New Technologies: What They Can Teach Us About Childhood Brain Disorders

NSTA Workshop

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...and may others

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Goals

- Functional Connectivity MRI
- The heterogeneity problem
- Graph theory
- Informing heterogeneity in samples via graph theory

The Heterogeneity Problem

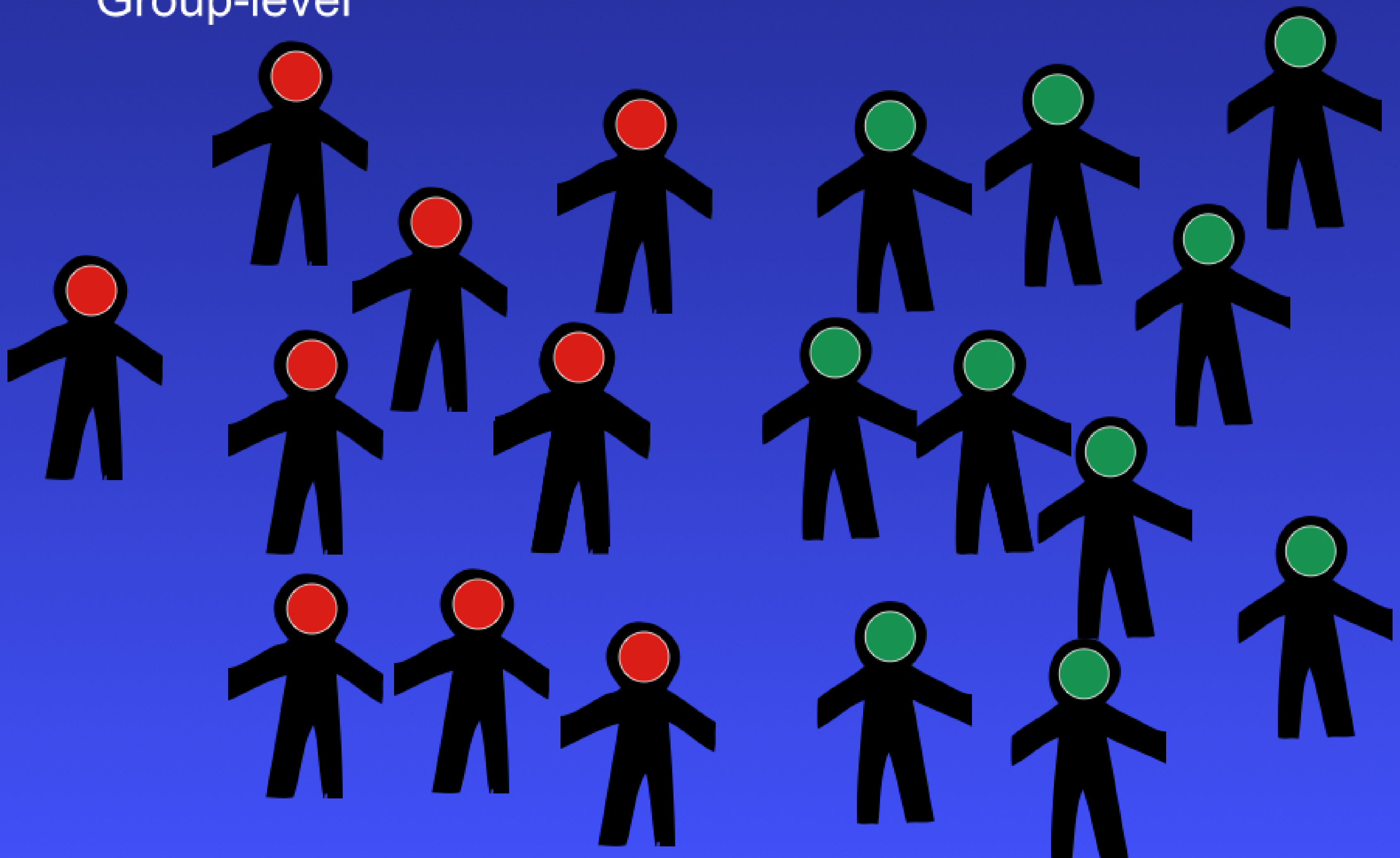
- One goal when examining complex behaviors or brain physiology in early youth is to determine whether this information directly associates with developmental trajectories or mental health issues now or later in life.

The Heterogeneity Problem

- Can information from non-invasive tools - psychiatric Dx (e.g., childhood ADHD), brain imaging, behavioral testing, etc. - at a given developmental stage assist in predicting future outcomes?
- Can this information help us tailor education or provide early interventions to improve health or other long-term outcomes of a given individual?

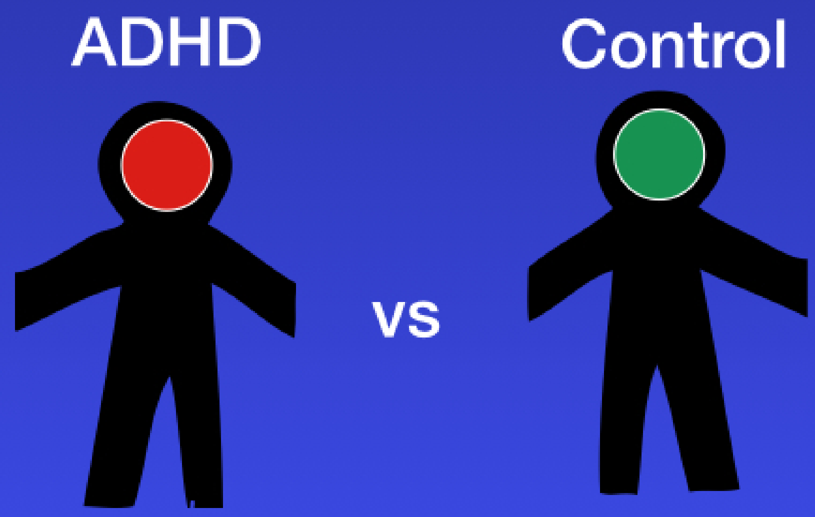
Traditional Group Studies

Group-level



Traditional Group Studies

Group-level

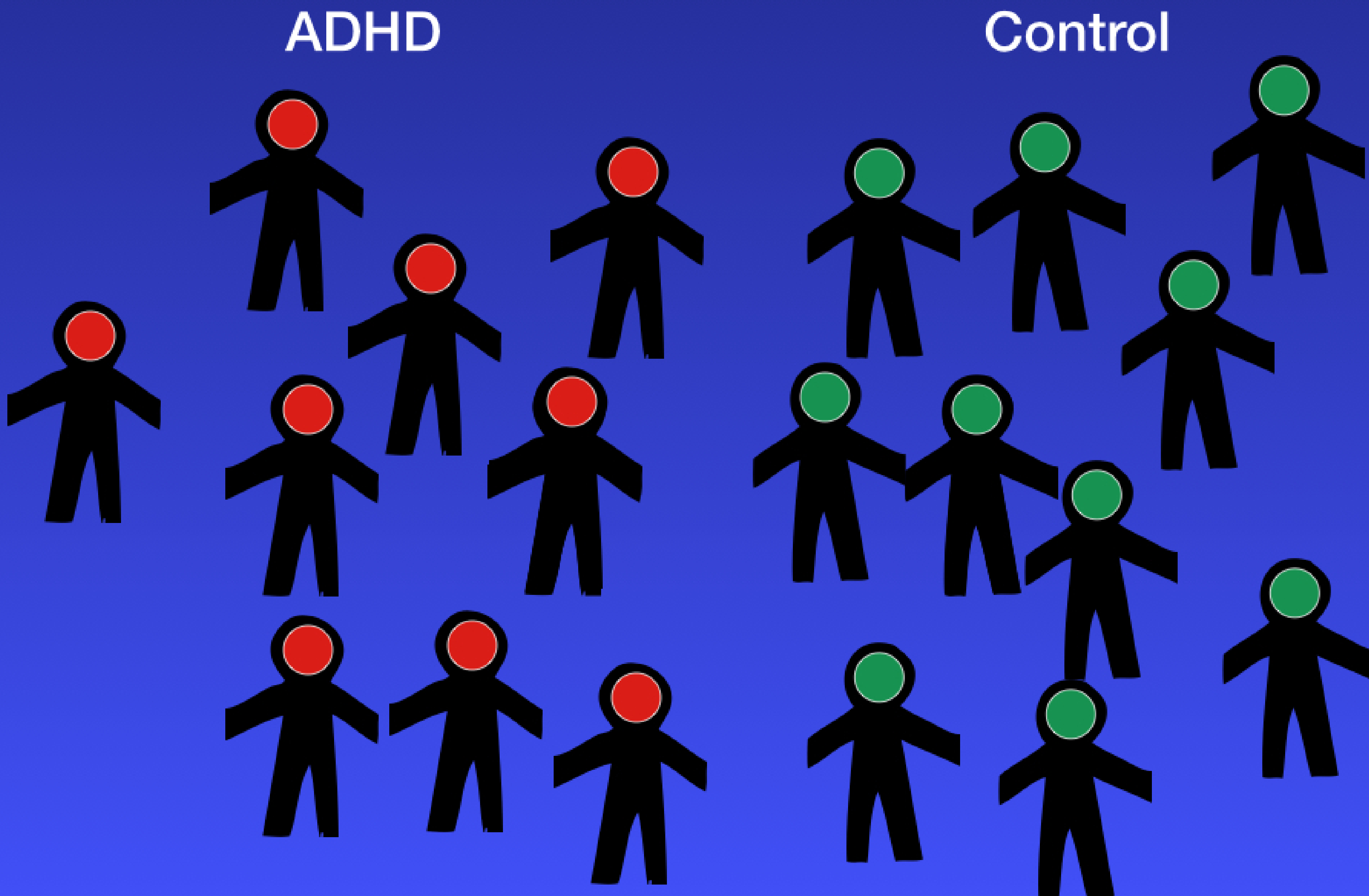


Traditional Group Studies

- **First:** This model largely relies on the assumption that our current diagnostic categories represents etiologically homogeneous syndromes.

- **Second:** the model also presumes that the control population represents one homogeneous group

Traditional Group Studies



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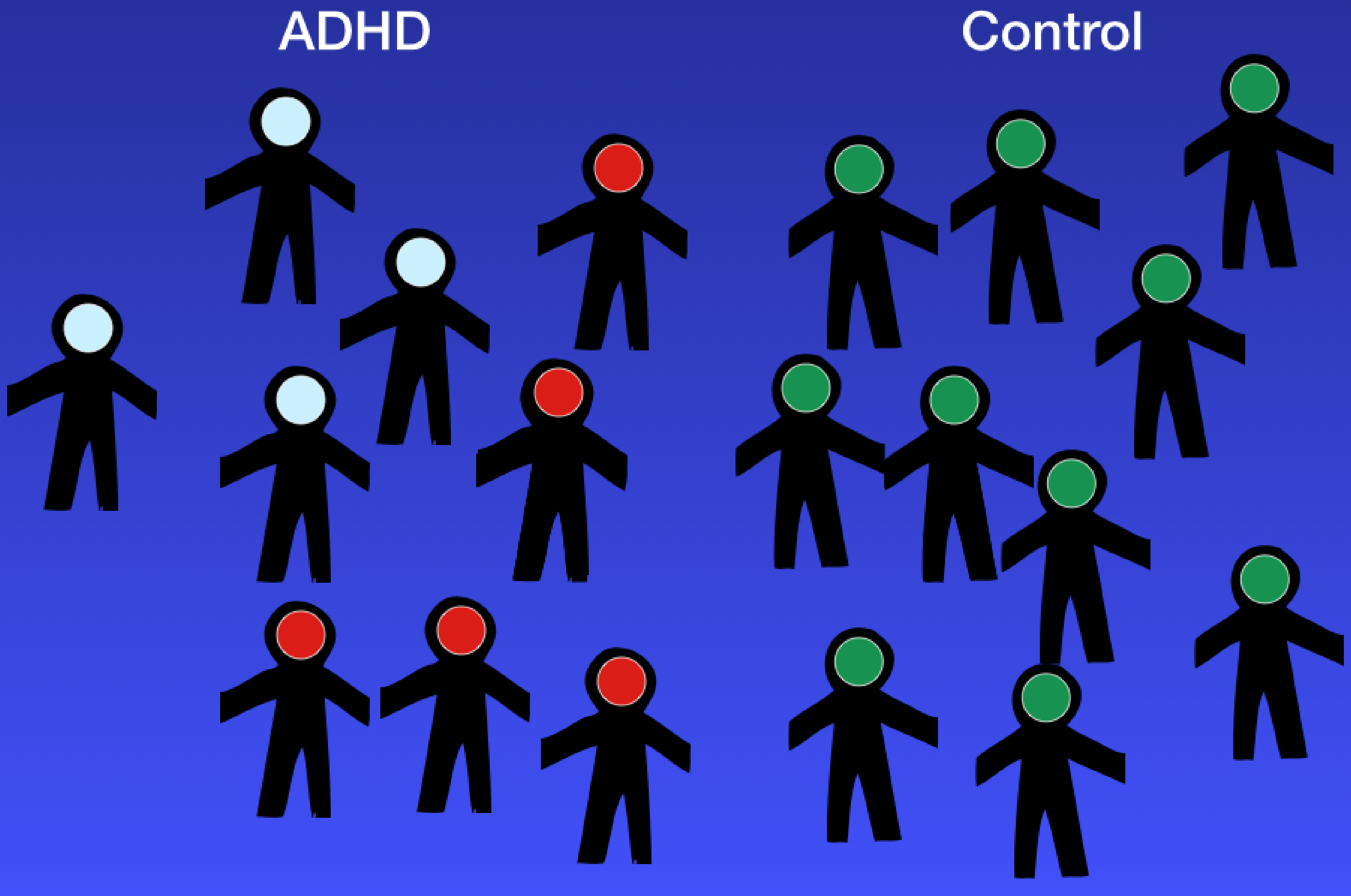

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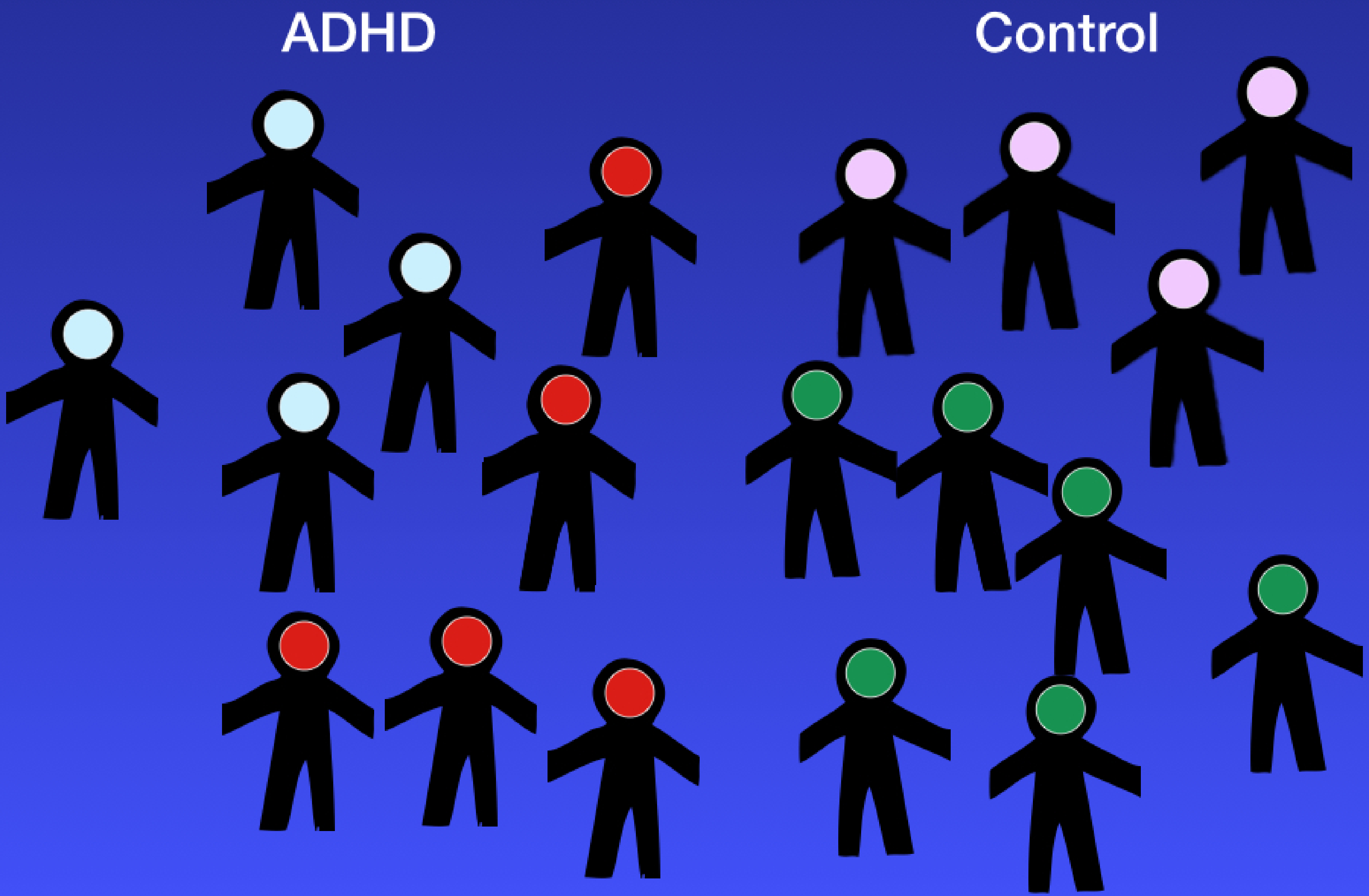

