Mapping Outcome-relevant Human Brain Connectivity and it's Genetic Basis

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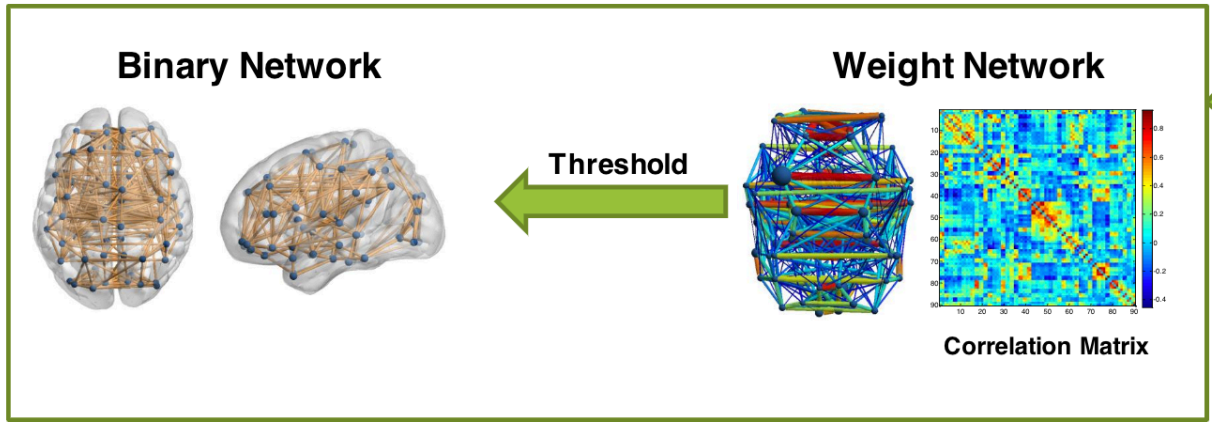
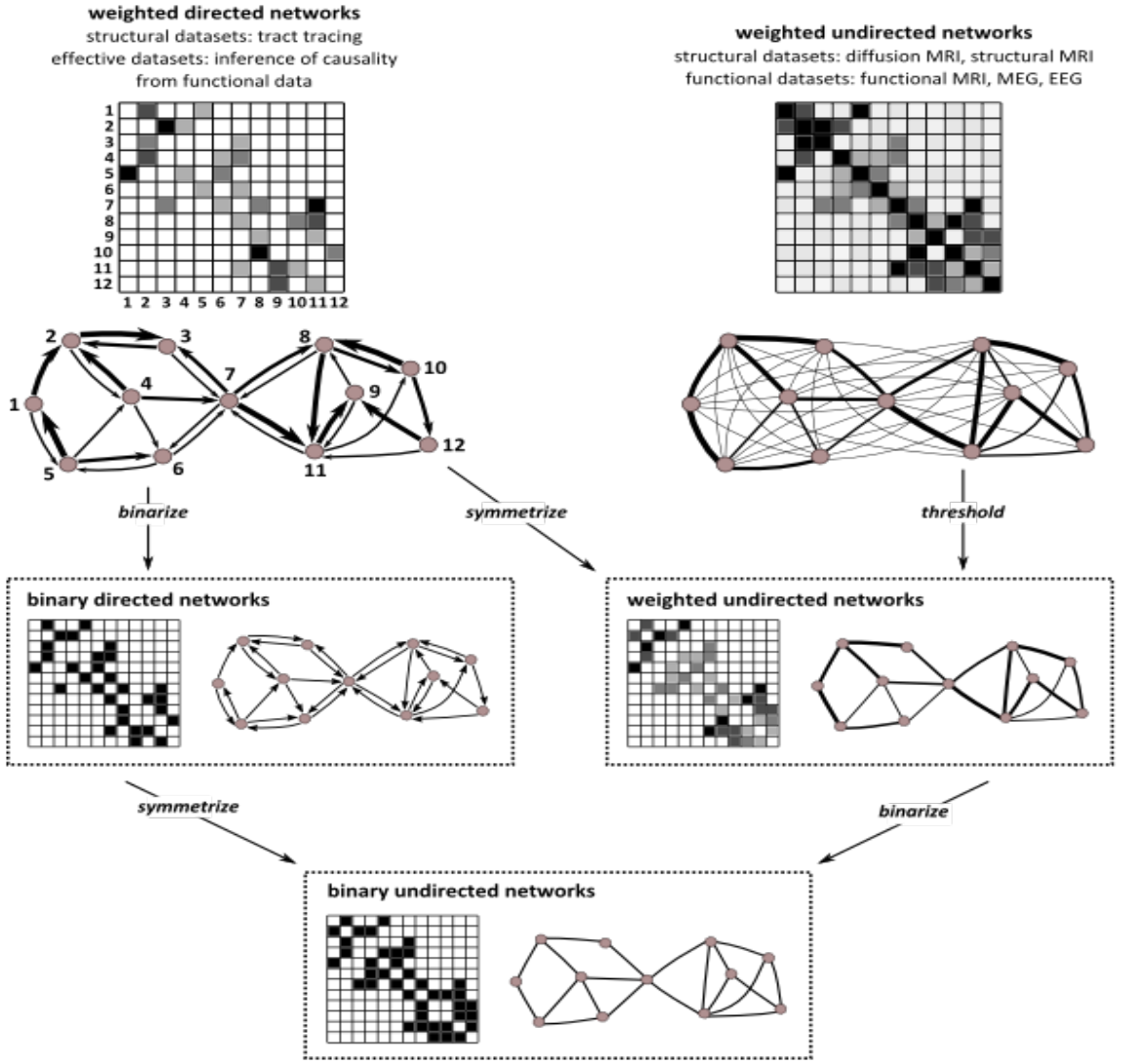
Construction of Brain Networks

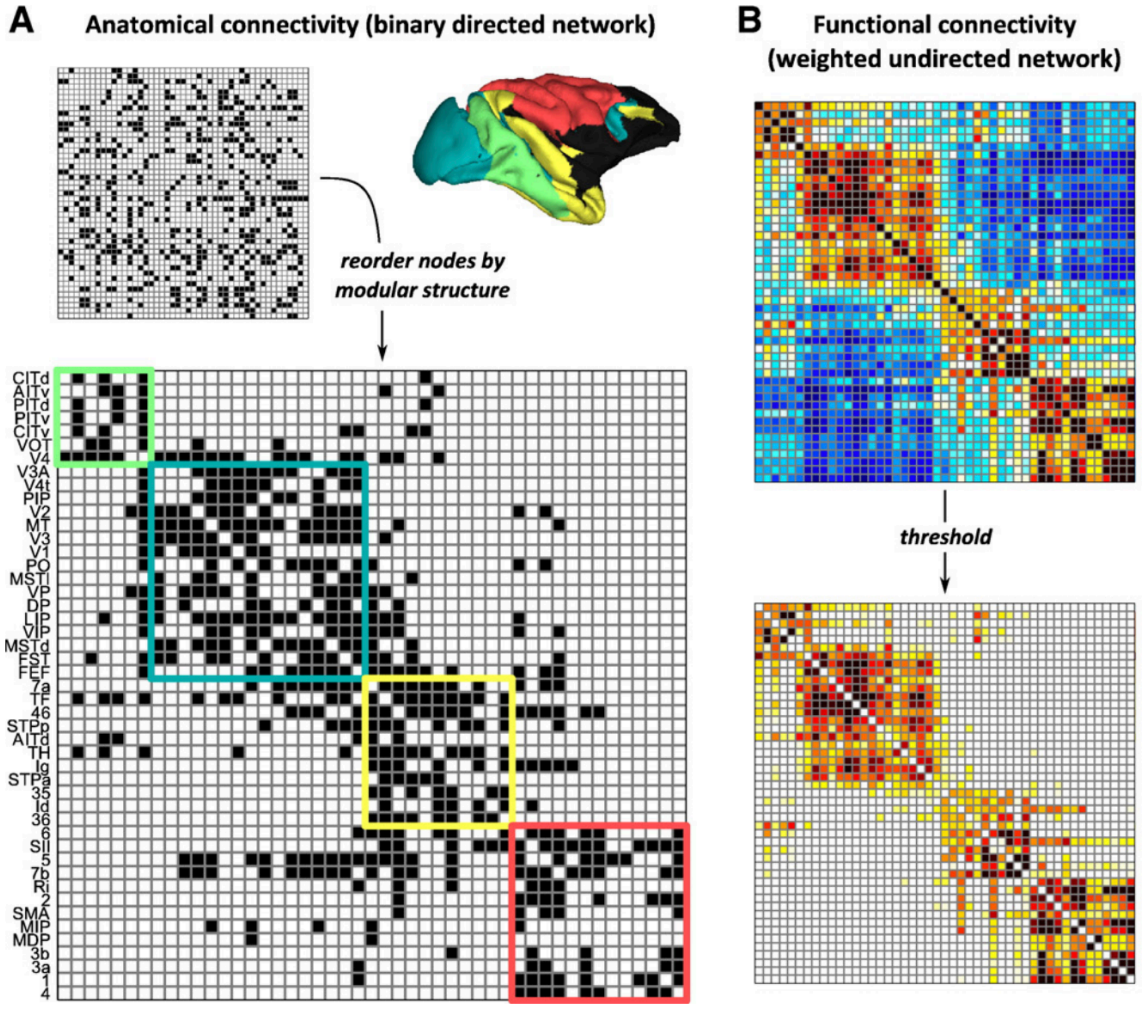
- Nodes represent brain regions
- Links represent anatomical, functional, or effective connections
- Anatomical Networks
  - Constructed from histological tract tracing studies
  - Links: white matter tracts between pairs of nodes
- Functional Networks
  - Constructed from time series of brain dynamics
  - Links: Magnitudes of temporal correlation in activity possibly between anatomically unconnected regions





