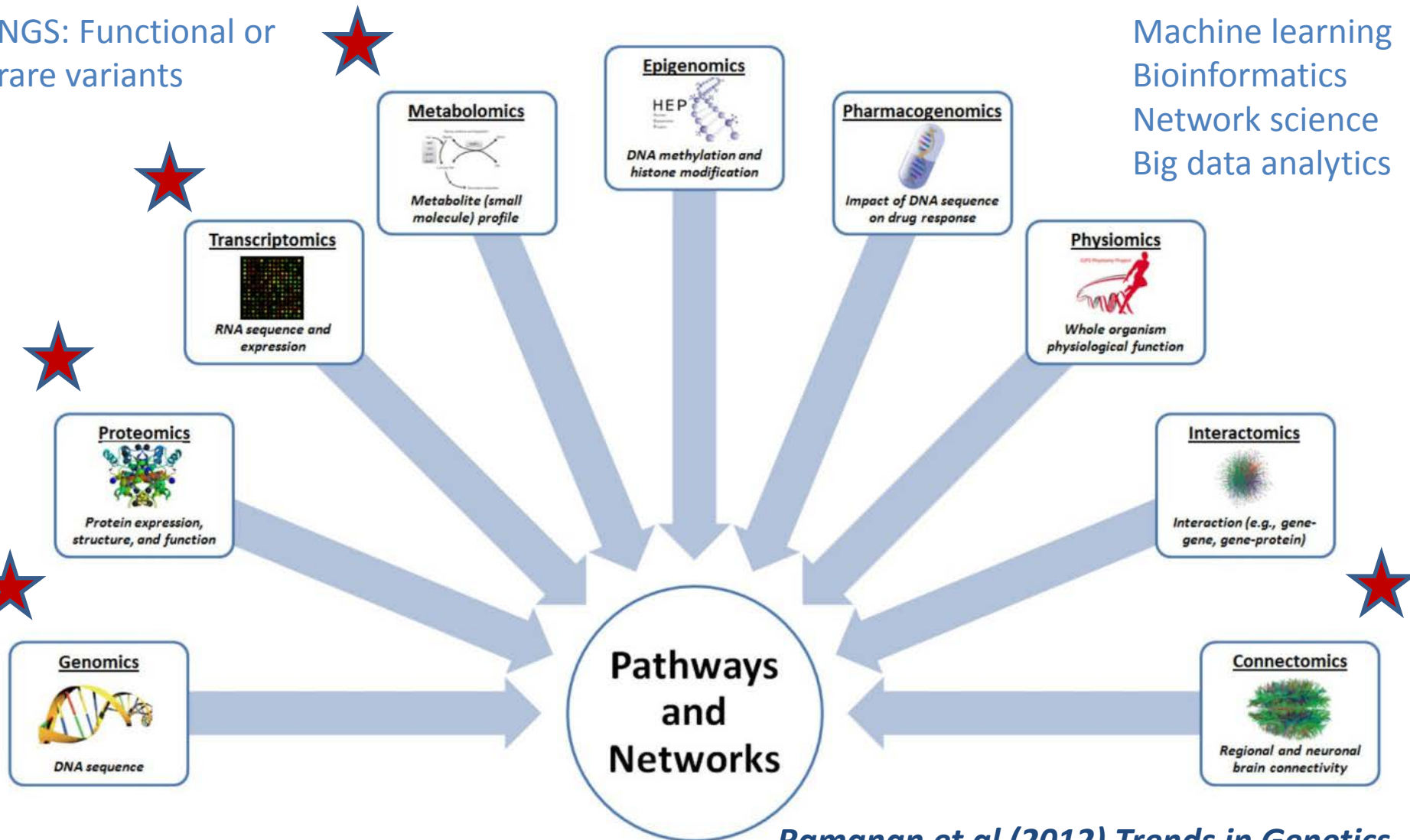
(c) Enrichment by Diseases: Top 5 results are shown.

#	Diseases	pValue	FDR p	Hit Genes	Total Genes
1	Alzheimer Disease	2.7E-25	2.2E-22	45	1244
2	Tauopathies	4.1E-25	2.2E-22	45	1256
3	Mental Disorders	9.3E-25	3.1E-22	68	3388
4	Alzheimer disease, late onset	1.3E-24	3.1E-22	30	432
5	Psychiatry and Psychology	1.4E-24	3.1E-22	68	3412

NGS and Convergent “Omics”

NGS: Functional or rare variants

Machine learning
Bioinformatics
Network science
Big data analytics



Acknowledgements



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