Traditional Group Studies

Executive Dysfunction and Delay Aversion in Attention Deficit Hyperactivity Disorder: Nosologic and Diagnostic Implications

Edmund J.S. Sonuga-Barke PhD[a, b, c], Joseph A. Sergeant PhD[d], Joel Nigg PhD[e], Erik Willcutt PhD[f]

Traditional Group Studies

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Pathologies of brain attentional networks

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NEUROSCIENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE SEARCH FOR ENDOPHENOTYPES

F. Xavier Castellanos and Rosemary Tannock‡*

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Temperament and Attention Deficit Hyperactivity Disorder: The Development of a Multiple Pathway Model

Joel T. Nigg
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Psychological heterogeneity in AD/HD—a dual pathway model of behaviour and cognition

Edmund J.S. Sonuga-Barke *

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Received 23 December 2000; accepted 13 August 2001

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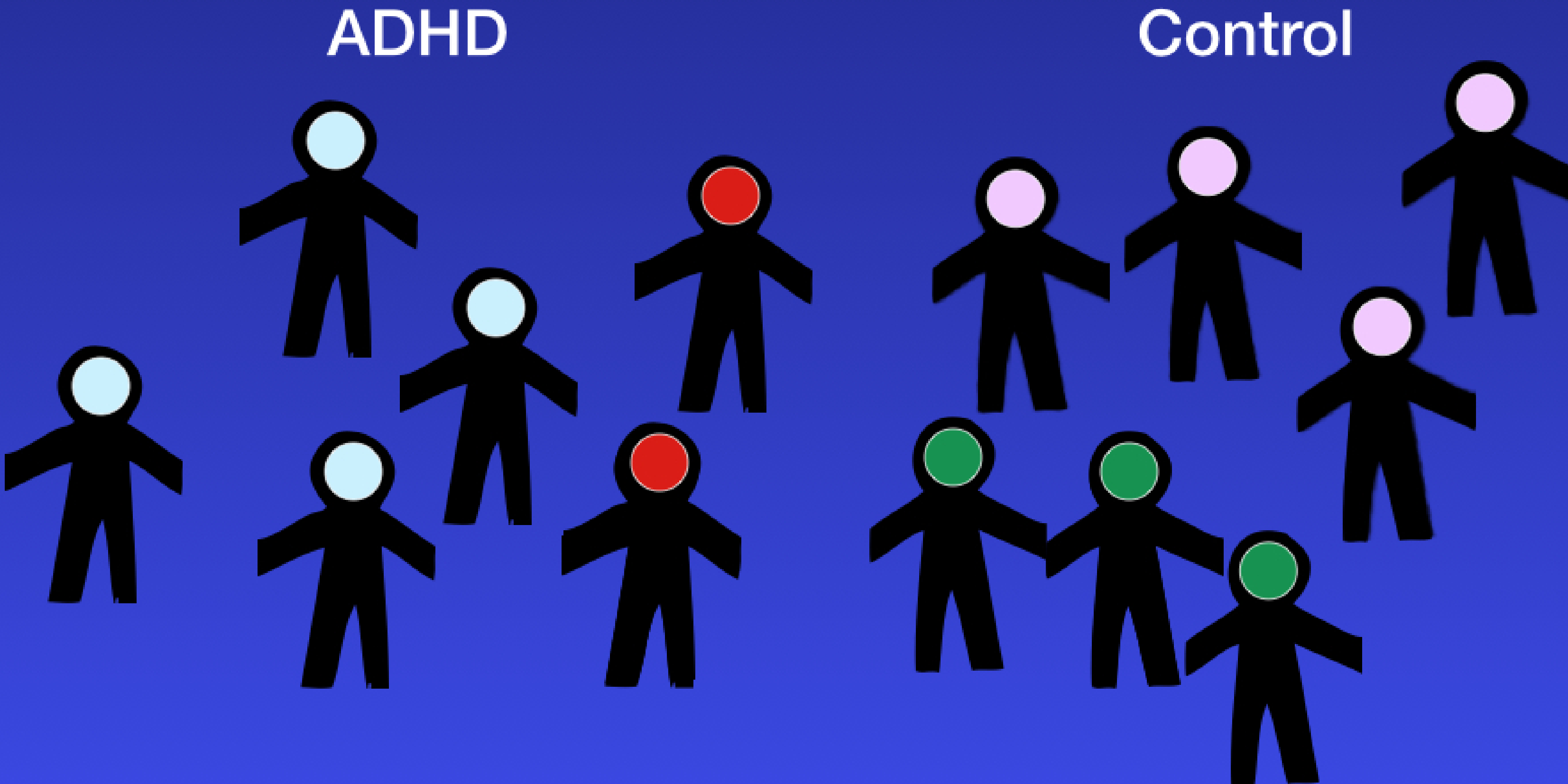
Causal Heterogeneity in Attention-Deficit/Hyperactivity Disorder: Do We Need Neuropsychologically Impaired Subtypes?

Joel T. Nigg, Erik G. Willcutt, Alysa E. Doyle, and Edmund J.S. Sonuga-Barke

Traditional Group Studies

- Although it is easy to propose conceptually that there must be distinct subgroups within mental disorders (or typical populations), empirically demonstrating such subgroups is not straightforward.

Traditional Group Studies



Total Number of Partitions of Sets of Size n

n =	3	4	5	6	7	8	9	10..........	15...............	20.....
partitions =	2	5	15	52	203	877	4,140	21,147	1.38e+09	5.17e+13

Goals

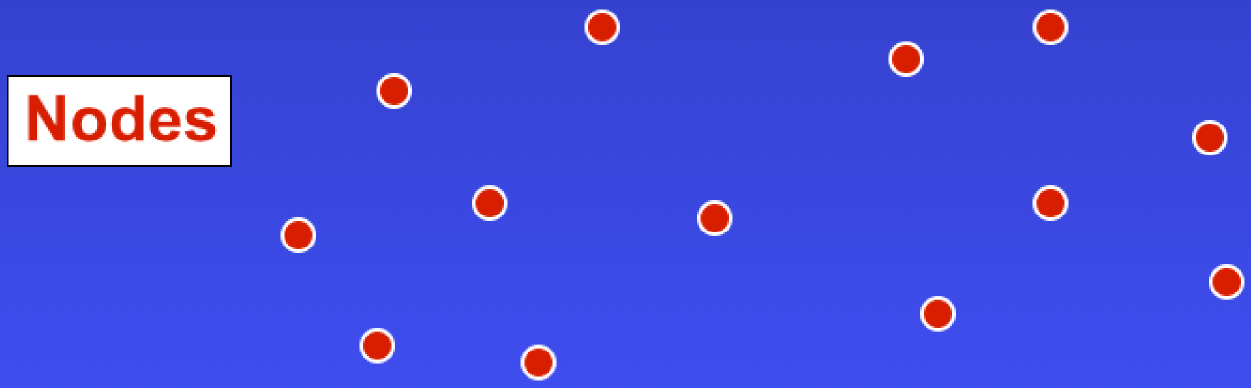
- Functional Connectivity MRI
- The heterogeneity problem
- Graph theory
- Informing heterogeneity in samples via graph theory

Graph theoretical Analyses

- What is a Network?

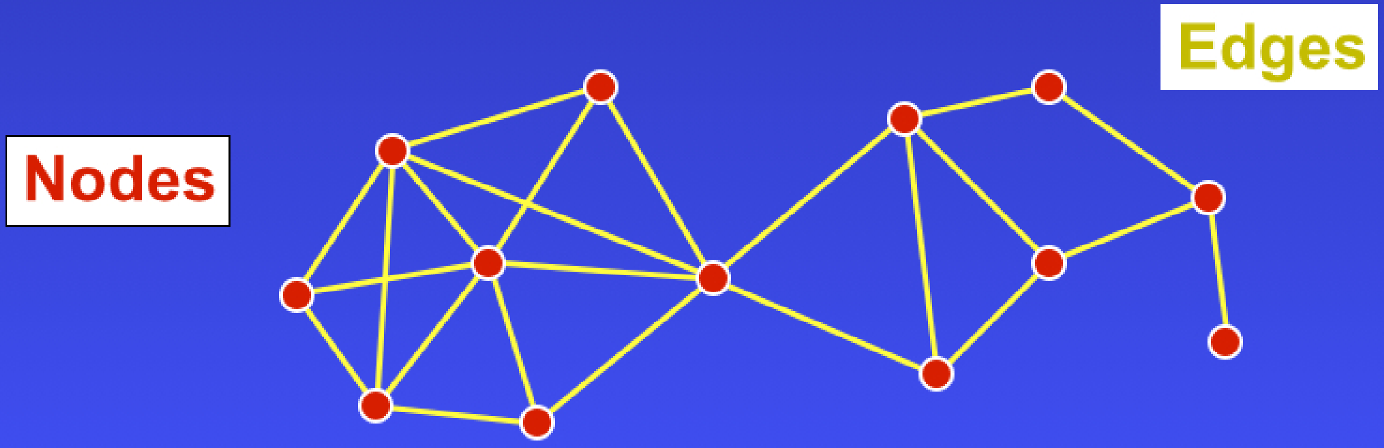
Graph theoretical Analyses

- What is a Network?
  - In its simplest form, a network is a collection of points (or nodes) ...



Graph theoretical Analyses

- What is a Network?
  - In its simplest form, a network is a collection of points (or nodes) ... joined by lines or edges



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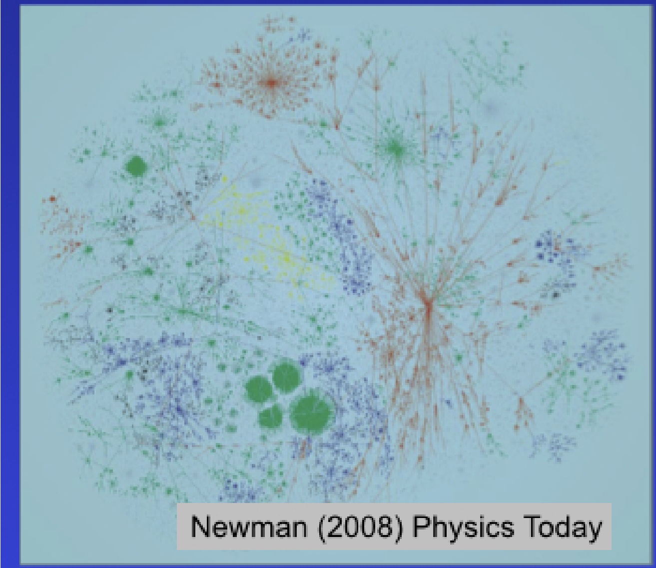
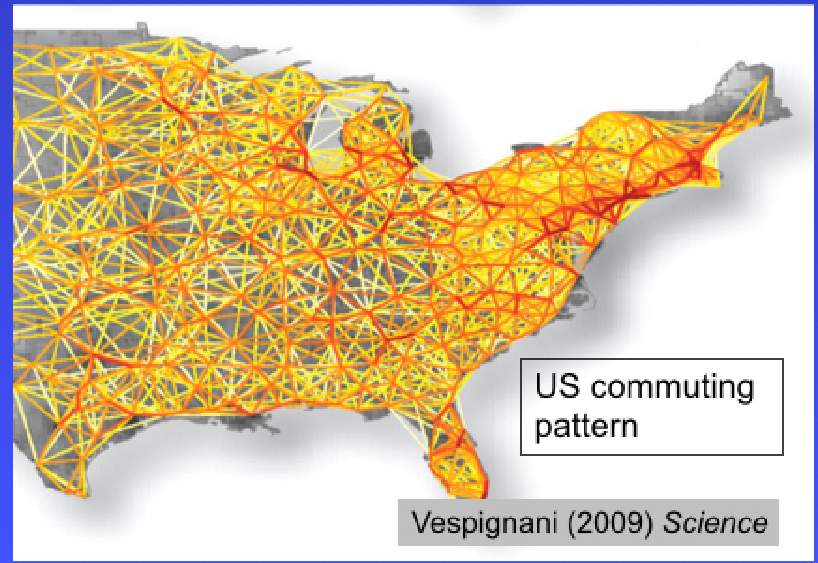


Newman (2008) Physics Today

Networks of the Internet

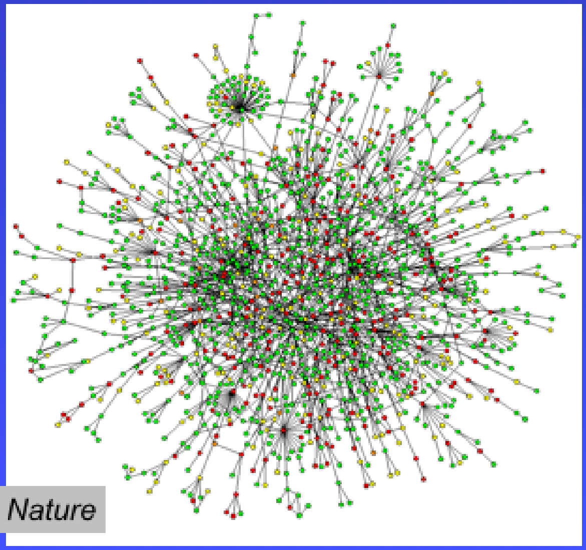
US House of Representatives committees and subcommittees

Porter et al. (2009) *Notices of the AMS*



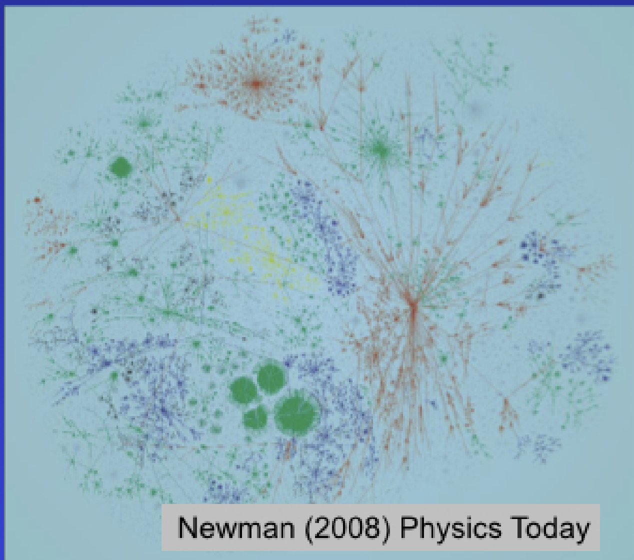
Vespignani (2009) *Science*

Yeast Interactome



Jeong et al. (2001) *Nature*

Graph theoretical Analyses



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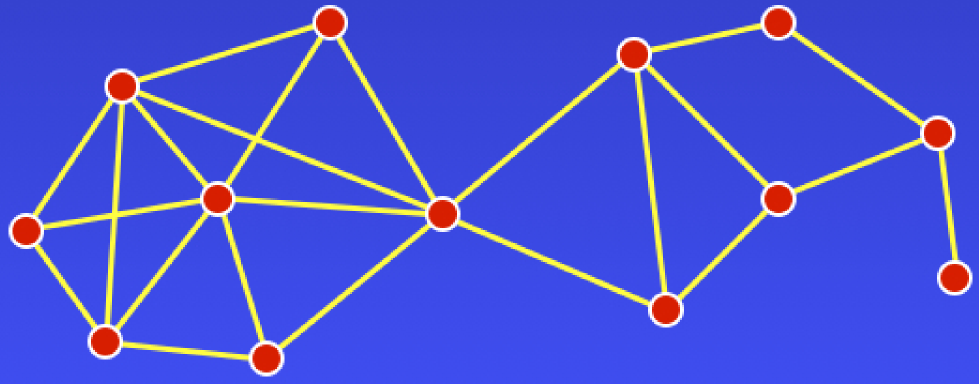
How do we quantify these patterns?

What do they mean with regard to the nature of the system?