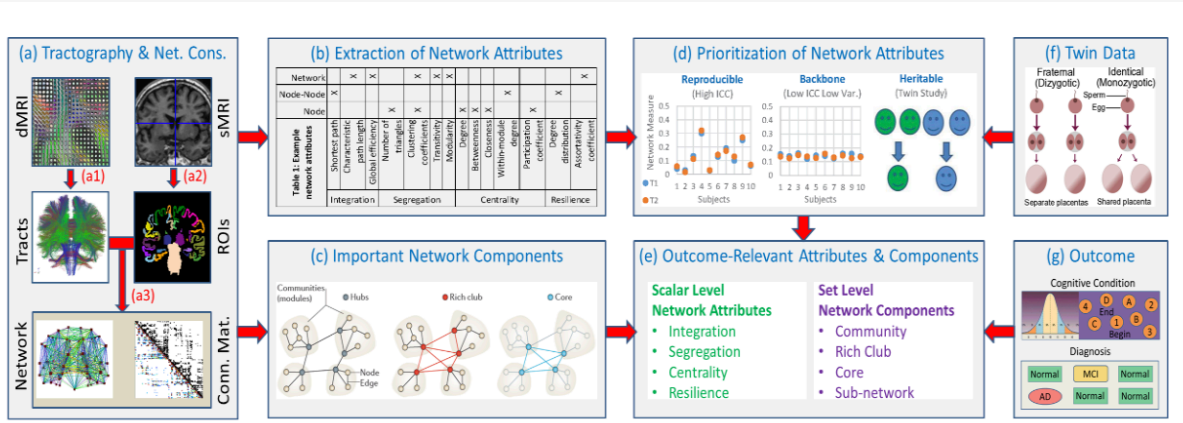
The Nature of Nodes and Links

- Nodes: regions of the brain with coherent patterns of extrinsic anatomical or functional connections.
  - Defined by parcellation schemes
- Binary links denote the presence or absence of connections between nodes
- Weighted links also contain information about connection strengths.
  - Anatomical weights represent the size, density, or coherence of anatomical tracts
  - Functional weights represent the magnitudes of correlational or casual interactions
- Modules: clusters of nodes that are densely interconnected



First Goal

- Identify individual structural and functional network measures that significantly differ between outcomes
- Network Measures
  - Detect aspects of functional integration and segregation
  - Quantify the importance of individual brain regions
  - Characterize patterns of local anatomical circuitry
  - Test resilience of networks to insult
- Brain Connectivity Toolbox

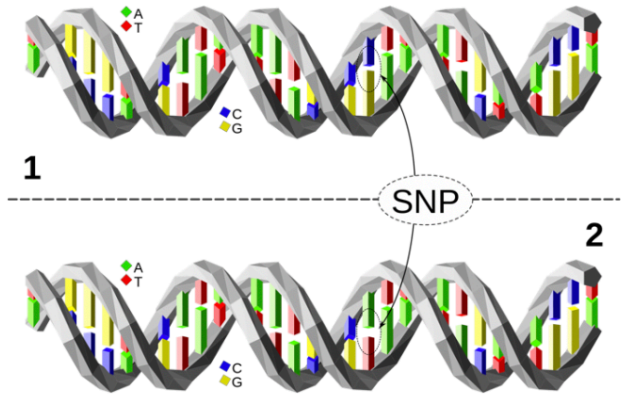


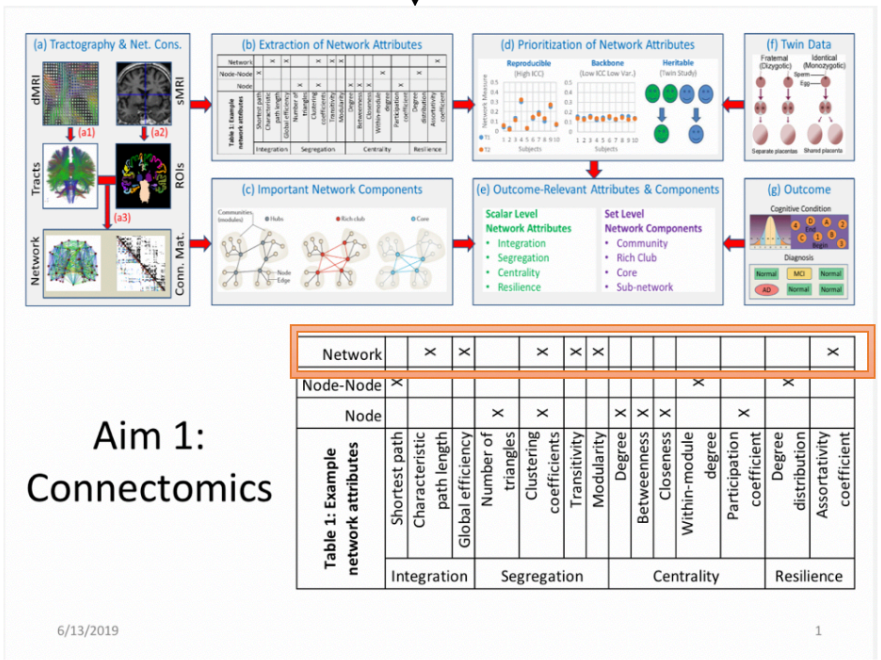
Aim 1: Connectomics

Table 1: Example network attributes	Shortest path	Characteristic path length	Global efficiency	Number of triangles	Clustering coefficients	Transitivity	Modularity	Degree	Betweenness	Closeness	Within-module degree	Participation coefficient	Degree distribution	Assortativity coefficient
Network		X	X		X	X	X							X
Node-Node	X										X		X	
Node				X	X			X	X	X		X		
	Integration			Segregation				Centrality					Resilience	

The ”Road Map”

