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

NSTA Workshop
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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

ADHD vs Control
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

ADHD

Control
Traditional Group Studies

ADHD

Control
Traditional Group Studies

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

Edmund J.S. Sonuga-Barke PhD\textsuperscript{a,b,c}, Joseph A. Sergeant PhD\textsuperscript{d}, Joel Nigg PhD\textsuperscript{e}, Erik Willcutt PhD\textsuperscript{f}
Traditional Group Studies

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Willcutt PhD

Pathologies of brain attentional networks

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Traditional Group Studies

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NEUROSCIENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE SEARCH FOR ENDOPHENOTYPES
F. Xavier Castellanos* and Rosemary Tannock

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

F. Xavier Castellanos* and Rosemary Tannock e

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

Joel T. Nigg
Psychology Department, Michigan State University

H. Hill Goldsmith
Psychology Department, University of Wisconsin-Madison

Jennifer Sacheck
Department of Psychology, Michigan State University
Traditional Group Studies

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Psychological heterogeneity in AD/HD—a dual pathway model of behaviour and cognition
Edmund J.S. Sonuga-Barke

Traditional Group Studies

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Edmund J.S. Sonuga-Barke PhD, Joseph A. Sergeant PI

Pathologies of brain attentional networks

A. Berger, M.I. Posner

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

Joel T. Nigg

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.
Traditiona] Group Studies

ADHD

Control

Total Number of Partitions of Sets of Size $n$

$n = 3 4 5 6 7 8 9 10 \ldots 15 \ldots 20 \ldots$

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
Graph theoretical Analyses

Networks of the Internet

US House of Representatives committees and subcommittees
Porter et al. (2009) Notices of the AMS

Yeast Interactome

US commuting pattern
Vespignani (2009) Science

Jeong et al. (2001) Nature
Graph theoretical Analyses

Networks of the Internet

US House of Representatives committees and subcommittees

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

Making a connection with... Kevin Bacon

AN EXPLANATION

1. Making a connection with Kevin Bacon
2. A Famous Inquiry
3. "Six Degrees of Kevin Bacon"}

[Diagram showing connections among people through Kevin Bacon]

[Miscellaneous connections and names]

1. "Moonlighting"
2. "Footloose"
3. "Apollo 13"
4. "Hollow Man"
5. "Ungodly Hour"
6. "The Last Boy Scout"
7. "Cast Away"
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100. "Cast Away"
Small World Networks

High Clustering
Small World Networks

High Clustering

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

Short Paths
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

Modularity

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

- \( Q \) = (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.
Graph theoretical Analyses

Nodes

Edges
Graph theoretical Analyses
Graph theoretical Analyses

Nodes

Edges
Graph theoretical Analyses

Nodes

Edges
Traditional fMRI

Graph theoretical Analyses

Nodes

Edges

Inhibition
Working Memory
Arousal/Activation
Response Variability
Temporal Information Processing
Memory Span
Graph theoretical Analyses

ADHD

Control
Goals

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

Community Detection Based Profiles

A. TDC

<table>
<thead>
<tr>
<th>Profile</th>
<th>N</th>
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<tbody>
<tr>
<td>1</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
</tr>
</tbody>
</table>

C. ADHD

B. Graph Communities

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

A. All TDC vs All ADHD

Legend
- ADHD
- TDC

Z-score
-0.5 -1.5
Inhibition WorkMem Arousal RespVar TIP Span Speed

Community Detection Based Profiles

A. TDC

C. ADHD

Profiles
1 2 3 4
1 2A 2B 3 4A 4B

VS

VS
Heterogeneity in ADHD

A.

All TDC vs All ADHD

Legend

- ADHD
- TDC

B.

Profile 1

Profile 2A

Profile 2B

Profile 3

Profile 4A

Profile 4B

Z-score

Inhibition, WorkMem, Arousal, RespVar, TIP, Span, Speed

TDC
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

- Inhibition
- Working Memory
- Arousal/Activation
- Response Variability
- Temporal Information Processing
- Memory Span

Nodes

Edges

Nodes
Imaging and Variability

Imaging Features

Nodes

Edges

Nodes

Edges
Imaging and Variability

Imaging Features

Edges

Community Detection

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

Imaging Features

Edges

Community Detection

\[ Q = \frac{1}{m} \sum_{ij} \left[ A_{ij} - \frac{k_{i}^{in}k_{j}^{out}}{m} \right] (s_{i}s_{j} + 1) \]
The importance of Cortical-Subcortical interactions in ADHD

Reward Systems

Imaging Features

Ventral Striatum

Edges

N = 114;
TDC = 60;
ADHD = 54

Costa Dias et al, in prep
The importance of Cortical-Subcortical interactions in ADHD

Reward Systems

Imaging Features

- Edges
  - N = 114;
  - TDC = 60;
  - ADHD = 54

Ventral Striatum

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

Group A

Controls (N=24)

ADHD (N=9)

Controls vs. ADHD

Z>0 or Controls>ADHD

Z<0 or Controls<ADHD

Costa Dias et al, in prep
The importance of Cortical-Subcortical interactions in ADHD

<table>
<thead>
<tr>
<th>Group B</th>
<th>Controls (N=29)</th>
<th>ADHD (N=17)</th>
<th>Controls vs. ADHD</th>
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Z>0 or Controls>ADHD

Z<0 or Controls<ADHD

Costa Dias et al, in prep
The importance of Cortical-Subcortical interactions in ADHD

Group C

Controls (N=11)

ADHD (N=15)

Controls vs. ADHD

Z>0 or Controls>ADHD

Z<0 or Controls<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:

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<td>N</td>
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Karalunas et al, 2014
Subtypes of ADHD based on temperament domains (emotional regulation)

Temperament and Middle Childhood Questionnaire

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Uncomplicated:
N = 64

Karalunas et al, 2014
Subtypes of ADHD based on temperament domains (emotional regulation)

Temperament and Middle Childhood Questionnaire

1. Activity Level:
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3. Anger/Frustration:
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Uncomplicated: N = 64
Surgent: N = 85

Karalunas et al, 2014
Subtypes of ADHD based on temperament domains (emotional regulation)

Temperament and Middle Childhood Questionnaire

1. Activity Level:
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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

Latent Group Characteristics

Karalunas et al, 2014
Subtypes of ADHD based on temperament domains (emotional regulation)

Temperament and Middle Childhood Questionnaire

Latent Group Characteristics

Karalunas et al, 2014
Subtypes of ADHD based on temperament domains (emotional regulation)

Temperament and Middle Childhood Questionnaire

Latent Group Characteristics

- Group 1 ("Uncomplicated" n=64)
- Group 2 ("Surgent" n=85)
- Group 3 ("Negative Emotion" n=98)

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) (N=93)

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

χ²(2) = 7.97, p < .01

- ADHD-I: uncomplicated (n=22)
- ADHD-II: surgent (n=33)
- ADHD-III: neg emotion (n=38)

- 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: Karalunus, 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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