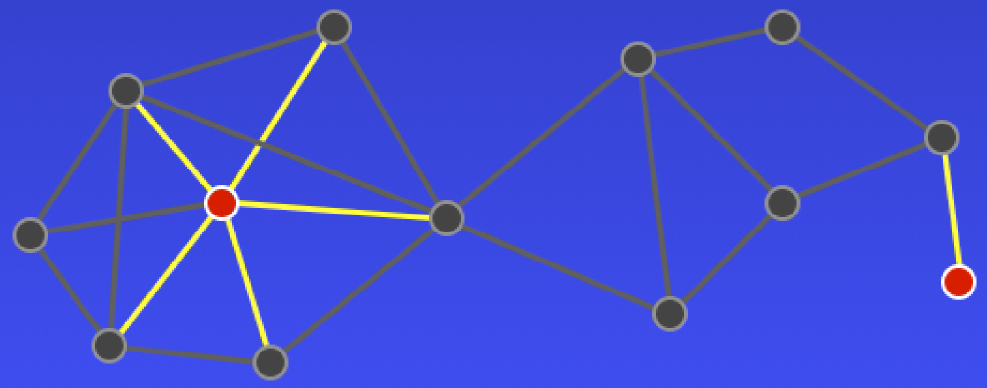
Graph theoretical Analyses

- Metrics regarding network structure



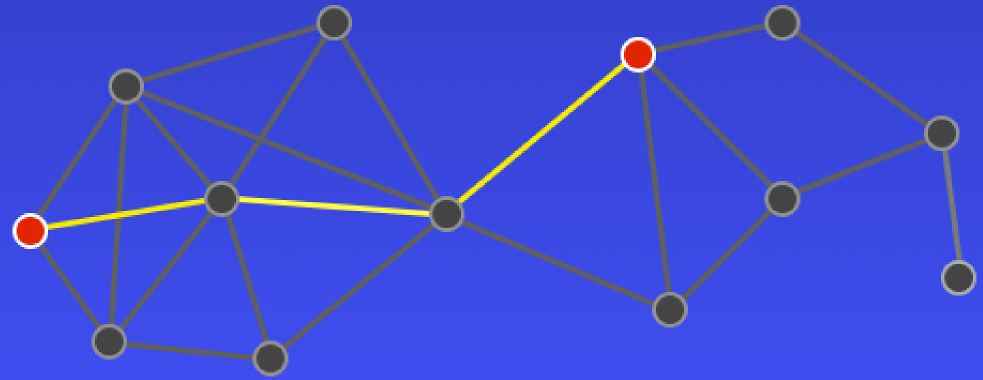
Graph theoretical Analyses

- Metrics regarding network structure
  - **Degree** - total number of edges for a node
    - Related to **Density** - number of actual connections over total possible



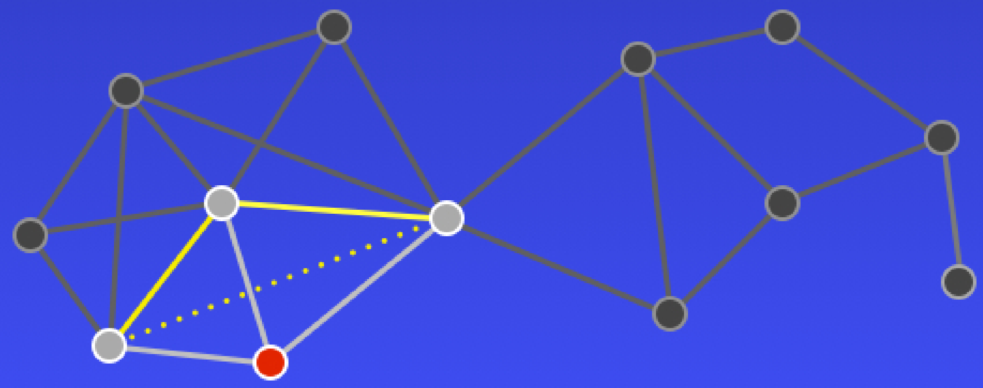
Graph theoretical Analyses

- Metrics regarding network structure
  - *Degree*
  - **Path length -** # of nodes crossed to reach another nodes .... 1/L describes the efficiency of the system

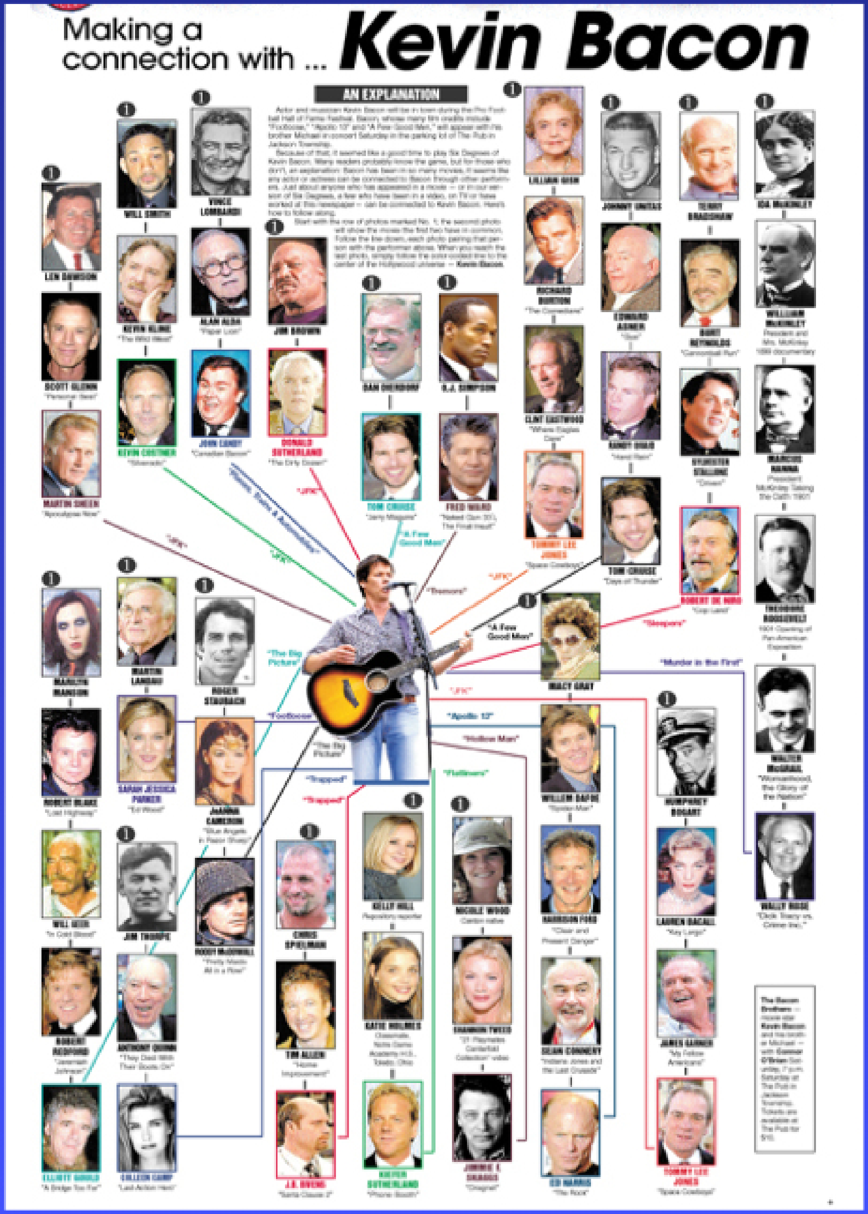


Graph theoretical Analyses

- Metrics regarding network structure
  - *Degree - Path length*
  - **Clustering Coefficient -** how many connections exist between a given node's neighbors (i.e. given N neighbors of X, what % of N-N edges exist?)

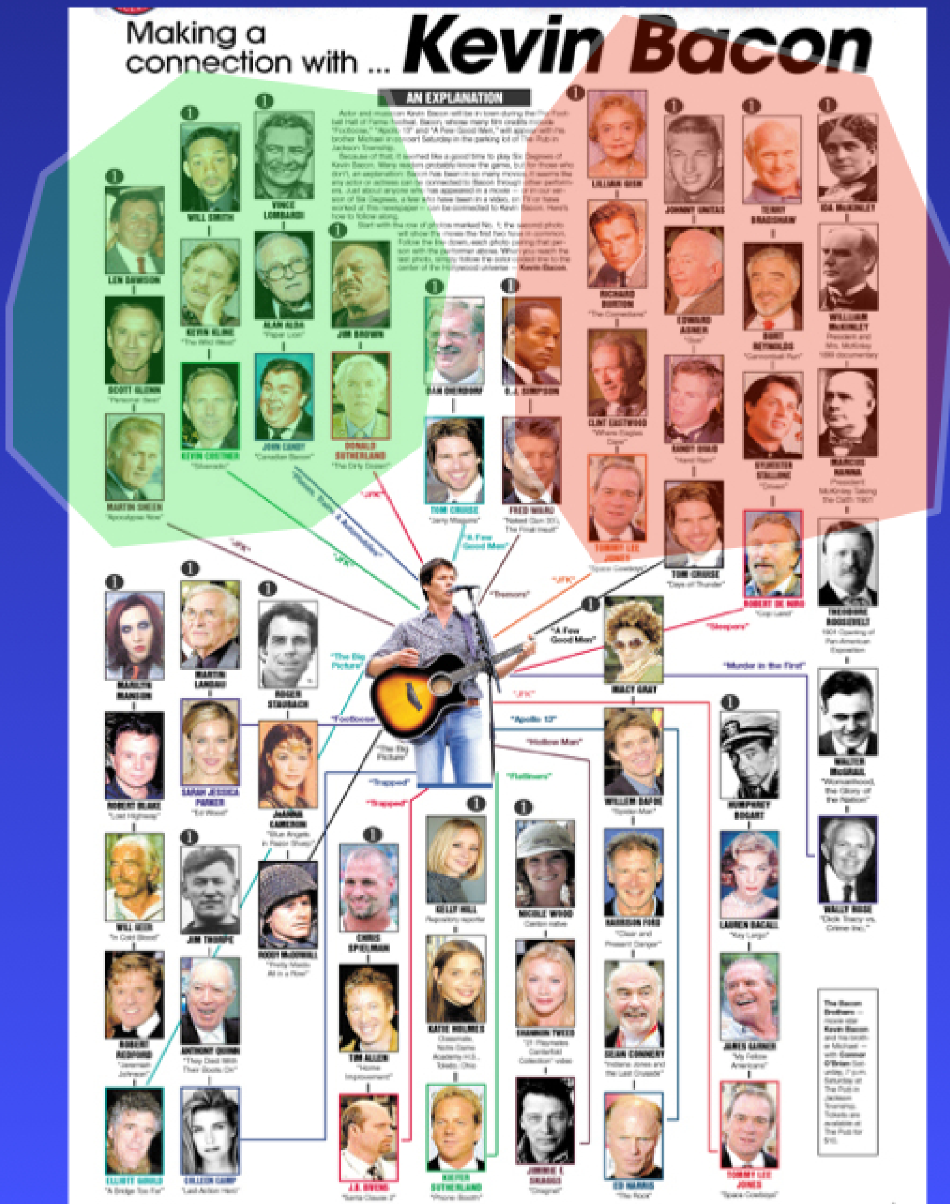


Small World Networks



Small World Networks

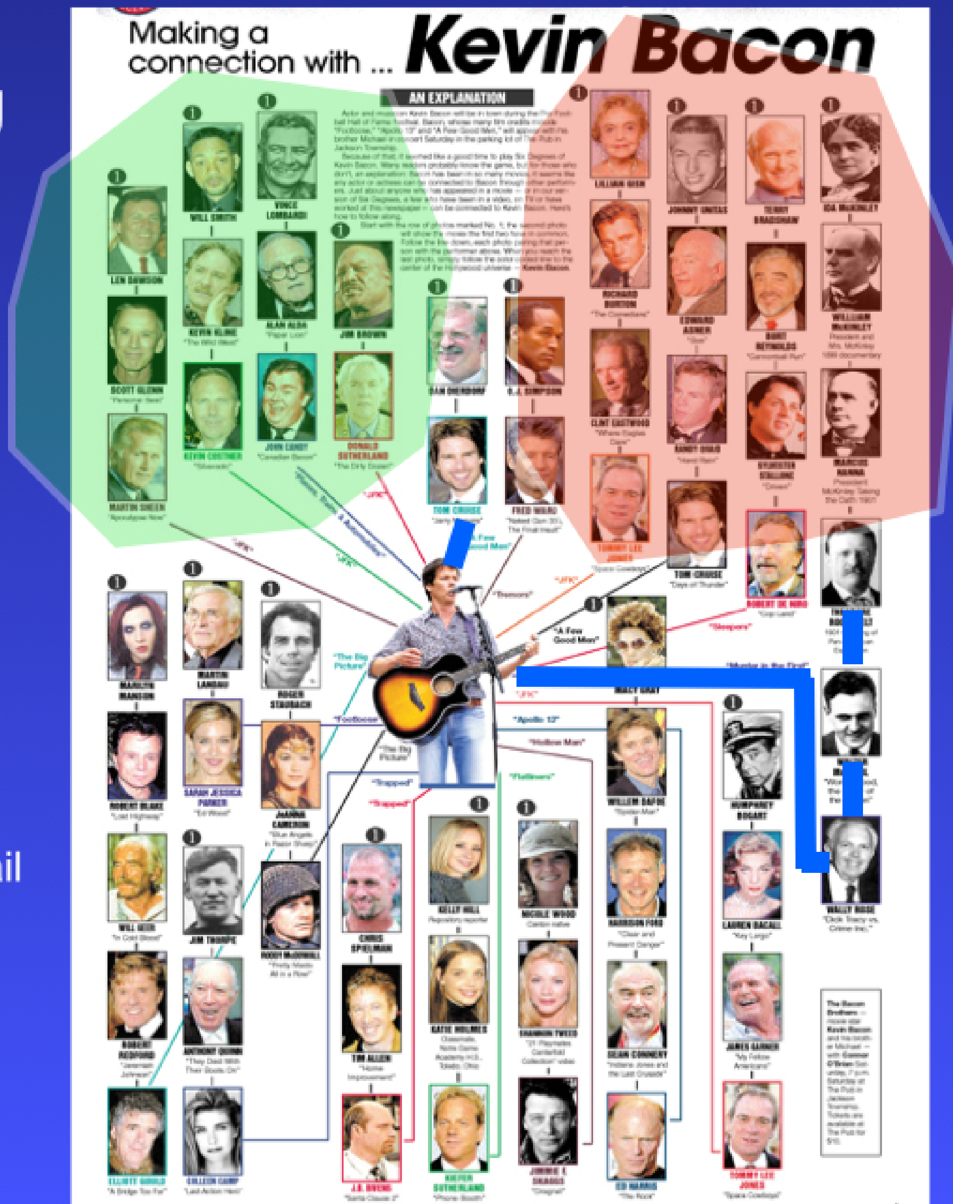
High Clustering



Small World Networks

High Clustering

Short Paths



Tom Cruise
“A few Good Men”
with Kevin Bacon

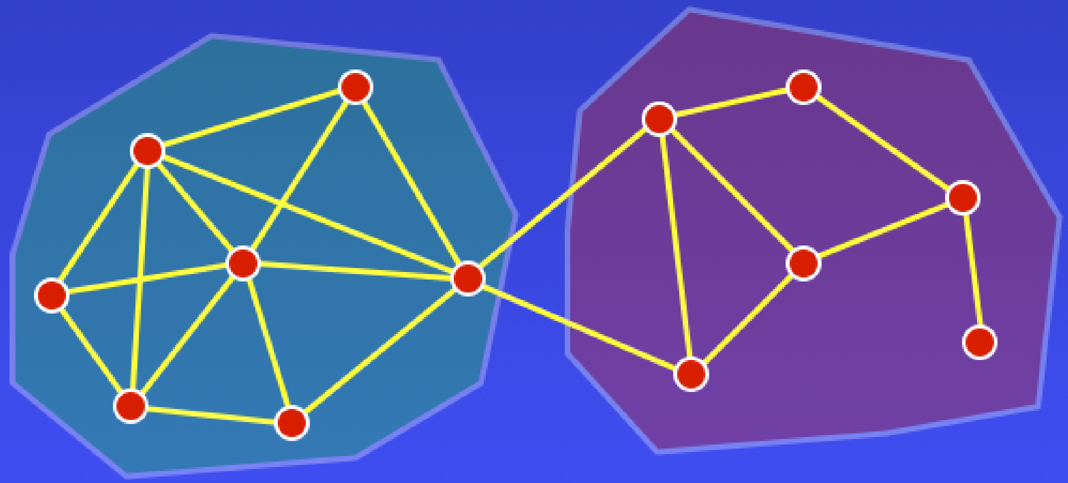
...who was in
“Murder in the First”
(1995) with Wally Rose

...who was in
“Dick Tracy vs Crime Inc
(1941) with Walter McGrail

...who was in
“Womanhood, the Glory
of the Nation (1917) with
Teddy

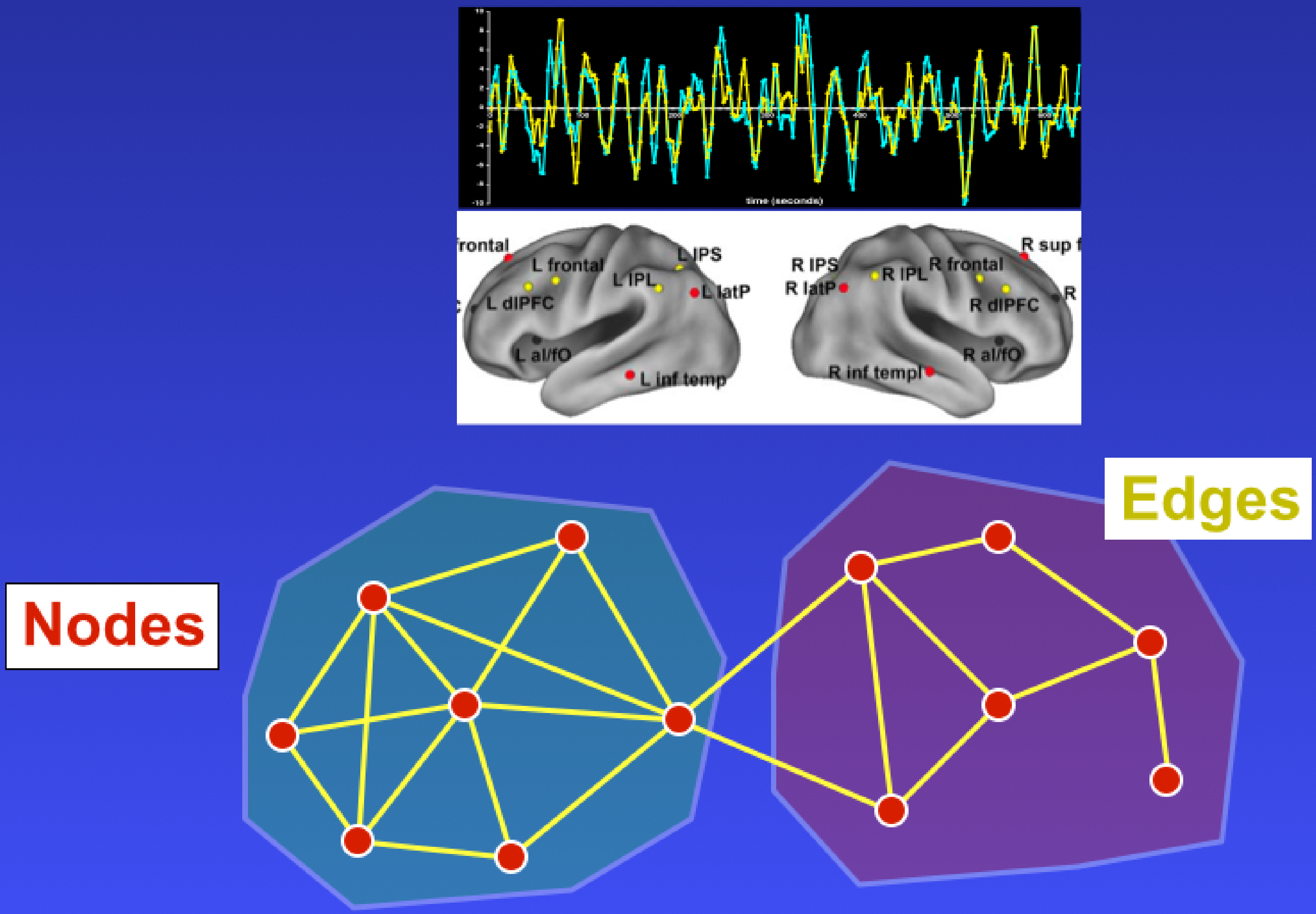
Graph theoretical Analyses

- Metrics regarding network structure
  - *Degree, Path length, Clustering Coef, Rich Club*
  - **Modules -** clusters of nodes that are densely connected