Genetic Basis → Functional/Structural Network Measurements → Outcome

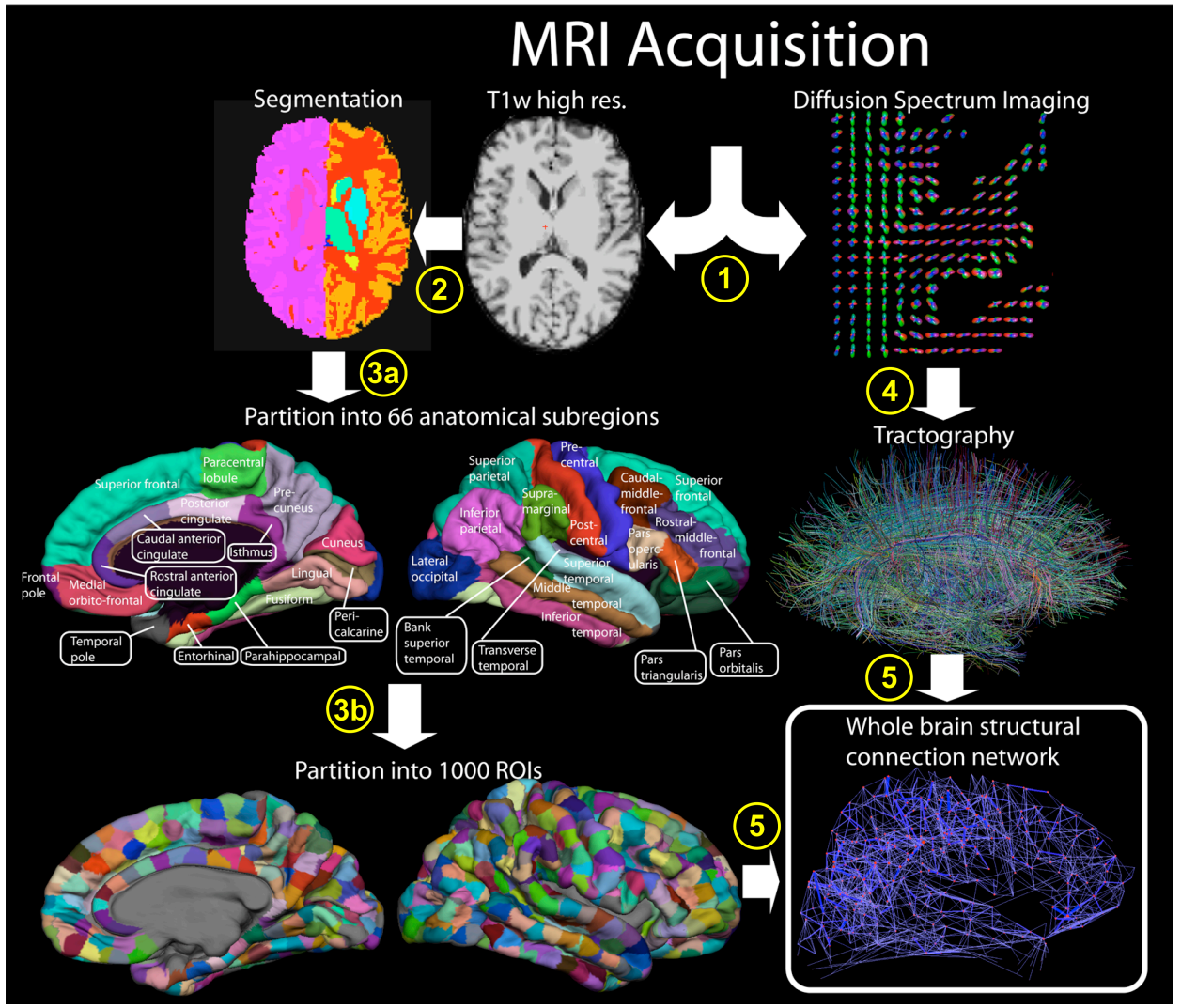




- Alzheimer’s Disease (AD)
- Mild Cognitive Impairment (MCI)
- Healthy Control (HC)

The Data Sets

- Alzheimer's Disease Neuroimaging Initiative (ADNI)
- Functional connectivity
  - Partial correlation matrices
  - 33 AD subjects
  - 49 MCI subjects
  - 44 HC subjects
- Structural connectivity
  - Lausanne
  - AAL Atlas
  - 41 AD subjects
  - 73 MCI subjects
  - 56 HC subjects

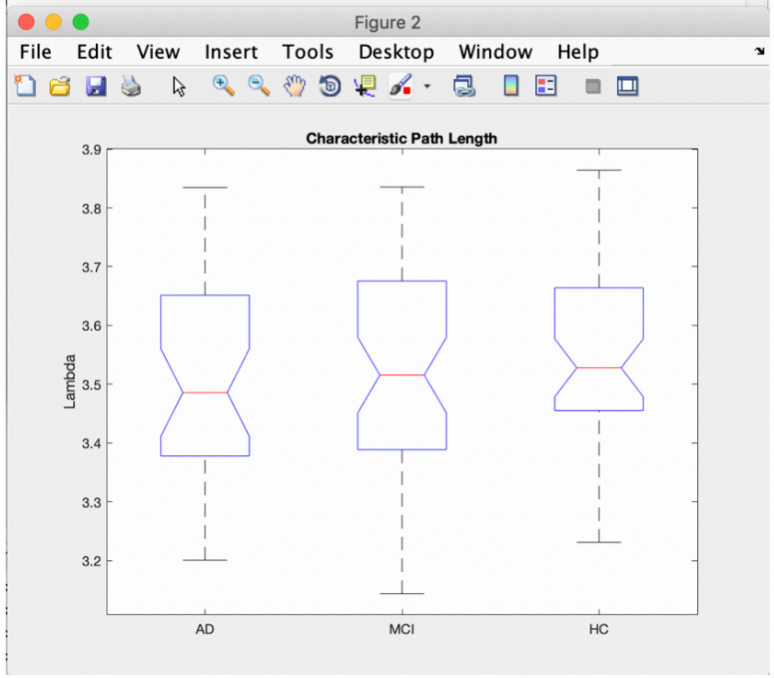


Characteristic Path Length

Functional:

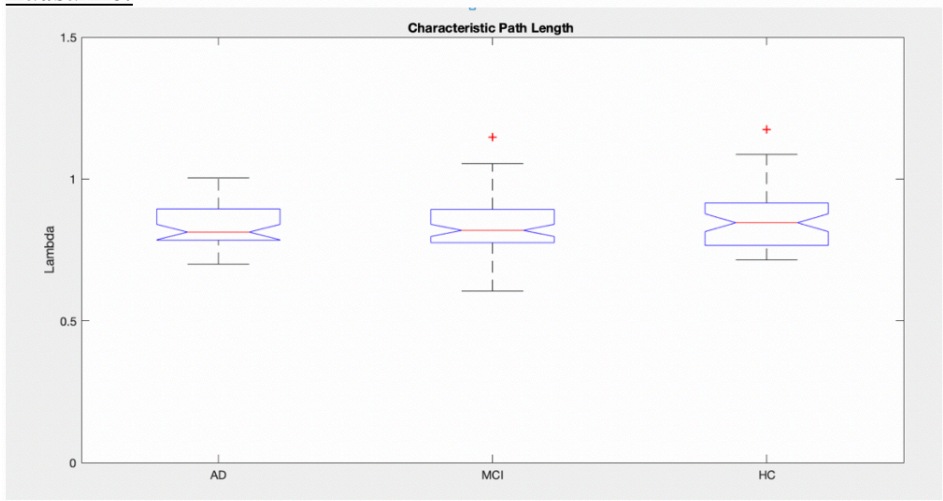
ANOVA Table

Source	SS	df	MS	F	Prob>F
Groups	0.03608	2	0.01804	0.61	0.5471
Error	3.66063	123	0.02976		
Total	3.6967	125			



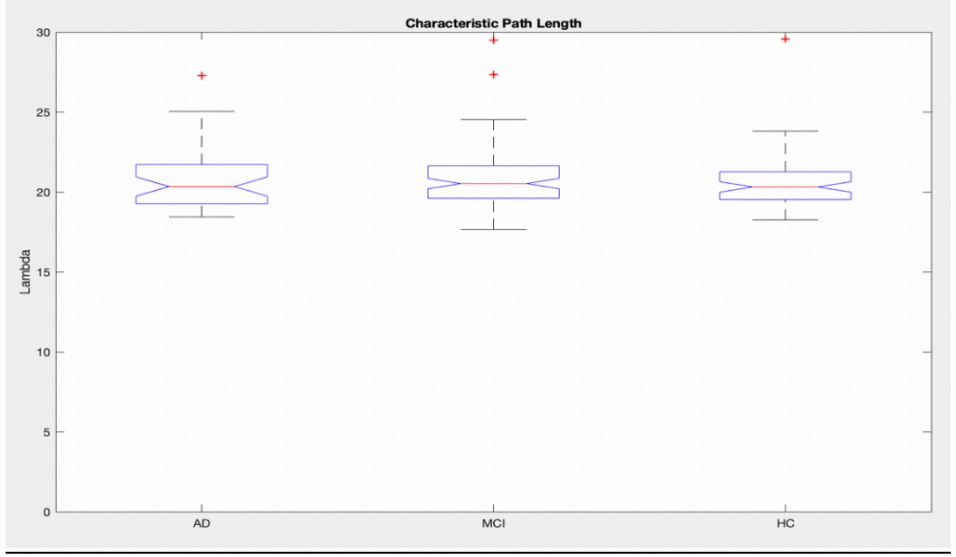
$p > 0.05$, thus we fail to reject the null hypothesis that the mean characteristic path lengths are the same for all treatments.

Lausanne:



The p value was calculated to be $0.6456 > 0.05$, thus we fail to reject the null hypothesis that the mean characteristic path lengths are the same for all treatments.

AAL:



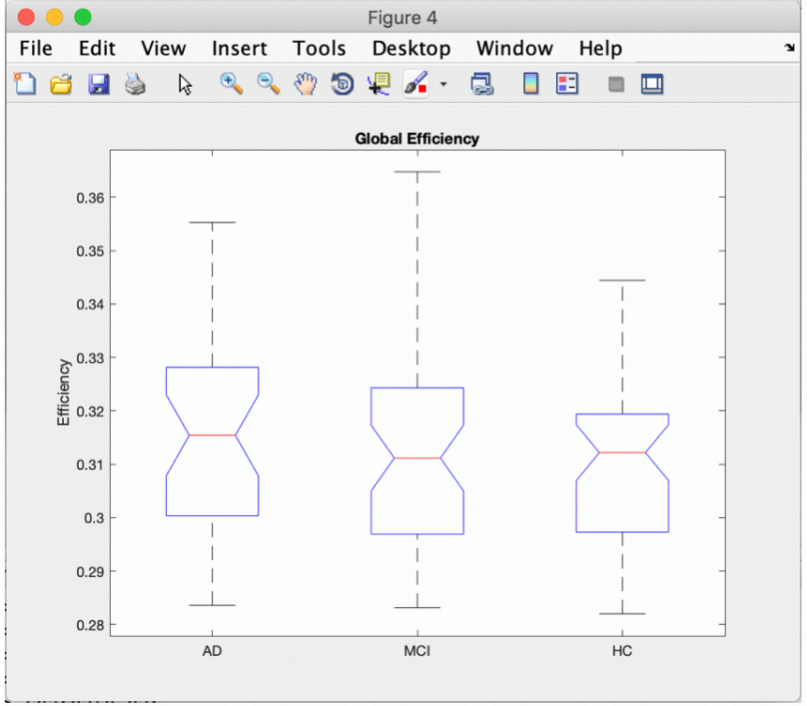
The p value was calculated to be $0.5358 > 0.05$, thus we fail to reject the null hypothesis that the mean characteristic path lengths are the same for all treatments.

Global Efficiency

Functional:

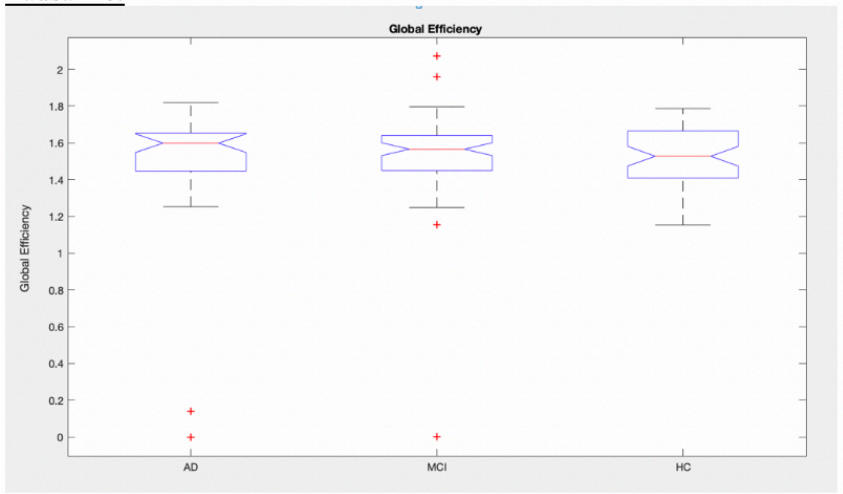
ANOVA Table

Source	SS	df	MS	F	Prob>F
Groups	0.00047	2	0.00023	0.71	0.4942
Error	0.0405	123	0.00033		
Total	0.04097	125			



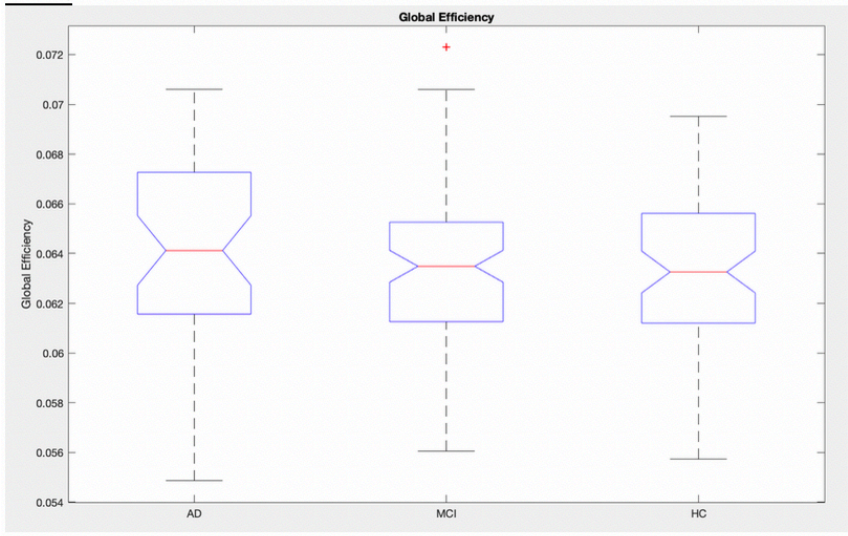
$p > 0.05$, thus we fail to reject the null hypothesis that the mean global efficiency is the same for all treatments.

Lausanne:



The p value was calculated to be $0.8117 > 0.05$, thus we fail to reject the null hypothesis that the mean global efficiencies are the same for all treatments.

AAL:



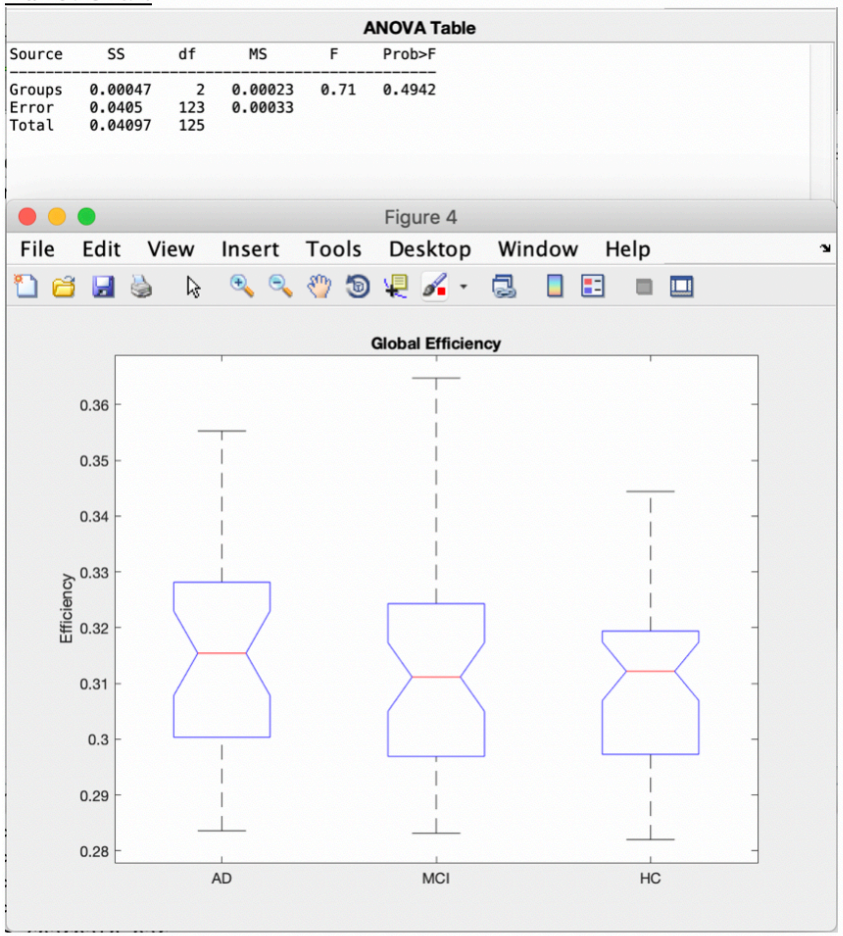
The p value was calculated to be $0.8376 > 0.05$, thus we fail to reject the null hypothesis that the mean global efficiencies are the same for all treatments.