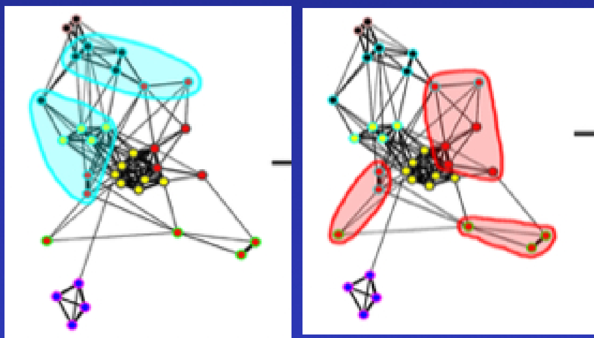


The modularity is… the number of edges falling within groups minus the expected number in an equivalent network with edges placed at random." -Newman, 2006

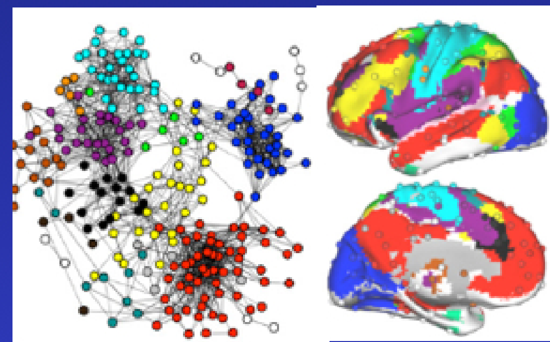
Graph theoretical Analyses



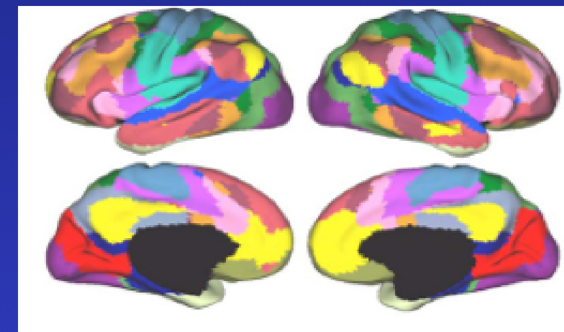
rs-fcMRI: Network structure of the brain



Fair et al, 2009



Power et al, 2011



Yeo et al, 2011

$$Q = 1/m \sum_{ij} \left[A_{ij} - \frac{k_i^{in} k_j^{out}}{m} \right] (s_i s_j + 1)$$

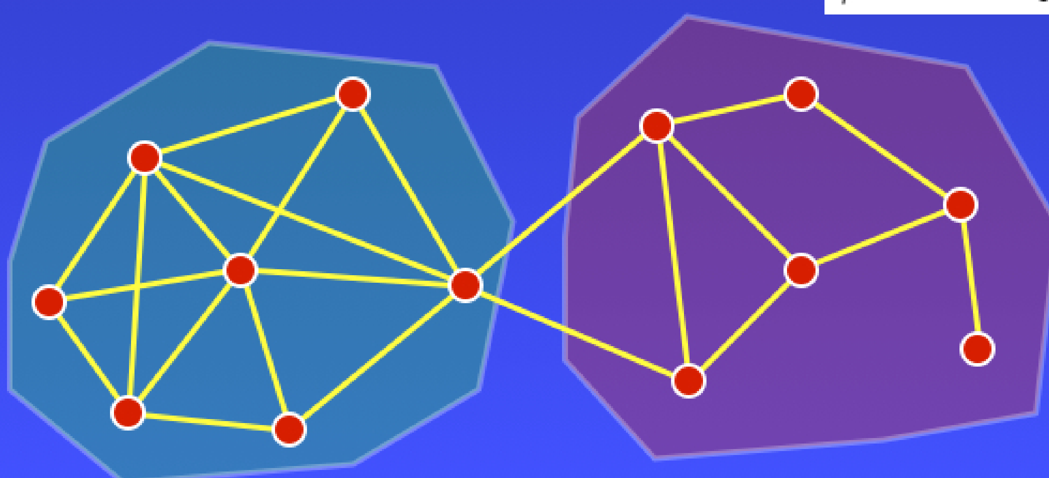
Modularity

Q = (fraction of edges within communities) – (expected fraction of such edges)

k_i = in degree of vertex i

m = total number of edges in network

s_i = +1 if assigned to same as j, -1 if diff.



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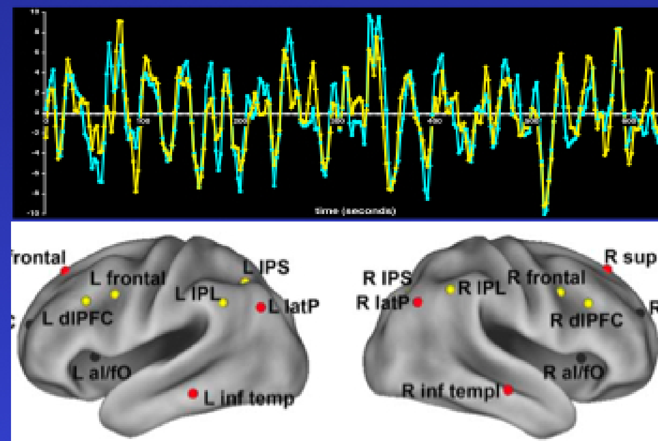

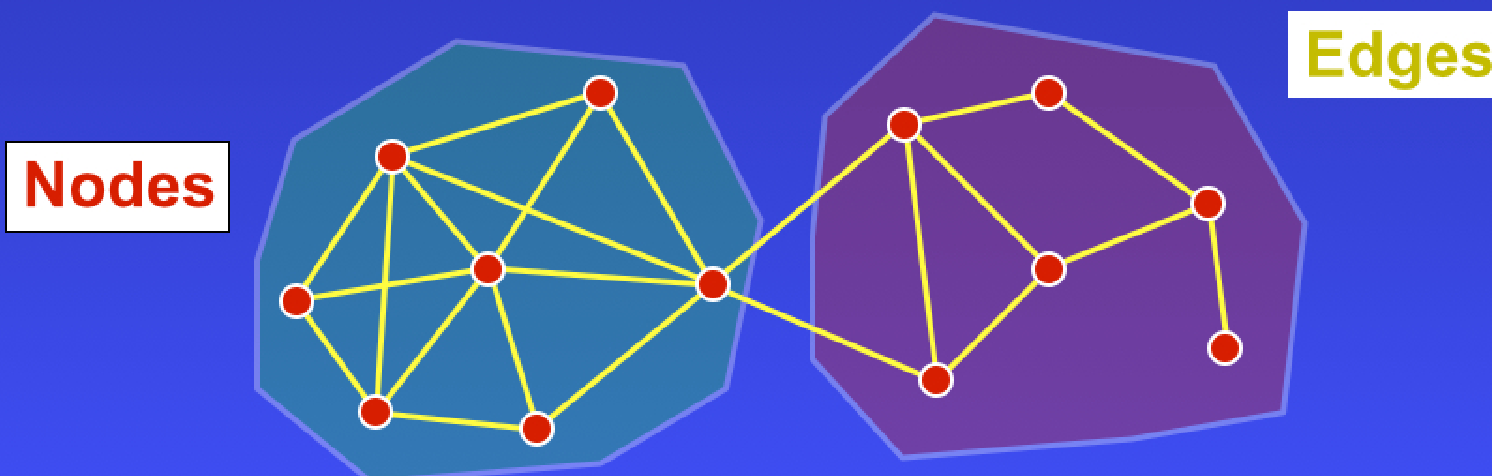

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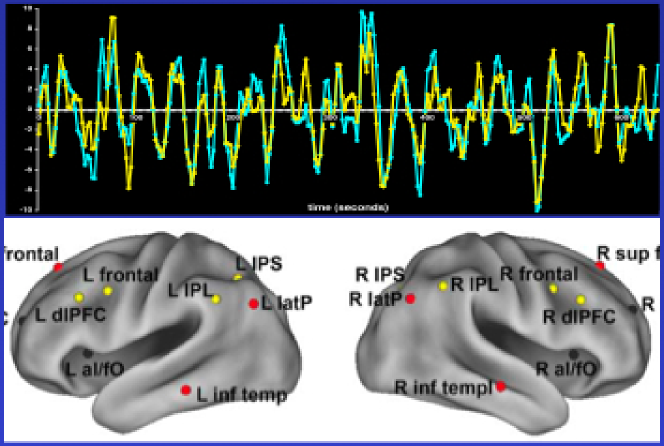
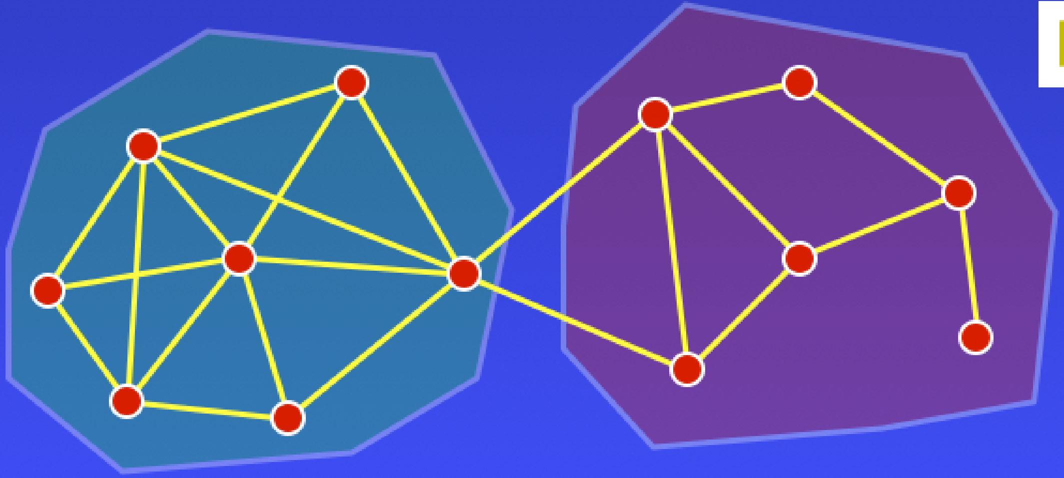