Transitivity

Functional:

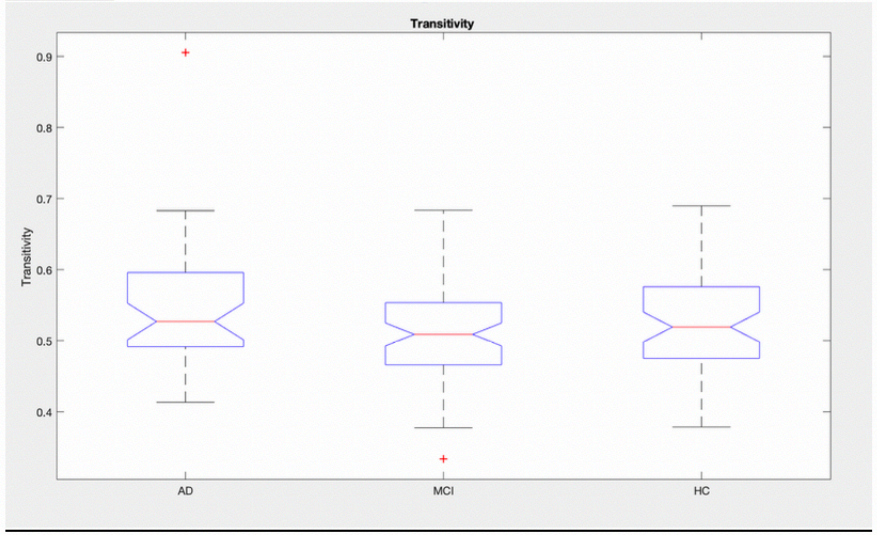
ANOVA Table

Source	SS	df	MS	F	Prob>F
Groups	0.00047	2	0.00023	0.71	0.4942
Error	0.0405	123	0.00033		
Total	0.04097	125			



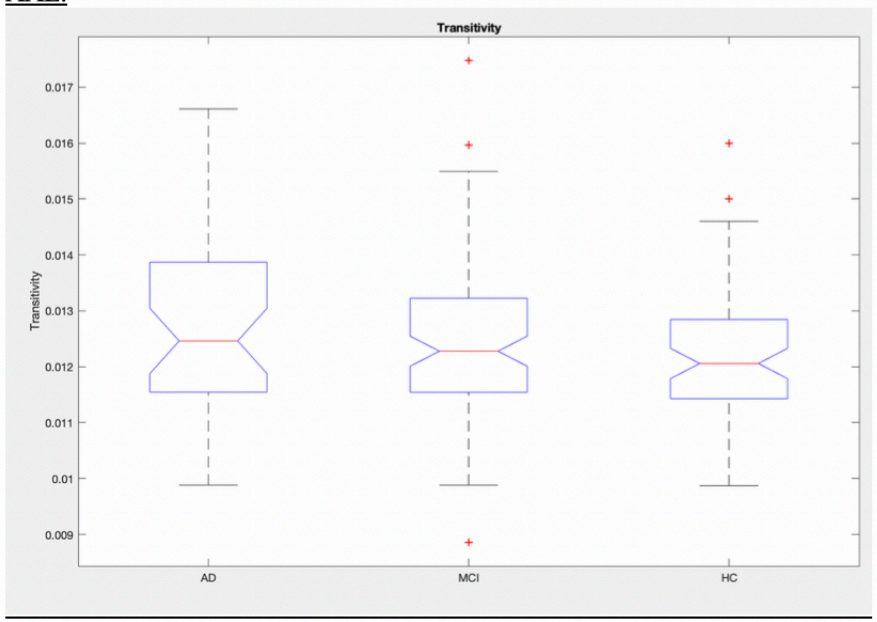
$p > 0.05$, thus we fail to reject the null hypothesis that the mean global efficiency is the same for all treatments.

Lausanne:



The p value was calculated to be $0.1384 > 0.05$, thus we fail to reject the null hypothesis that the mean transitivity is the same for all treatments.

AAL:



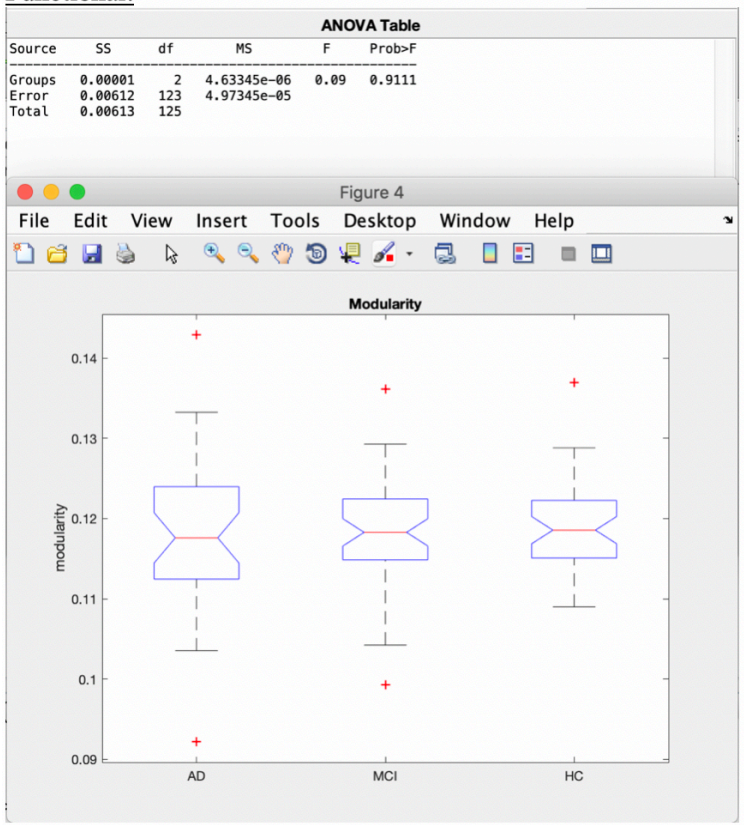
The p value was calculated to be $0.1674 > 0.05$, thus we fail to reject the null hypothesis that the mean transitivity is the same for all treatments.

Modularity

Functional:

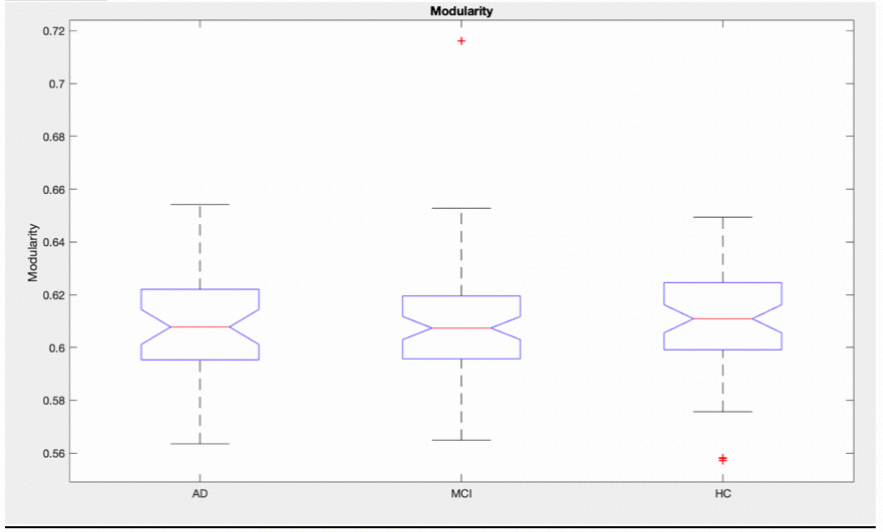
ANOVA Table

Source	SS	df	MS	F	Prob>F
Groups	0.00001	2	4.63345e-06	0.09	0.9111
Error	0.00612	123	4.97345e-05		
Total	0.00613	125			



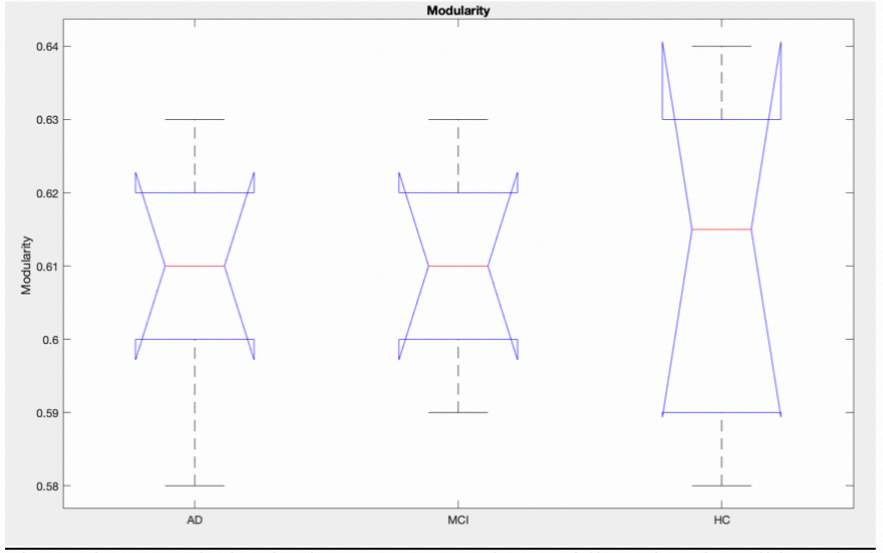
p > 0.05, thus we fail to reject the null hypothesis that the mean modularity is the same for all treatments.

Lausanne:



The p value was calculated to be 0.8822 > 0.05, thus we fail to reject the null hypothesis that the mean modularity is the same for all treatments.

AAL:



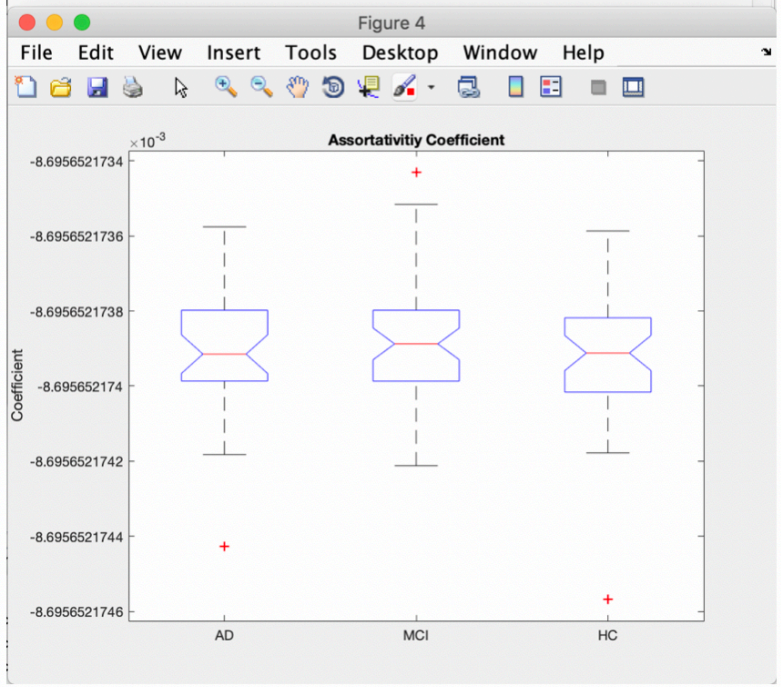
The p value was calculated to be 0.9046> 0.05, thus we fail to reject the null hypothesis that the mean modularity is the same for all treatments.

Assortativity Coefficient

Functional:

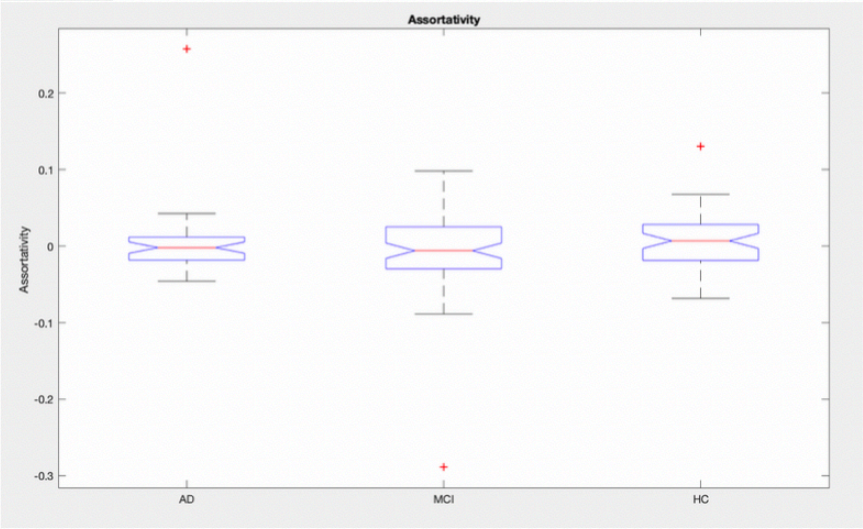
ANOVA Table

Source	SS	df	MS	F	Prob>F
Groups	4.17851e-26	2	2.08925e-26	0.75	0.4737
Error	3.4181e-24	123	2.77895e-26		
Total	3.45989e-24	125			



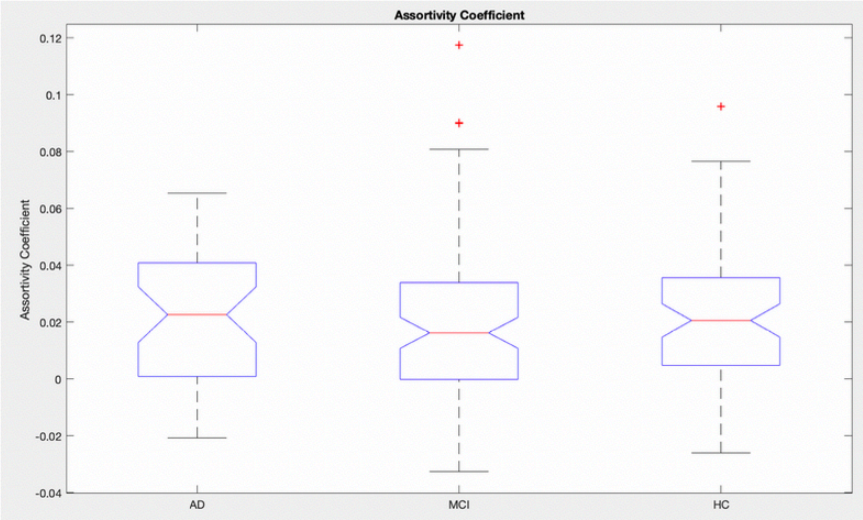
$p > 0.05$, thus we fail to reject the null hypothesis that the mean assortativity coefficient is the same for all treatments.

Lausanne:



The p value was calculated to be $0.5268 > 0.05$, thus we fail to reject the null hypothesis that the mean assortativity is the same for all treatments.