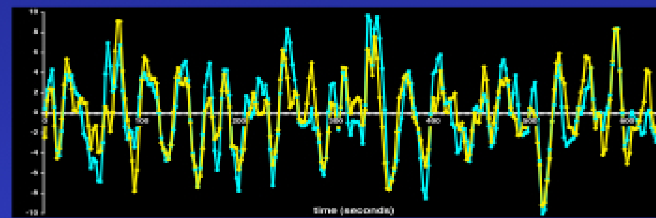
Nodes



Nodes

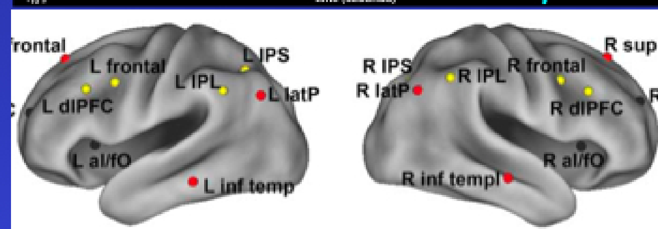
Edges

Graph theoretical Analyses



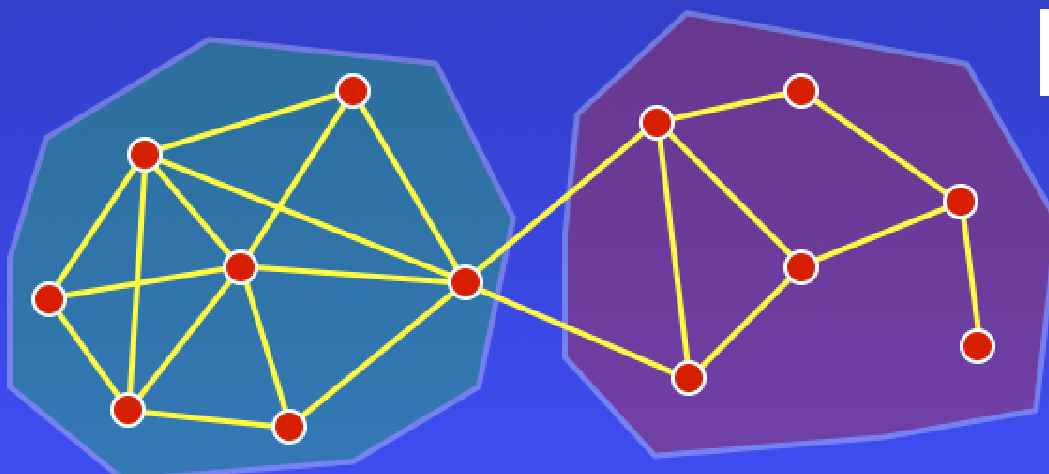
Edges

Nodes



Edges

Nodes



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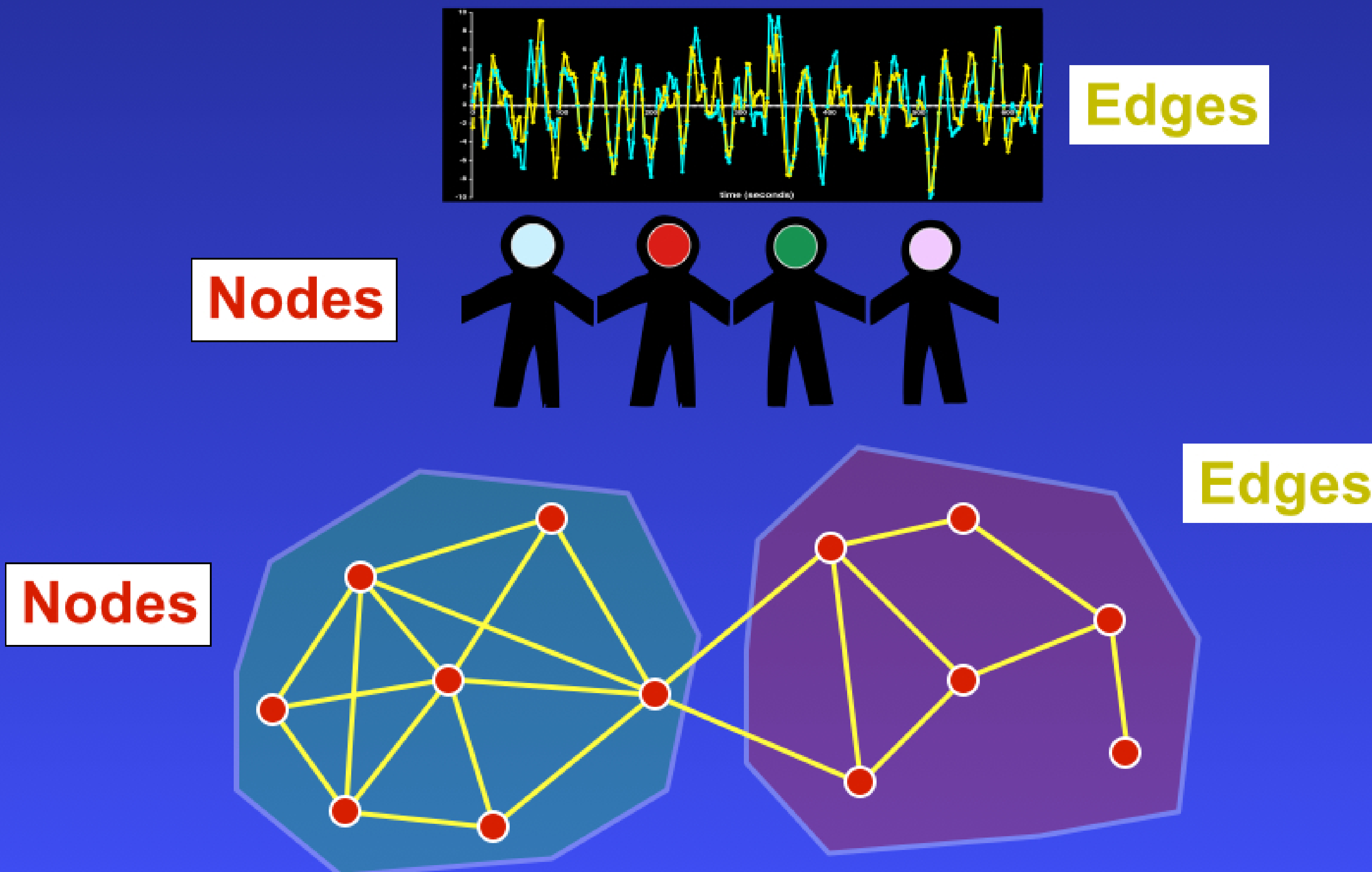
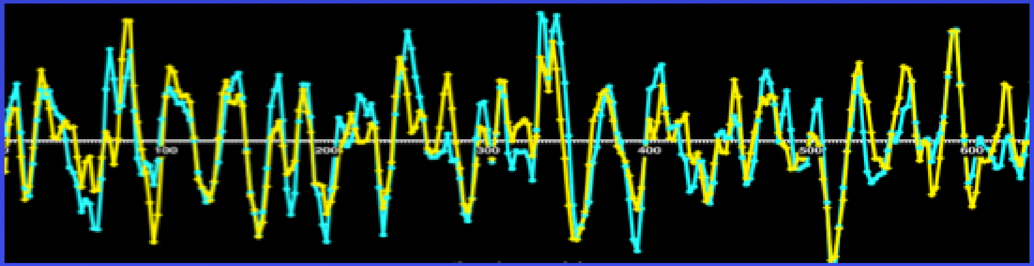
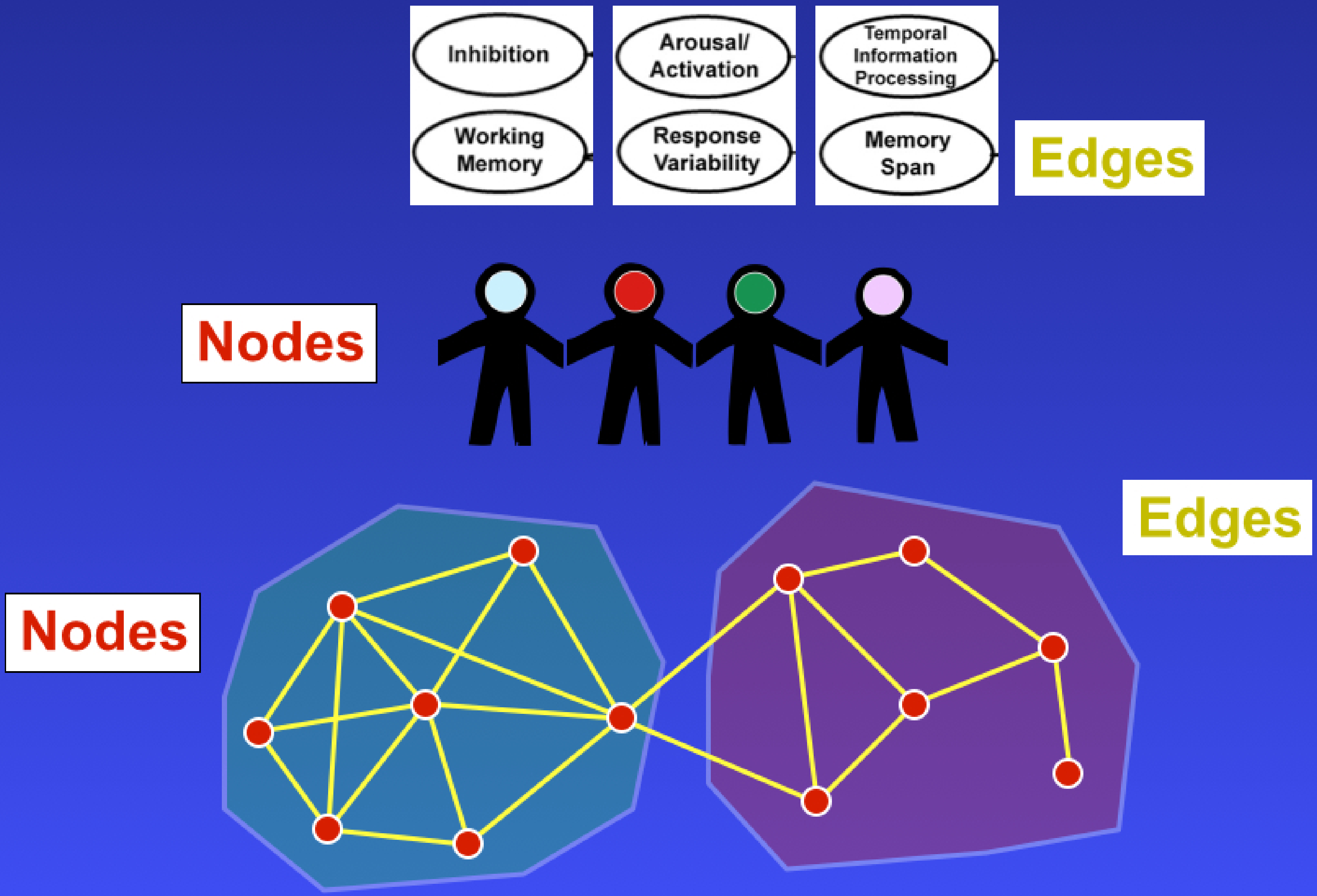


Traditional fMRI



Biswal et al, (1995)

Graph theoretical Analyses



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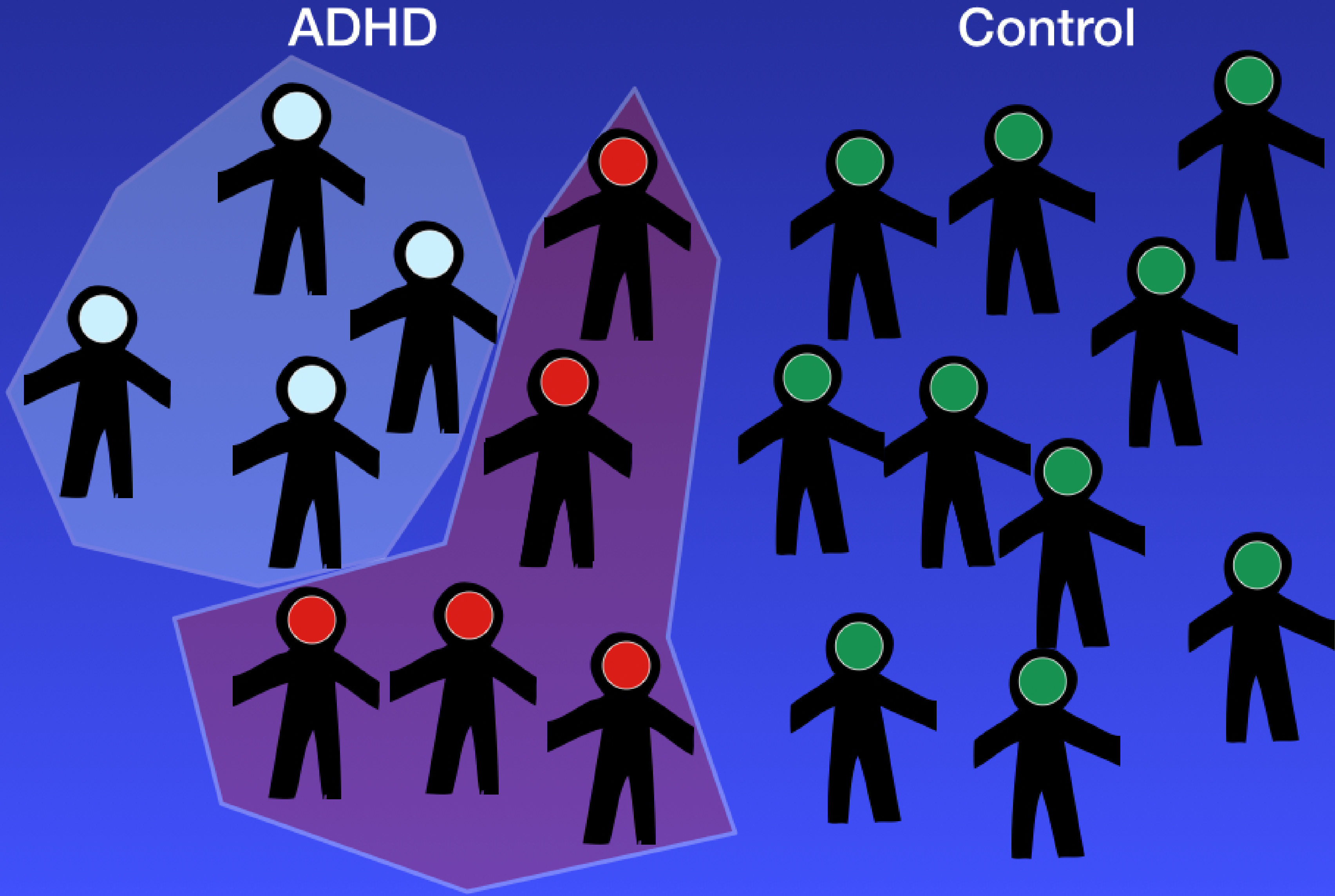

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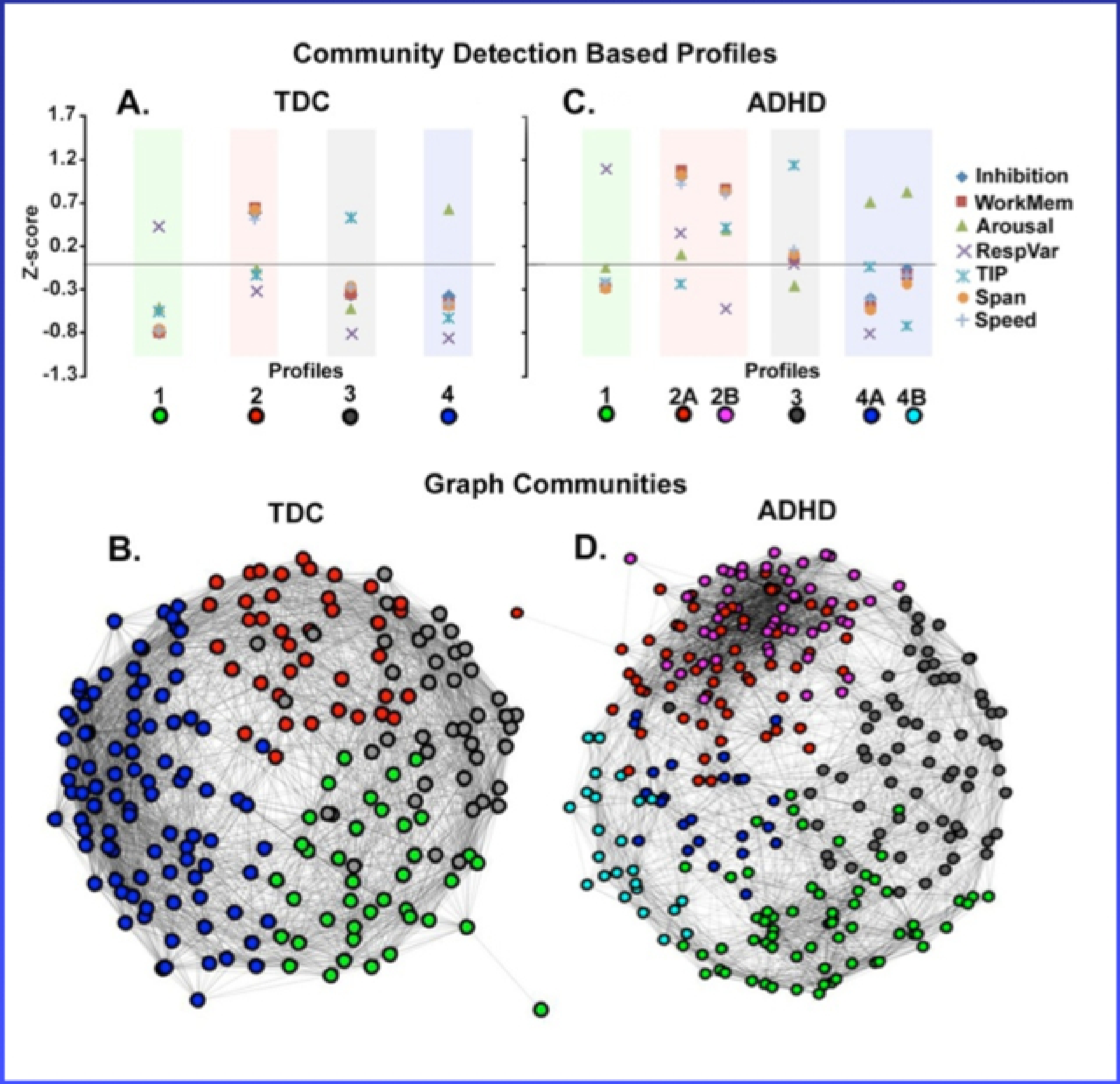
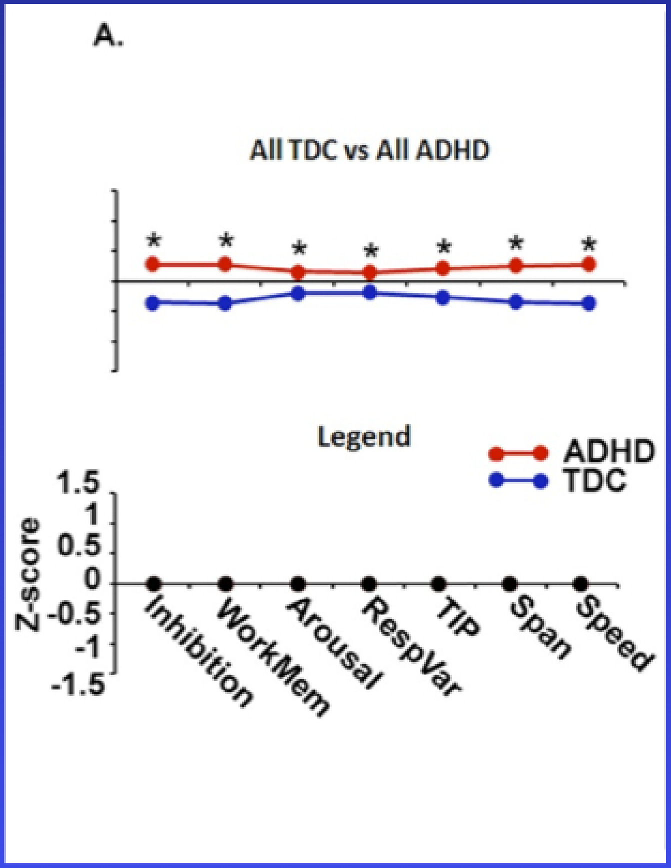
Heterogeneity in ADHD



N
Profile 1 = 92
Profile 2 = 43
Profile 3 = 39
Profile 4 = 39

N
Profile 1 = 61
Profile 2A = 49
Profile 2B = 56
Profile 3 = 71
Profile 4A = 24
Profile 4B = 24

Heterogeneity in ADHD



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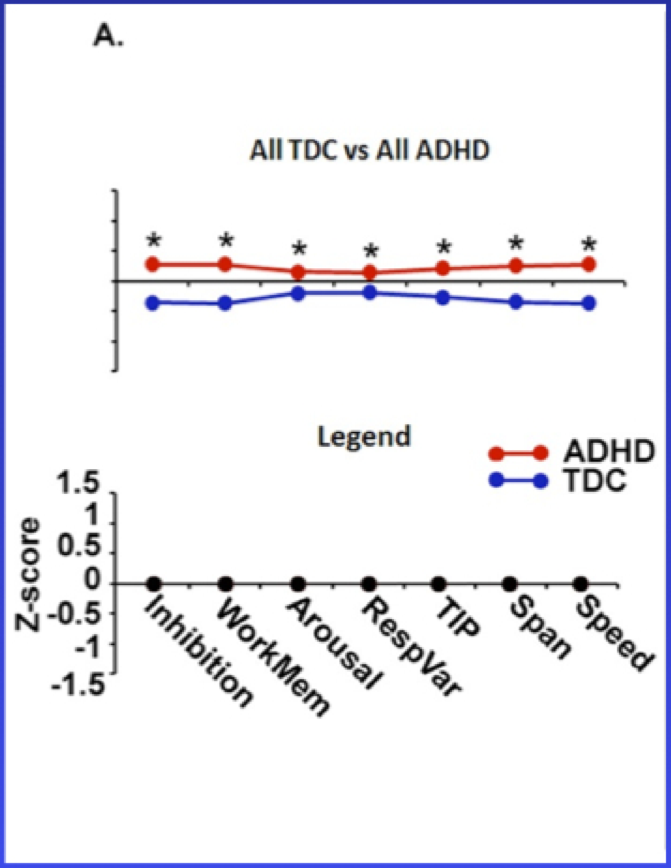