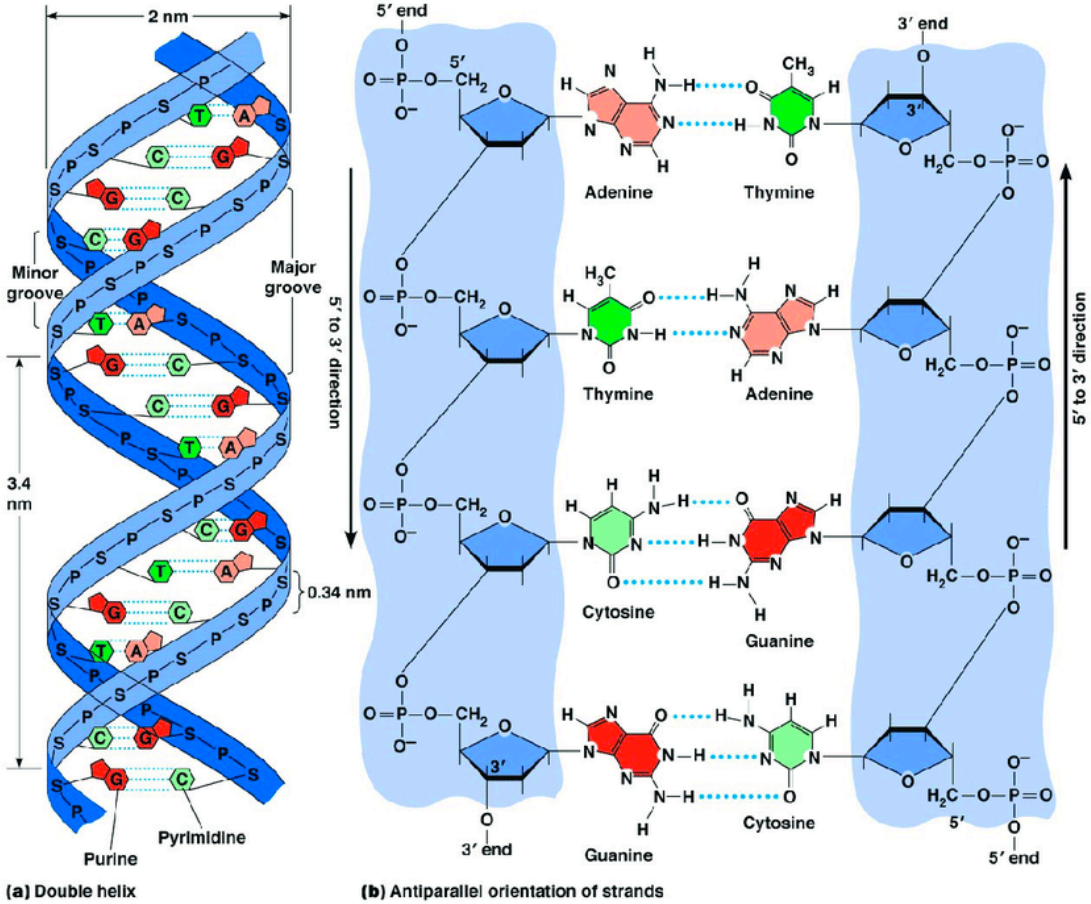
AAL:



The p value was calculated to be $0.7836 > 0.05$, thus we fail to reject the null hypothesis that the mean assortativity is the same for all treatments.

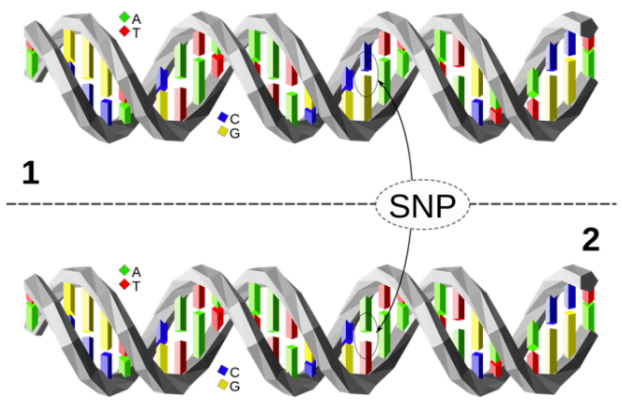
Second Goal

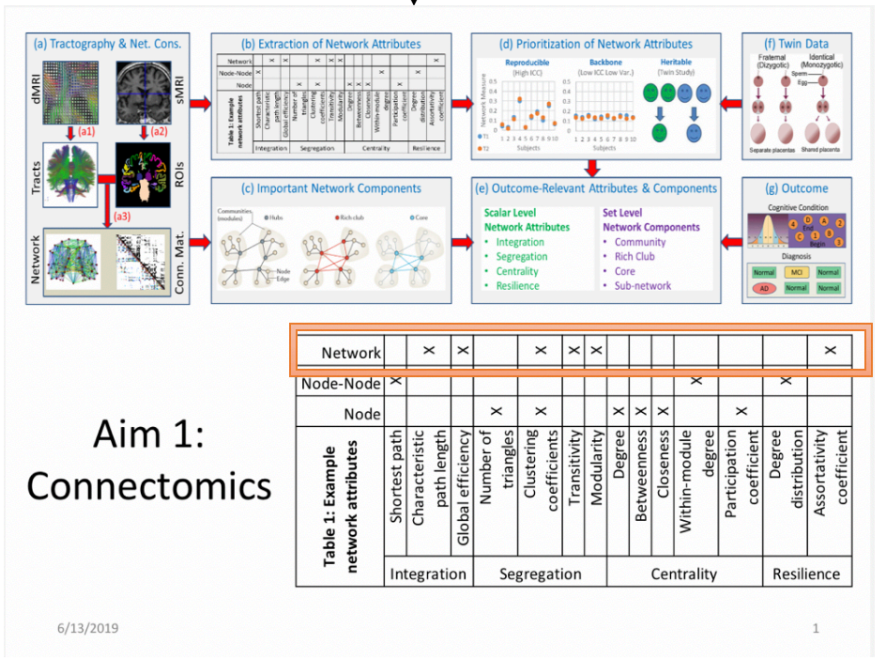
- Identify genetic markers associated with Alzheimer's Disease
  - Single nucleotide polymorphisms (SNPs)
- Plink
  - Open-source whole genome association analysis toolset
  - Analyzing genotypic and phenotypic data
- Linear regression
  - Jansen's SNPs → explanatory variables
  - Functional network measurements → response variables
  - Hypothesis: There is a significant linear relationship between the two variables



The “Road Map”