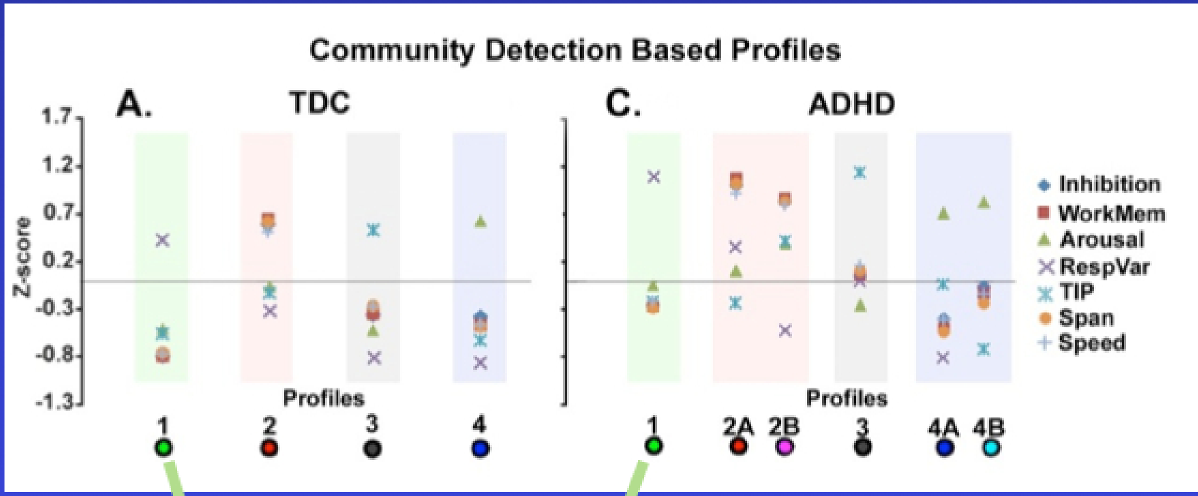

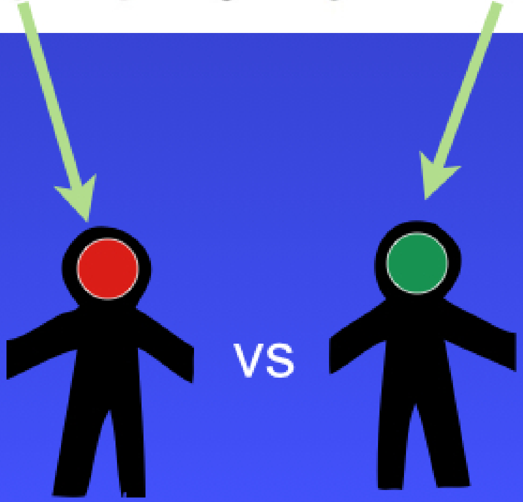

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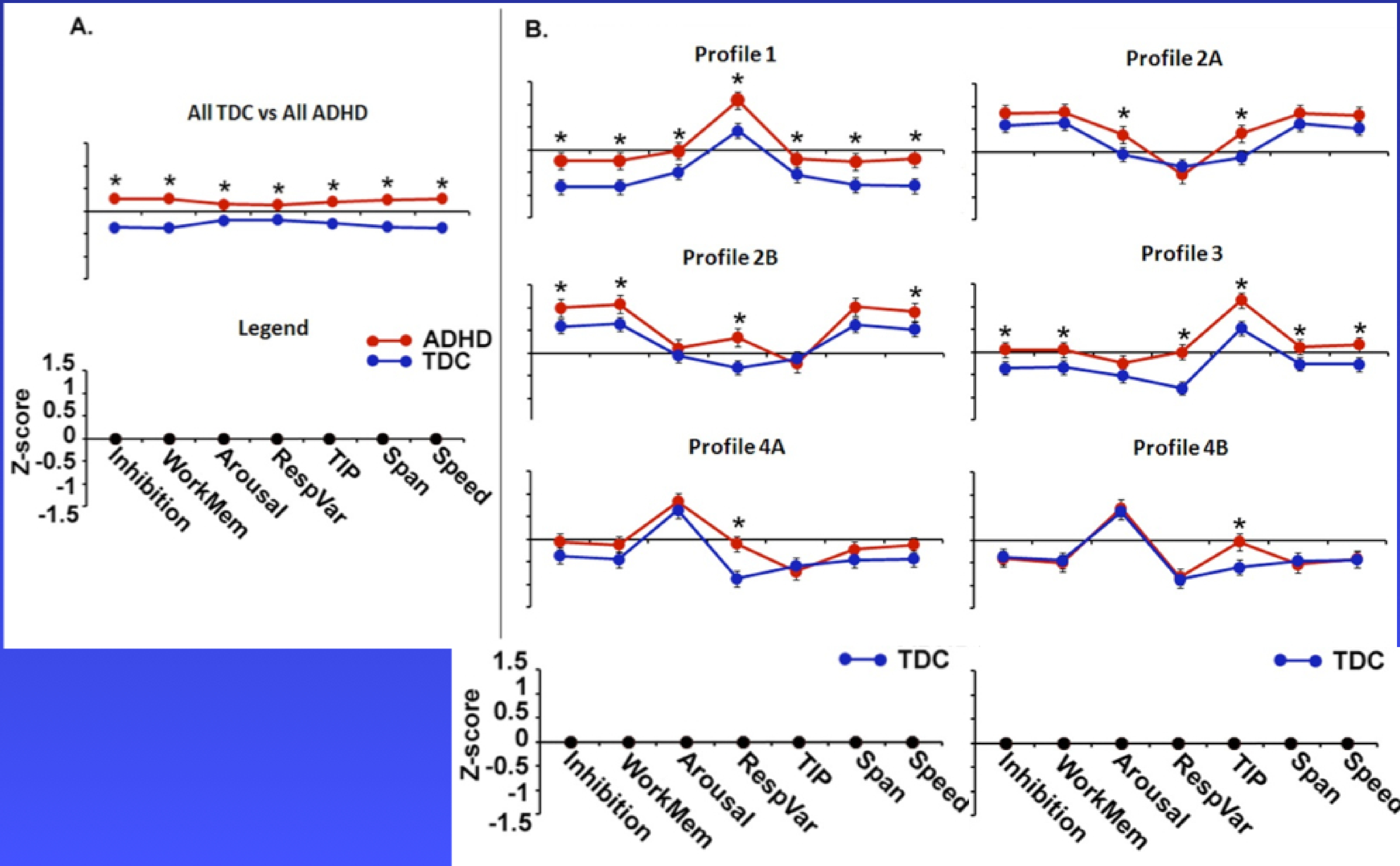


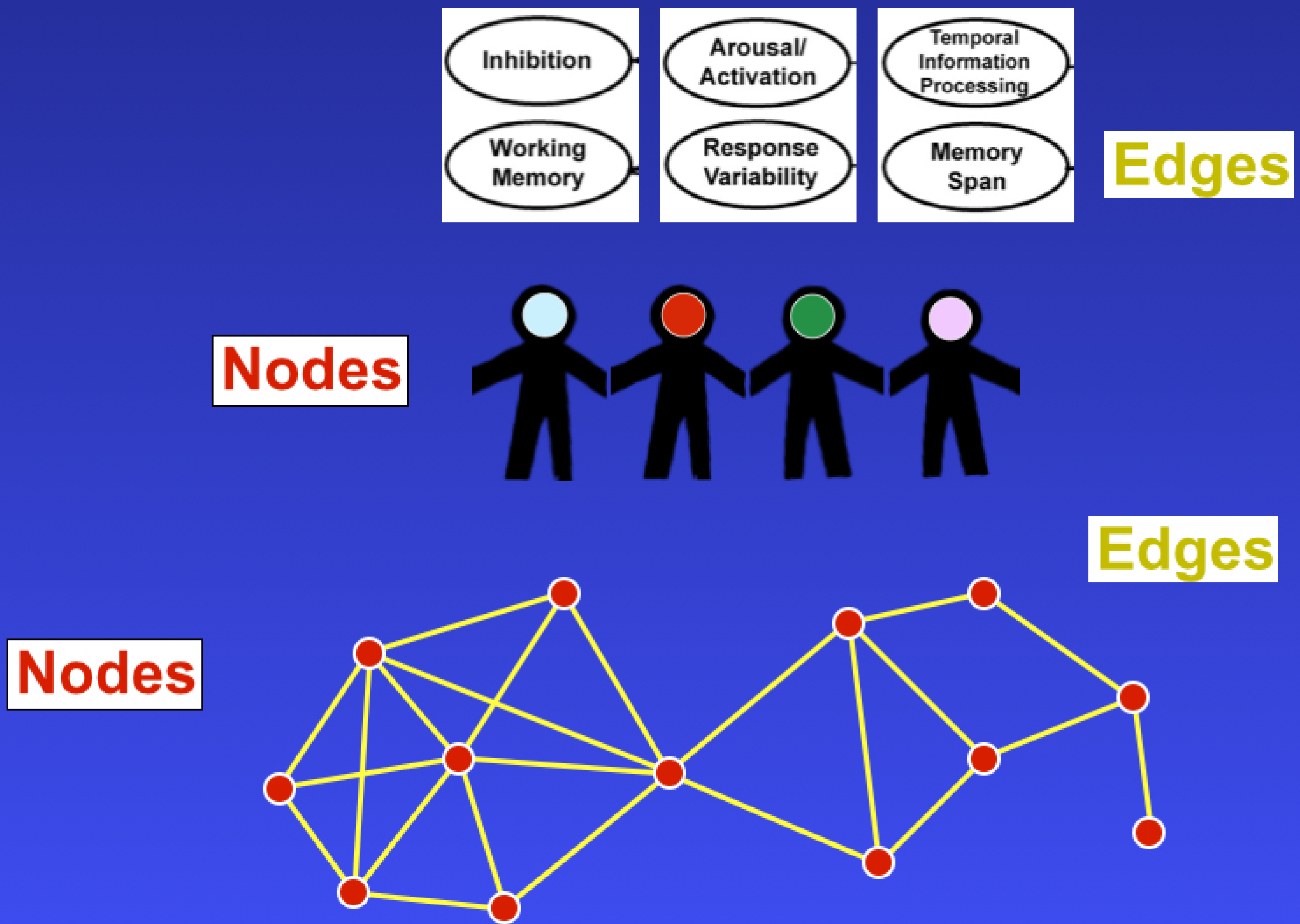
Conclusions

- Some of the variability we see in childhood behavior is not just simply part of a random unimodal normal distribution, rather there are likely multiple subgroups of children who approach problems in similar ways.
- Just as importantly, understanding this normal variation in typically developing children may help us understand more definitively the needs of a given child who has ADHD.

Imaging and Variability

- Can similar phenomena be demonstrated via functional brain imaging?

Imaging and Variability



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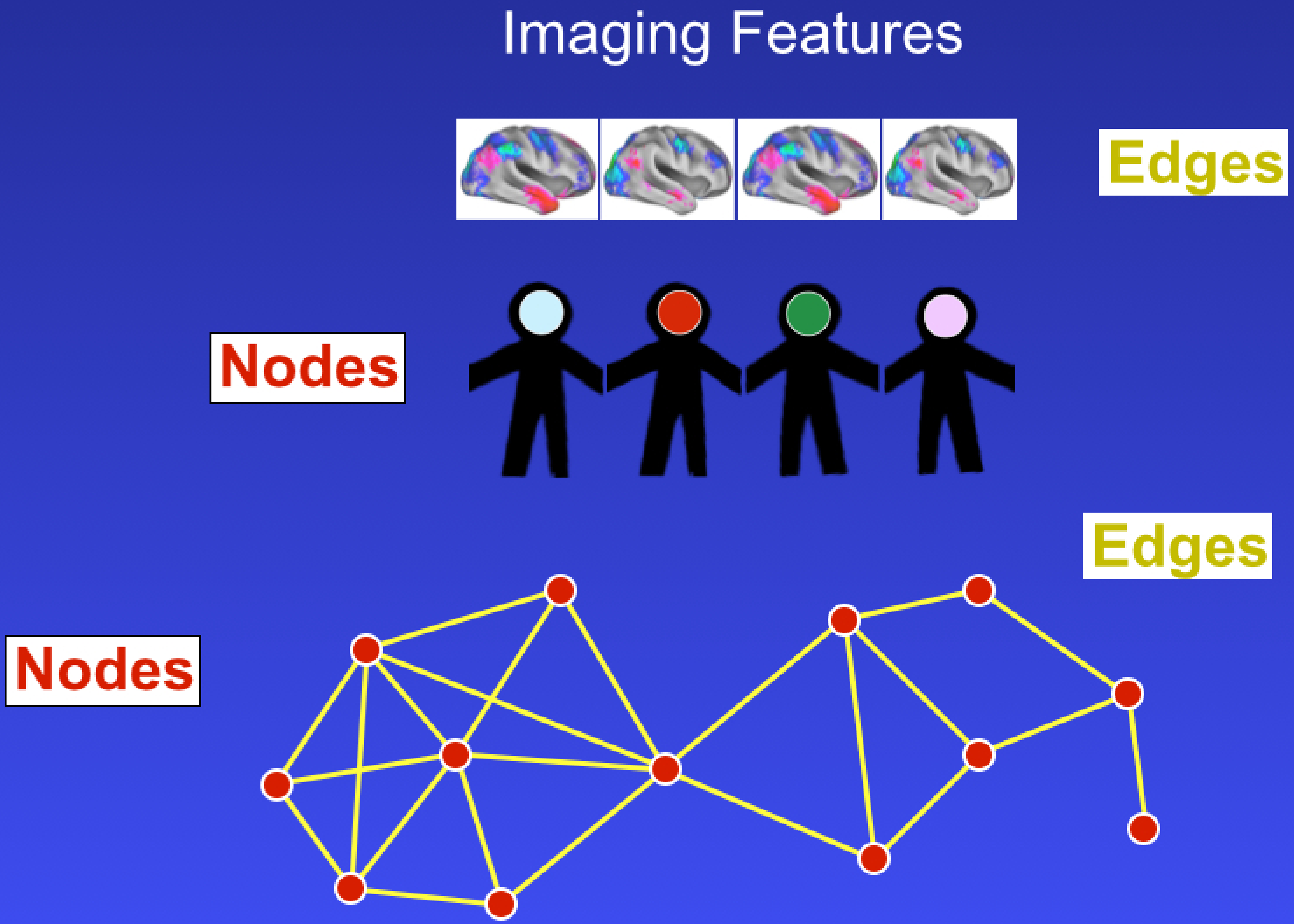
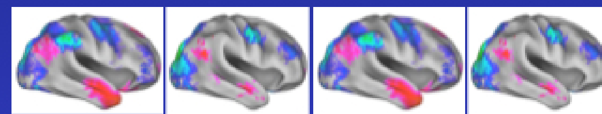
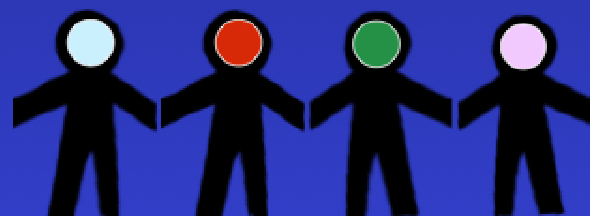


Imaging and Variability

Imaging Features

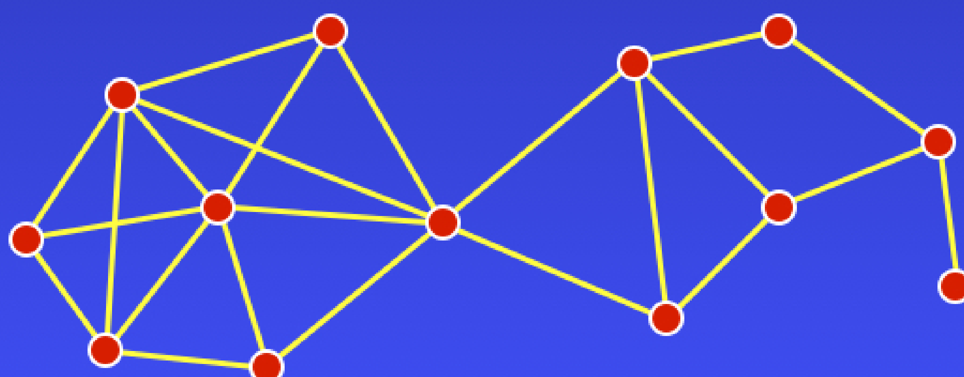


Edges



Community Detection

$$Q = 1/m \sum_{ij} \left[A_{ij} - \frac{k_i^{in} k_j^{out}}{m} \right] (s_i s_j + 1)$$



Imaging and Variability

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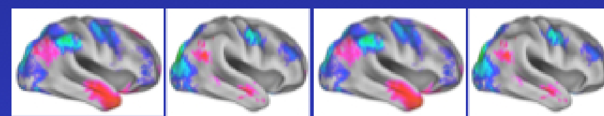
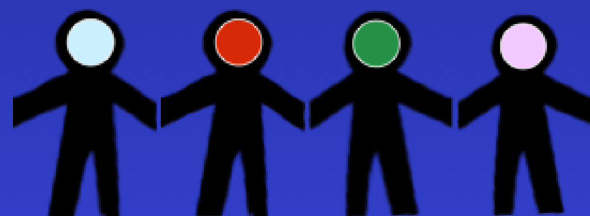
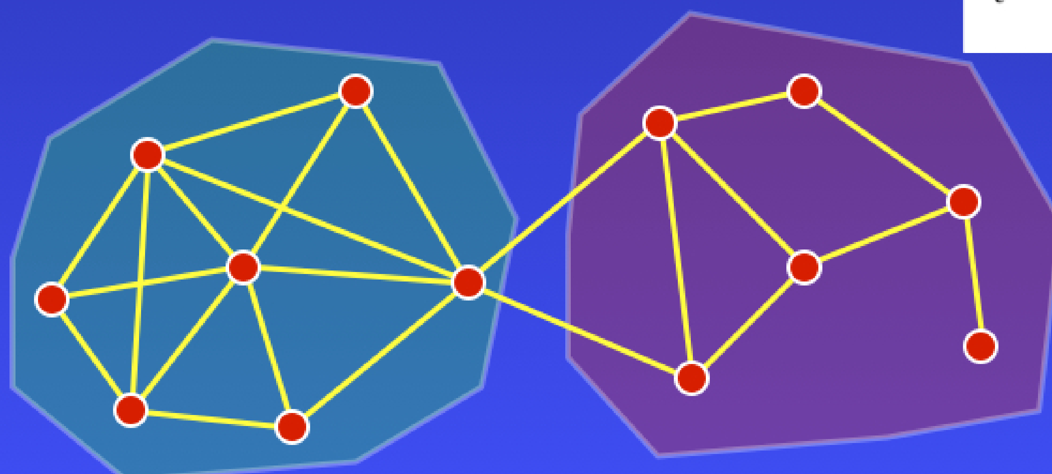