Genetic Basis → Functional/Structural Network Measurements → Outcome

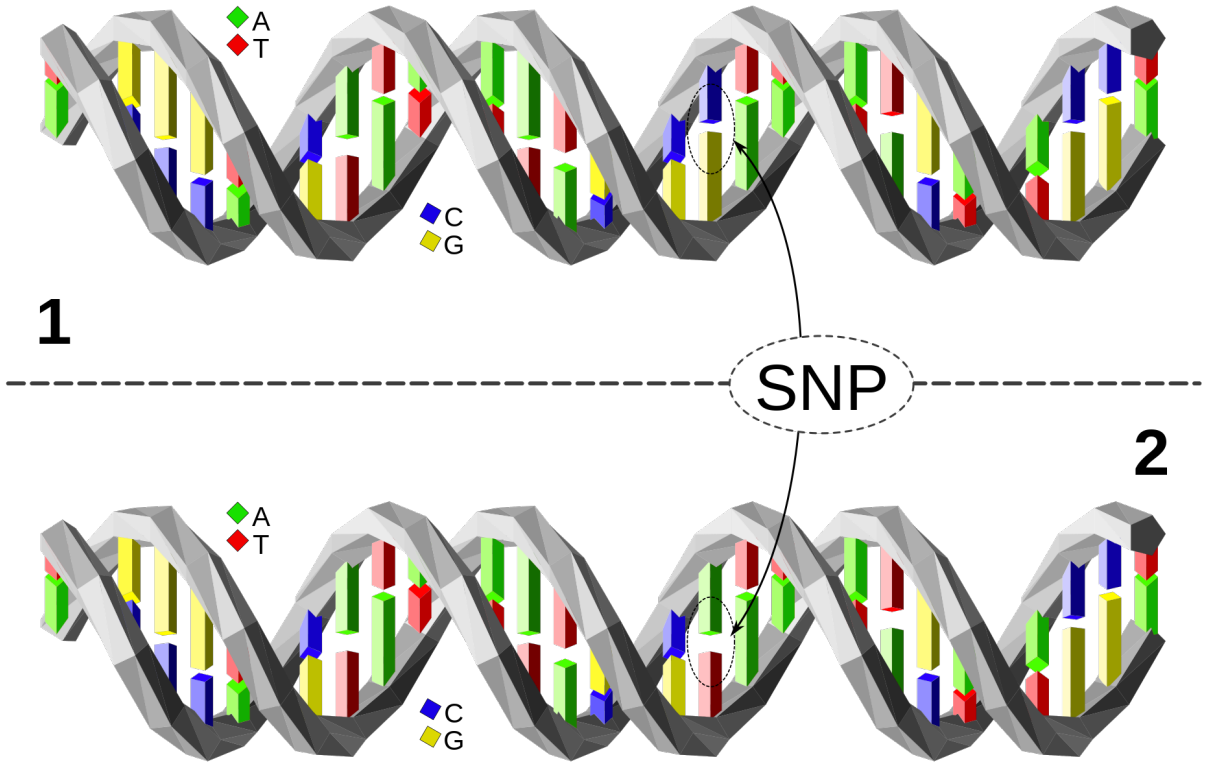




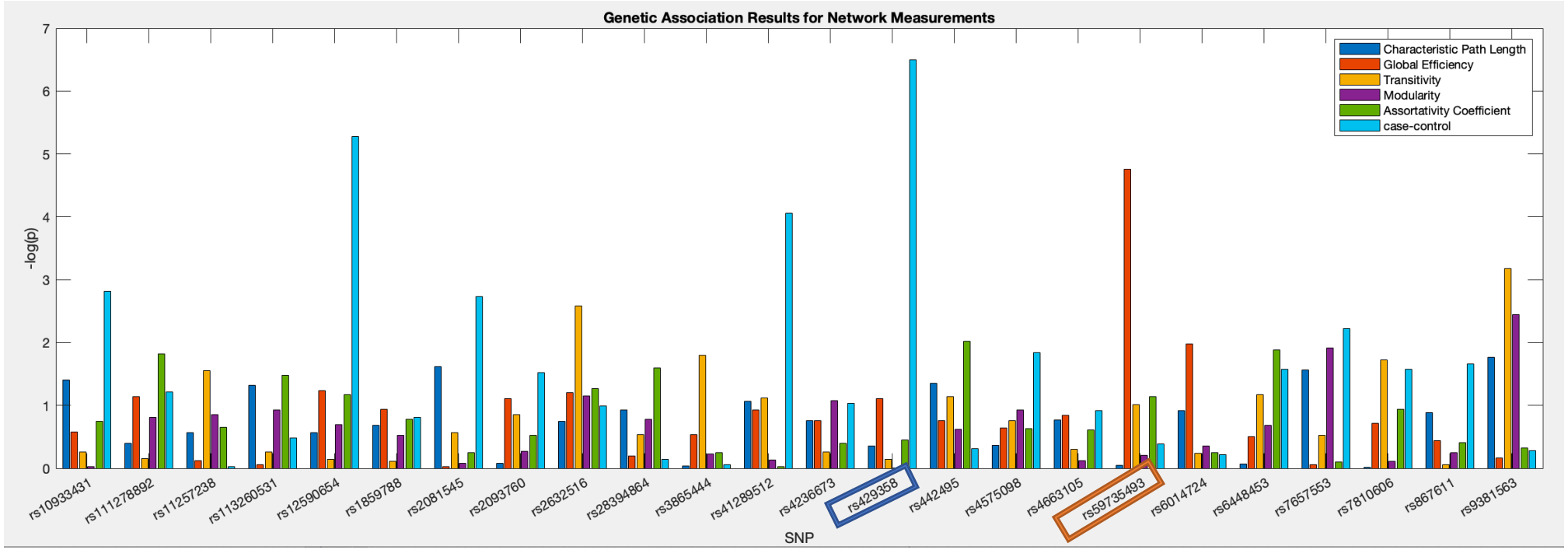
- Alzheimer’s Disease (AD)
- Mild Cognitive Impairment (MCI)
- Healthy Control (HC)

Understanding SNPs

- Substitution of a single nucleotide
  - Specific position in genome
  - Present to some appreciable degree within a population
- Focused on the presence of minor allele and if it increases/decreases phenotype mean
- SNPs are considered a form of genetic marker
  - Identify genes involved in inherited diseases such as AD



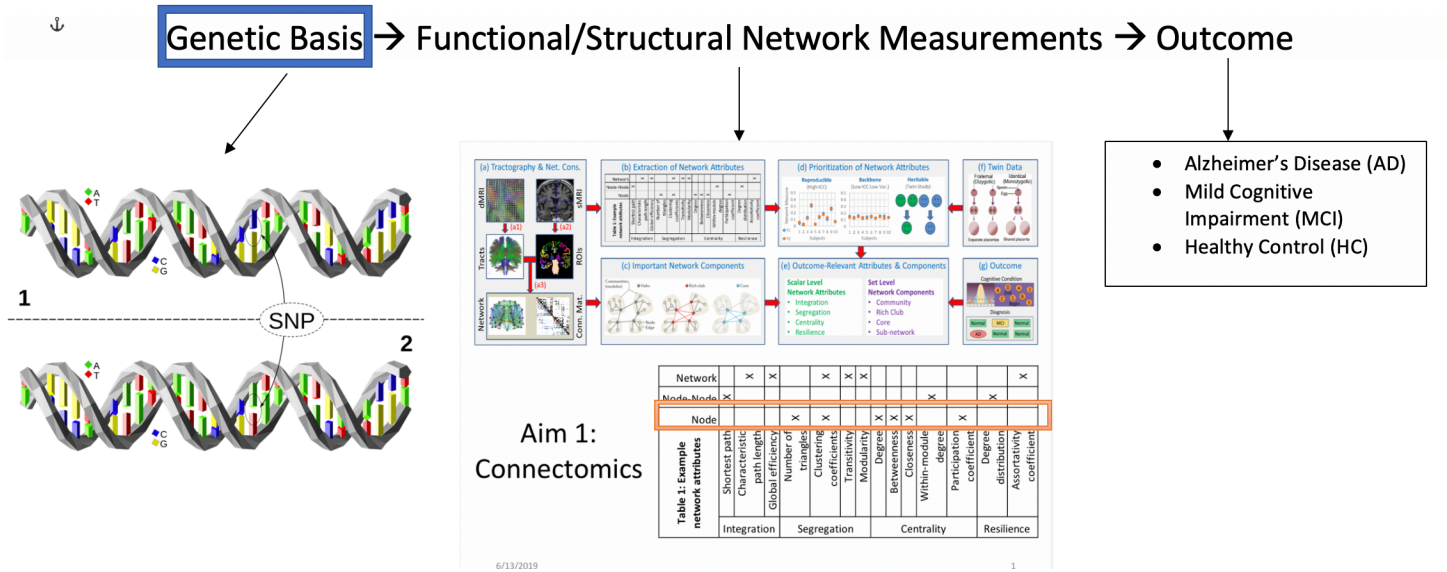
Results



Closest gene	CHR	SNP
ADAMTS4	1	rs4575098
CR1	1	rs2093760
BIN1	2	rs4663105
INPPD5	2	rs10933431
CLNK	4	rs6448453
HS3ST1	4	rs7657553
CD2AP	6	rs9381563
ZCWPW1	7	rs1859788
EPHA1	7	rs7810606
CLU/PTK2B	8	rs4236673
ECHDC3	10	rs11257238
MS4A6A	11	rs2081545
PICALM	11	rs867611
SLC24A4	14	rs12590654
ADAM10	15	rs442495
KAT8	16	rs59735493
SCIMP	17	rs113260531
ABI3	17	rs28394864
BZRAP1-AS1	17	rs2632516
ABCA7	19	rs111278892
APOE	19	rs41289512
APOE	19	rs429358
CD33	19	rs3865444
CASS4	20	rs6014724

Conclusion and Next Steps

- Structural connectivity analysis of network node measures
- Significant functional results
  - Within-module degree
  - Betweeness Centrality
- Conduct genetic association test with plink



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