Edges



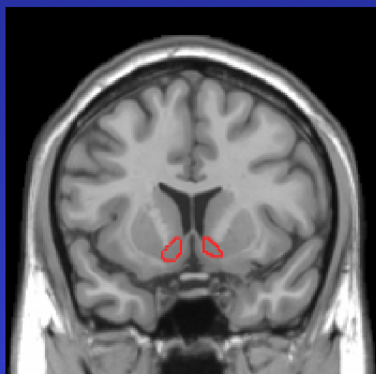
Community Detection

$$Q = 1/m \sum_{ij} \left[A_{ij} - \frac{k_i^{in} k_j^{out}}{m} \right] (s_i s_j + 1)$$



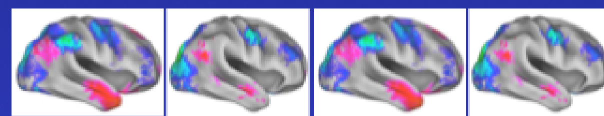
The importance of Cortical-Subcortical interactions in ADHD

Reward Systems

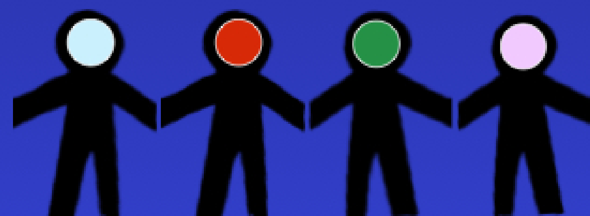


Ventral Striatum

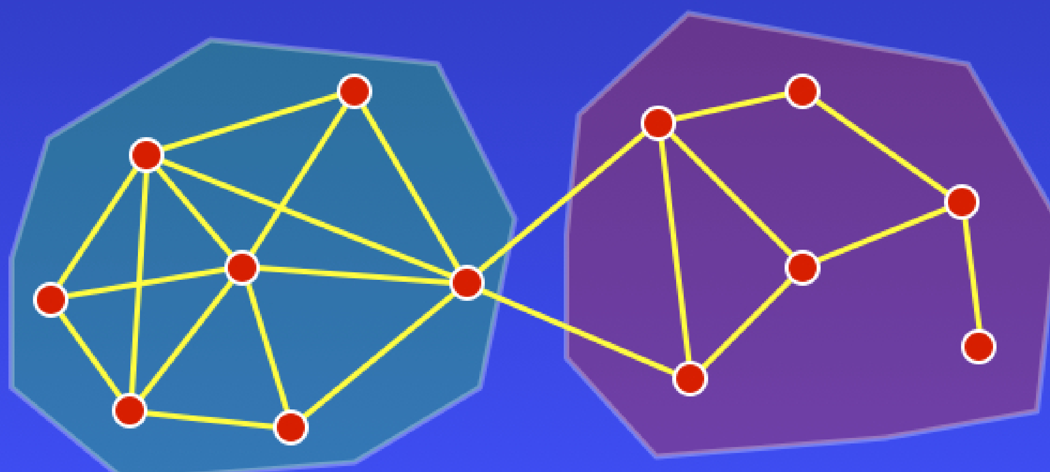
Imaging Features



Edges



N = 114;
TDC = 60;
ADHD = 54



Costa Dias et al, in prep

The importance of Cortical-Subcortical interactions in ADHD

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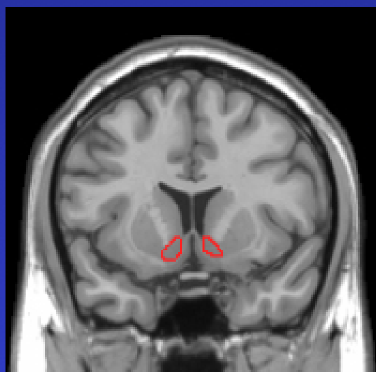

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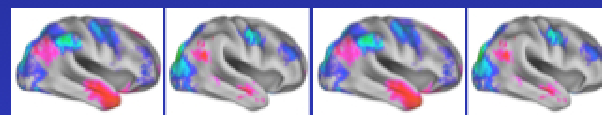
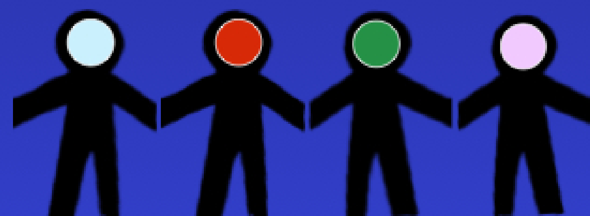


Edges



N = 114;
TDC = 60;
ADHD = 54

Group A (N = 33)

TDC = 24; ADHD = 9

Group B (N = 48)

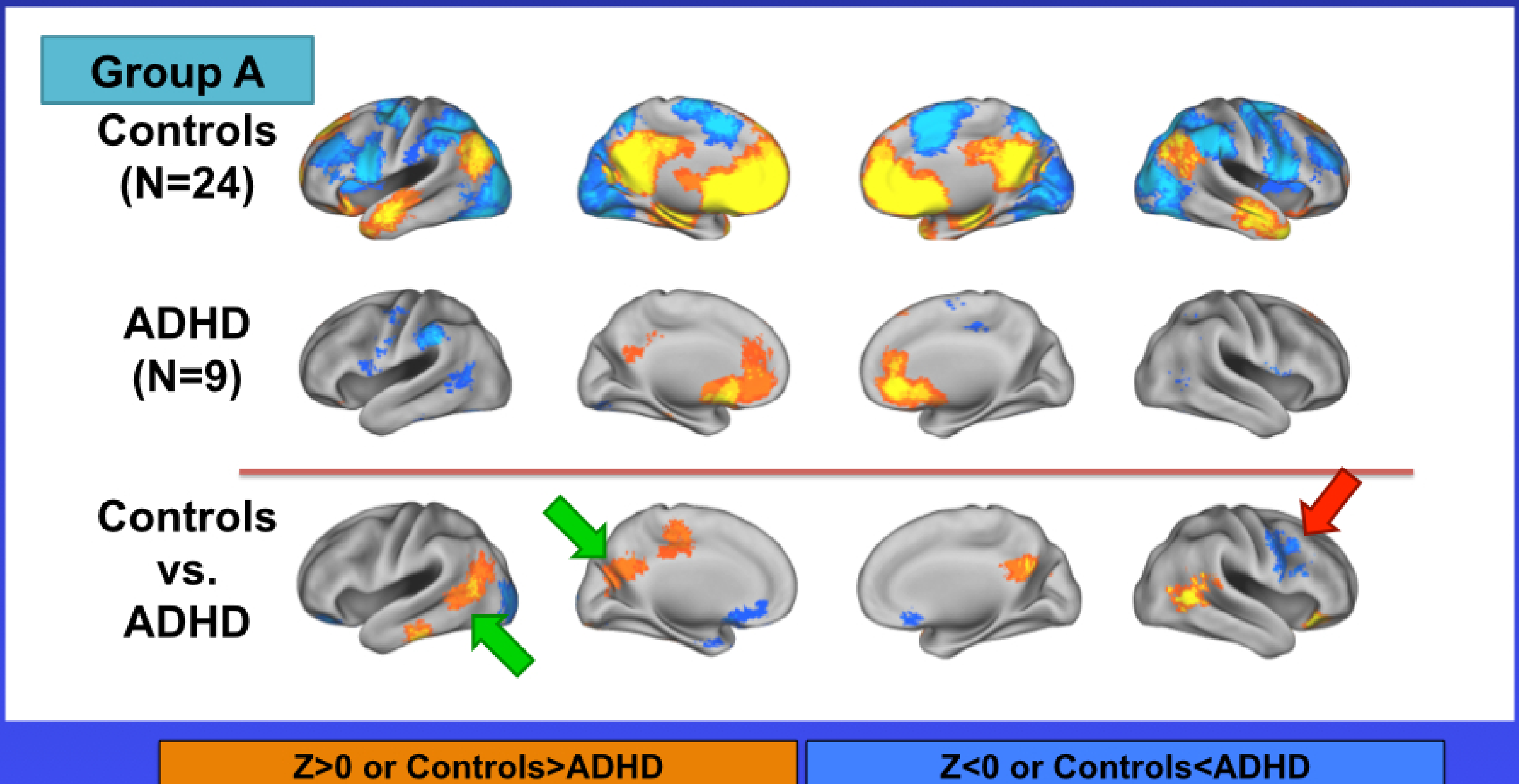
TDC = 29; ADHD = 17

Group C (N = 26)

TDC = 11; ADHD = 15

Costa Dias et al, in prep

The importance of Cortical-Subcortical interactions in ADHD



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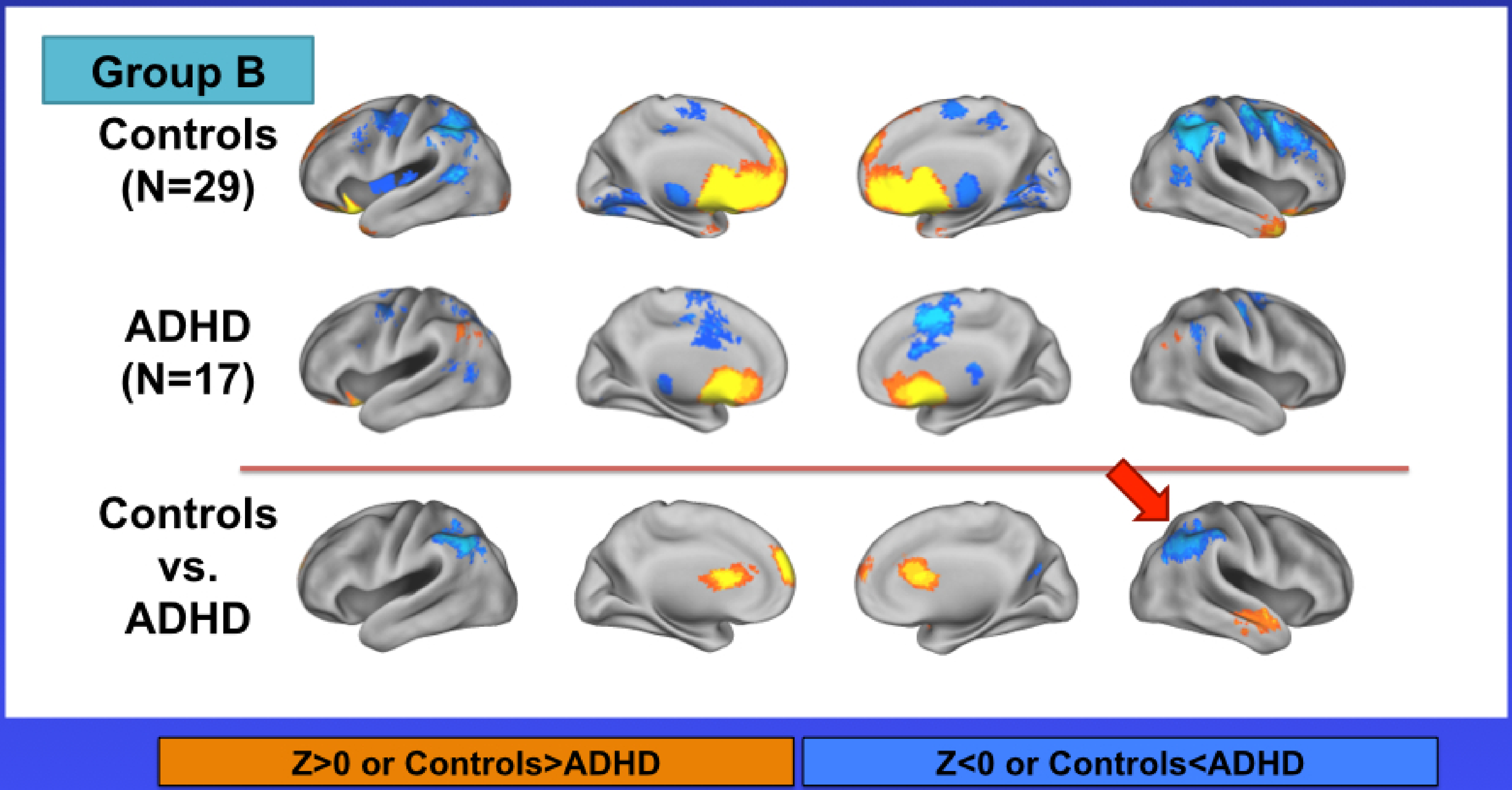
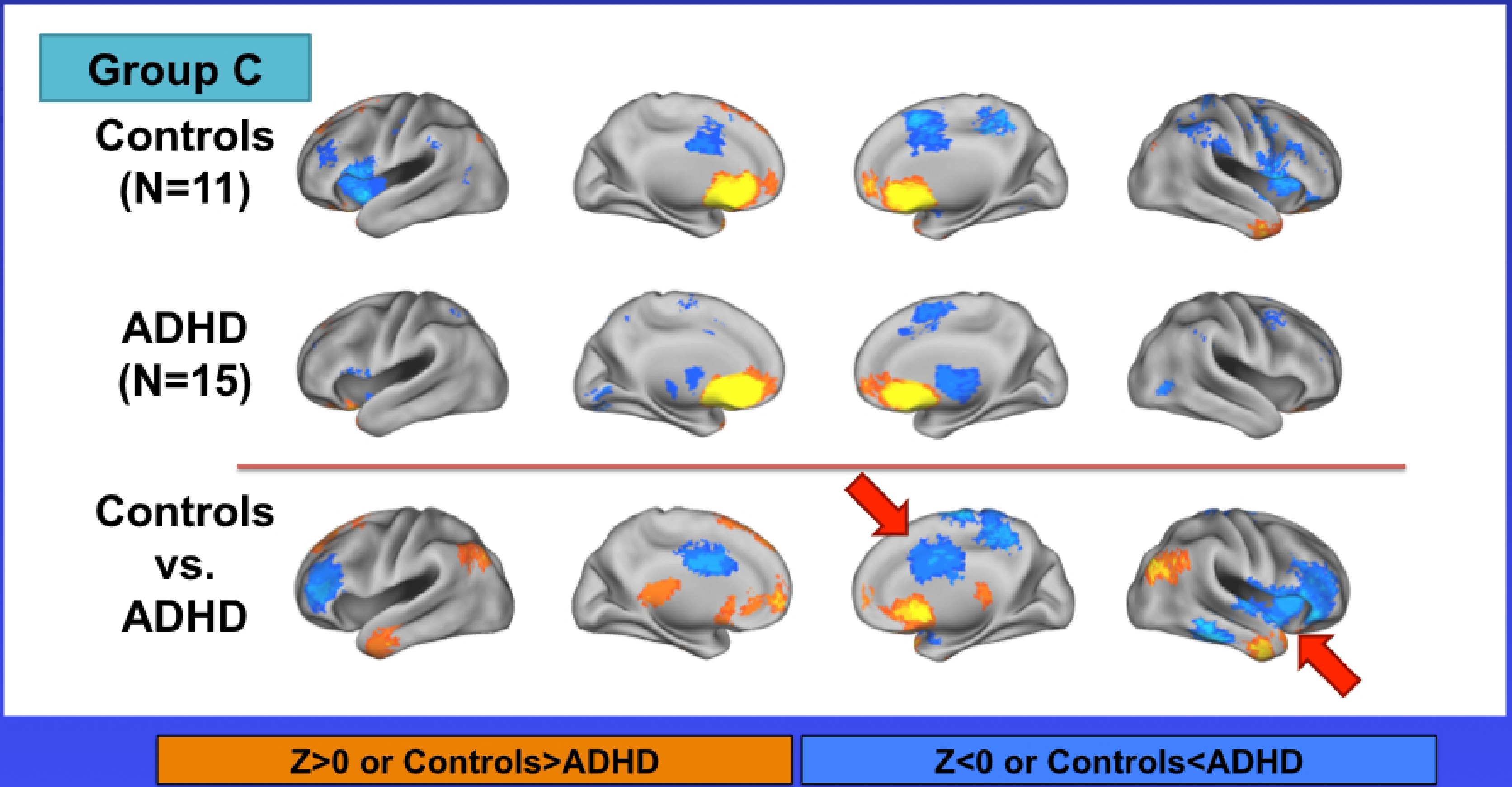
The importance of Cortical-Subcortical interactions in ADHD



Costa Dias et al, in prep

The importance of Cortical-Subcortical interactions in ADHD



Costa Dias et al, in prep

Conclusions

- The data suggests that portion of the variation observed in connectivity across typically developing populations is embedded in discrete communities.
- The data also suggests that the heterogeneity in individuals with ADHD appears in some instances to be "nested" in this normal variation.
- It may be that identifying a mechanism associated with a mental disorders, such as ADHD requires comparing individuals to well adjusted persons with the same cognitive style or network profile.

Conclusions

- But ....
- Can information from non-invasive tools - psychiatric Dx (e.g., childhood ADHD), brain imaging, behavioral testing, etc. - at a given developmental stage assist in predicting future outcomes?

Subtypes of ADHD based on temperament domains (emotional regulation)

Temperament and Middle Childhood Questionnaire

1. Activity Level:
2. Affiliation:
3. Anger/Frustration:
4. Assertiveness/Dominance:
5. Attentional Focusing:
6. Discomfort:
7. Fantasy/Openness:
8. Fear:
9. High Intensity Pleasure:
10. Impulsivity:
11. Inhibitory Control:
12. Low Intensity Pleasure:
13. Perceptual Sensitivity:
14. Sadness:
15. Shyness:
16. Soothability/Falling Reactivity:

	Control	ADHD	Total
N	193	247	440

Karalunas et al, 2014

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15. Shyness:
16. Soothability/Falling Reactivity:

	Control	ADHD	Total
N	193	247	440

Uncomplicated:
N = 64

Karalunas et al, 2014

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14. Sadness:
15. Shyness:
16. Soothability/Falling Reactivity:

	Control	ADHD	Total
N	193	247	440

Uncomplicated:
N = 64

Surgent:
N = 85

Karalunas et al, 2014

Subtypes of ADHD based on temperament domains (emotional regulation)

Temperament and Middle Childhood Questionnaire

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11. Inhibitory Control:
12. Low Intensity Pleasure:
13. Perceptual Sensitivity:
14. Sadness:
15. Shyness:
16. Soothability/Falling Reactivity:

	Control	ADHD	Total
N	193	247	440

Uncomplicated:
N = 64

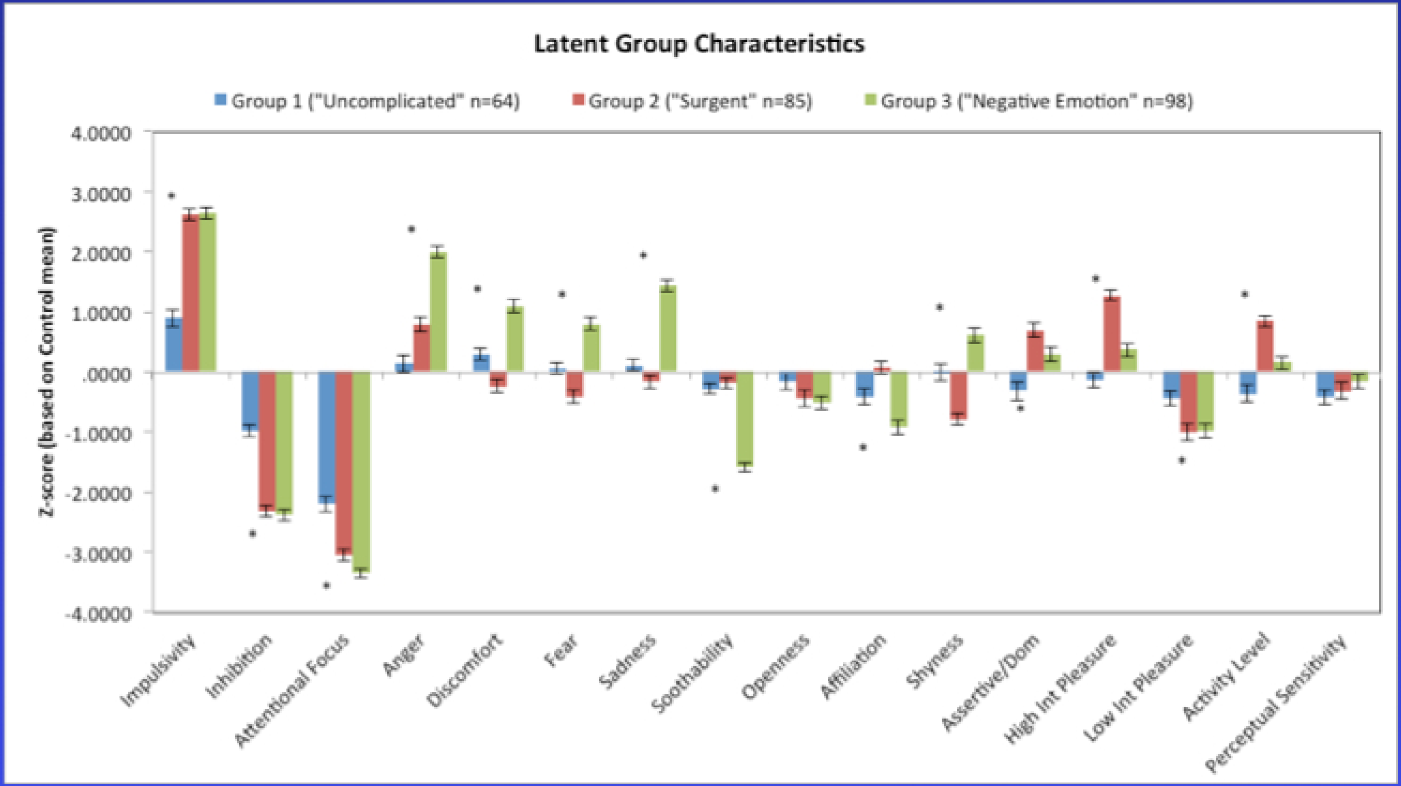
Surgent:
N = 85

Negative Emotion:
N = 98

Karalunas et al, 2014

Subtypes of ADHD based on temperament domains (emotional regulation)

Temperament and Middle Childhood Questionnaire



Karalunas et al, 2014

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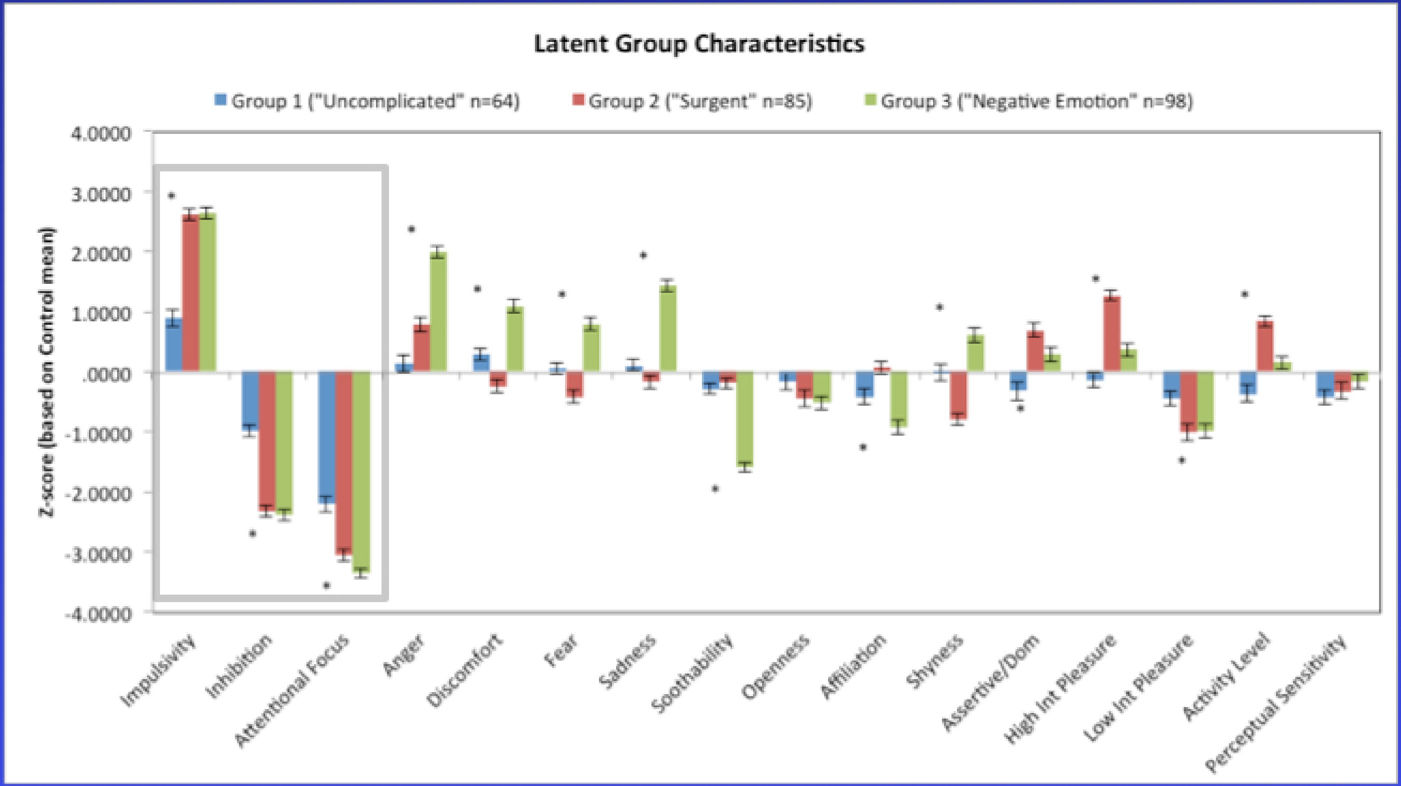
AGE Timeline

Subtypes of ADHD based on temperament domains (emotional regulation)

Temperament and Middle Childhood Questionnaire



Karalunas et al, 2014

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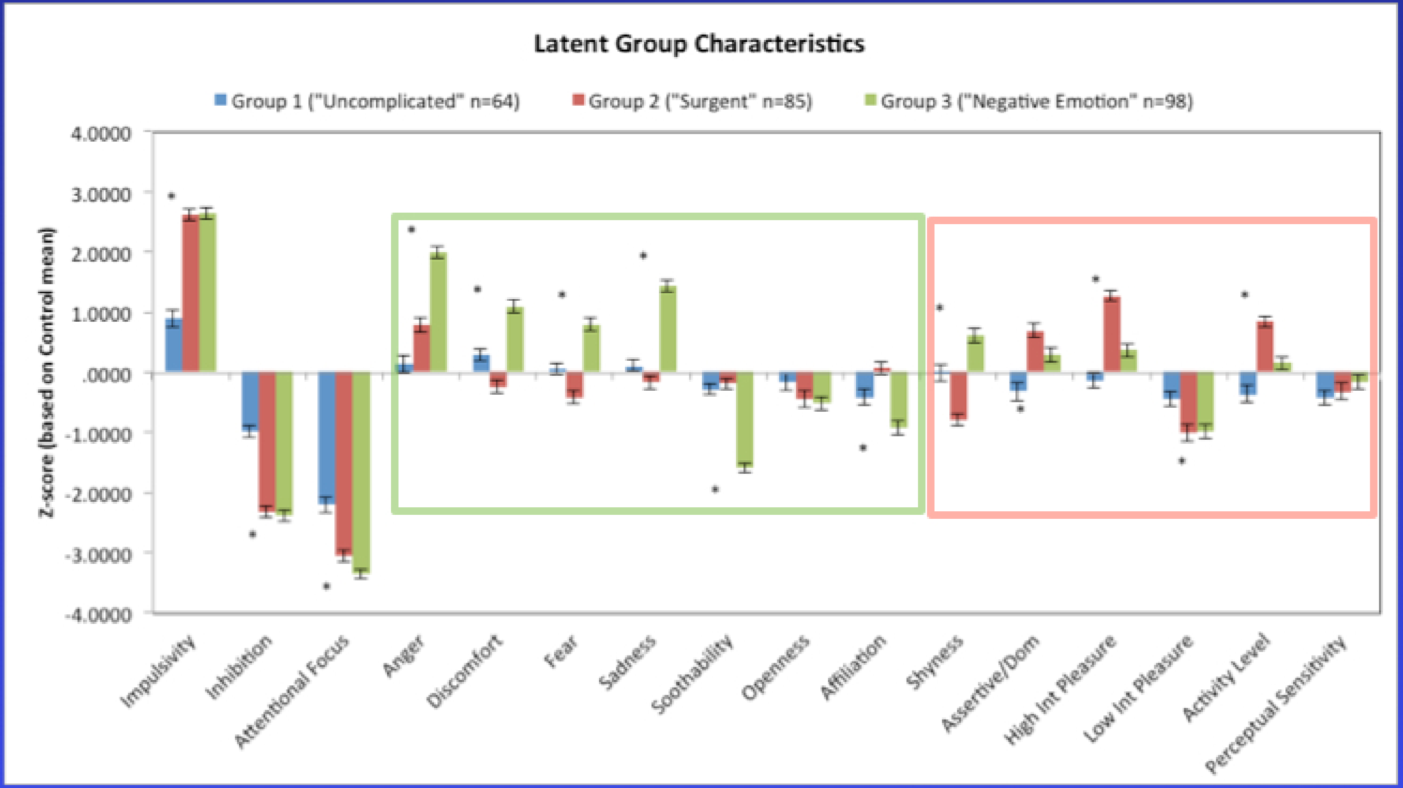
AGE Timeline

Subtypes of ADHD based on temperament domains (emotional regulation)

Temperament and Middle Childhood Questionnaire



Karalunas et al, 2014

Subtypes of ADHD based on temperament domains (emotional regulation)

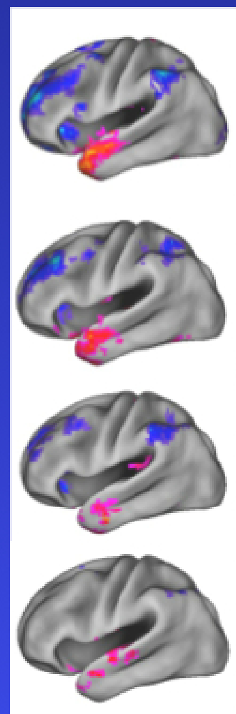
Amygdala Connectivity

Controls

Mild Imp

Surgent

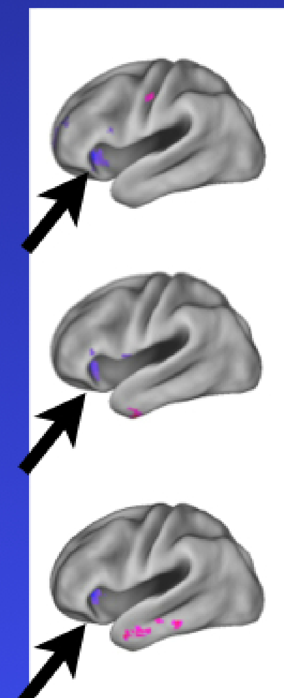
Neg. Emot



Controls vs NE

Surgent vs NE

Mild Imp vs NE



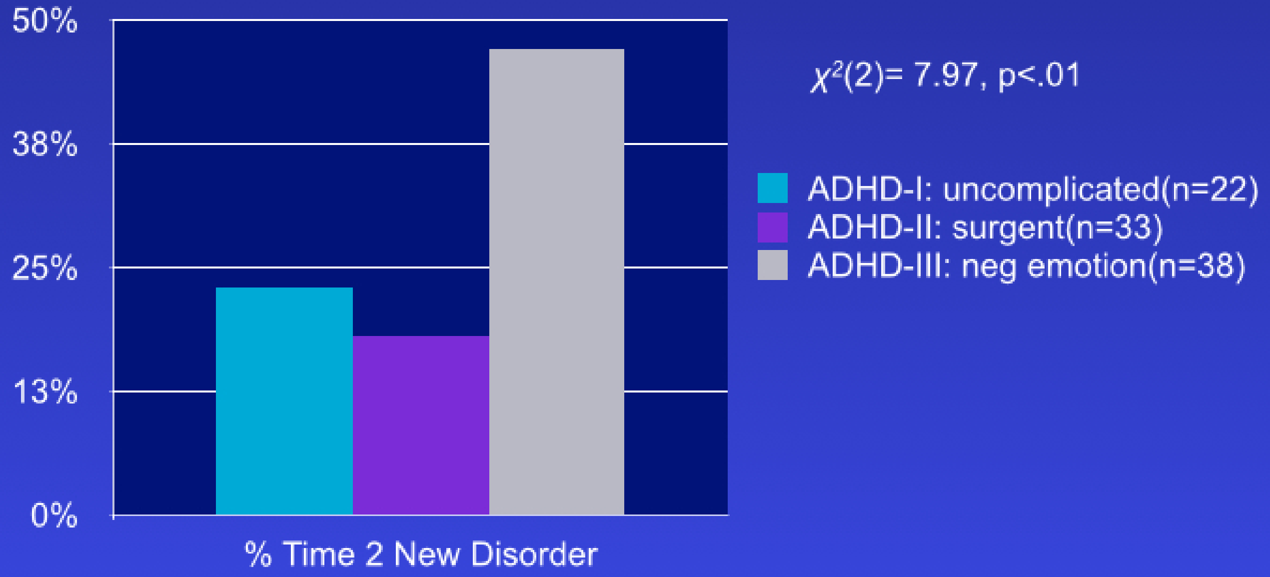
Karalunas et al, 2014

8

AGE Timeline

Subtypes of ADHD based on temperament domains (emotional regulation)

1-year follow up new disorder onset (course deterioration) (N=93)



- Temperament Group predicted Time 2 onset beyond ADHD sx ($R^2\Delta$=.06, *p*=.029)
- # ADHD Sx did *not* predict onsets after control for Temp. Group ($R^2\Delta$=.001, *p*=.953).

Source: Karalunas, et al, 2014

Conclusions

- So...
- Can information from non-invasive tools - psychiatric Dx (e.g., childhood ADHD), brain imaging, behavioral testing, etc. - at a given developmental stage assist in predicting future outcomes?

- Can this information help us tailor education or provide early interventions to improve health or other long-term outcomes of a given individual?

- Still work in progress, but characterizing the heterogeneity (a phenomenon explained, in part, by cortical-subcortical interactions) in typical and atypical populations is likely going to be a major component that will have to be improved before we are able to reveal the full potential.

Thank You

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