Neuroimaging and ADHD

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Fragile Power of the Human Brain
Neuroimaging in ADHD

- Paradox – functional (clinical) differences in ADHD are **LARGE**, but structural brain differences are often **small**

**WHY?**

- Sample size
  
  *matters for small effects*

- Noninvasive neuroimaging has poor signal-to-noise, i.e., *measurement error*

- Neuroimaging is poor at detecting *developmental* differences

- Neurobiology within a diagnosis is highly *heterogeneous*
Meta-Analysis of Structural and Functional Brain Abnormalities in ADHD

Structure – Voxel-Based Morphometry; 27 studies, 931 ADHD, 822 CON
Function – fMRI of inhibitory control; 33 studies; 489 ADHD, 591 CON
Structural Differences – decreased grey matter volume in right basal ganglia/insula & ventral medial orbitofrontal/medial prefrontal/anterior cingulate
Functional Differences – hypoactivation in ventral lateral PFC, putamen, right caudate
Overlap – right putamen

Norman et al., JAMA Psychiatry, 2016
Cross-Sectional Mega-Analysis: Subcortical Volume Differences in ADHD Children & Adults

- direct analysis of 1713 ADHD & 1529 control brains from 23 sites
- overall (children & adults) small but significant reductions in volumes of nucleus accumbens, amygdala, caudate, hippocampus, putamen
- no effects of stimulant use or symptom scores
- no significant differences in adult ADHD

Hoogman et al., *Lancet Psychiatry*, 2017
Neuroimaging in ADHD

• Neurodiversity (heterogeneity) in adult ADHD

  *two fMRI experiments*
Neurodiversity in Adult ADHD

• Does the adult definition of ADHD correspond to a neurobiological distinction?
  
  Persistent vs. Remitted ADHD
  (state & trait) vs. (trait only)

• Is there a neurobiological dissociation between executive function (working memory capacity/WMC) and ADHD?
  
  intact vs. impaired WMC in ADHD
Background

- Default Mode Brain (DMN) Network
- Resting State Functional Networks
Default-Mode Brain Network

- fMRI task activation studies compare activation differences between two conditions
- what is more active in the brain when people are doing nothing (no task) than doing most tasks?
Default Mode of Brain Functioning
Raichle et al., 2001, PNAS

Medial prefrontal cortex (MPFC); Posterior cingulate cortex (PCC)
Default-Mode Brain Network

• Default-Mode regions are deactivated during many tasks; activated during rest
• What activates Default-Mode Regions?

Default  Self  Overlap
also thinking about our past, our future, other people
Resting-State Functional Networks

• Intrinsic functional networks may be revealed by temporal correlations between fMRI (BOLD) signals in the resting brain
Resting-State Functional Networks

contralateral motor areas in a network

ipsilateral motor and visual areas not in a common network
Adult ADHD: Decreased Positive Correlations In Default-Mode Network Between PCC-MPFC

- 20 ADHD participants (mean age = 34.9; 16 male)
  - Ascertained retrospectively
- 20 Controls (mean age = 31.2; 14 male)

Castellanos et al., 2008
A Natural Fix for A.D.H.D.

By RICHARD A. FRIEDMAN   OCT. 31, 2014

ATTENTION deficit hyperactivity disorder is now the most prevalent psychiatric illness of young people in America, affecting 11 percent of them at some point between the ages of 4 and 17. The rates of both diagnosis and treatment have increased so much in the past decade that you may wonder whether something that affects so many people can really be a disease.

And for a good reason. Recent neuroscience research shows that people with A.D.H.D. are actually hard-wired for novelty-seeking — a trait that had, until relatively recently, a distinct evolutionary advantage. Compared with the rest of us, they have sluggish and underfed brain reward circuits, so much of everyday life feels routine and understimulating.

To compensate, they are drawn to new and exciting experiences and get famously impatient and restless with the regimented structure that characterizes our modern world. In short, people with A.D.H.D. may not have a disease, so much as a set of behavioral traits that don’t match the expectations of our contemporary culture.
Neurobiology of Persistent vs. Remitted Adult ADHD

Is there a neurobiological distinction between persistent vs. remitted ADHD?
Is there a neurobiological distinction between persistent vs. remitted ADHD?

• all participants uniformly characterized as having or not having ADHD in childhood

• about 16 years later, re-characterization & fMRI as adults
Neurobiology of Persistent vs. Remitted Adult ADHD

• 17 Controls (mean age = 28.7; 11 male)
• 22 Remitted ADHD (mean age = 27.5; 8 male)
• 13 Persistent ADHD (mean age = 28.3; 10 male)
  – Full DSM-IV criteria: 6 or more symptoms and all other diagnostic requirements (e.g., age of onset)
  – Subthreshold DSM-IV criteria: more then half but less than full diagnostic criteria (4 or 5 active symptoms) and all other diagnostic requirements

Mattfeld et al., *Brain*, 2014
Neurobiology of Persistent vs. Remitted Adult ADHD

No significant differences between Persistent & Remitted ADHD on 9 other neuropsychological tests or childhood severity of ADHD

PASGAF = Past Global Assessment of Functioning Scale; BRIEF = Behavior Rating Inventory of Executive Function
Neurobiology of Persistent vs. Remitted Adult ADHD

Controls

Persistent ADHD

Remitted ADHD?

Remitted ADHD?
Neurobiology of Persistent vs. Remitted Adult ADHD

Controls

Persistent ADHD

Remitted ADHD
Reduced MPFC-PCC Coupling Reflects Current Diagnostic State of ADHD

Seed Region

A
Control (N=17)

Remitting ADHD (N=22)

Persistent ADHD (N=13)

B
Control > Persistent ADHD

MPFC

C
Remitting ADHD > Persistent ADHD

MPFC
Neurobiology of Persistent vs. Remitted Adult ADHD

- Persistent ADHD – DMN connectivity
- Schizophrenia – DMN connectivity

CON  |  Rel  |  SZ

internal world  |  external world

www.mghcme.org
Heterogeneity in ADHD

Individuals with ADHD may vary in the extent to which one or more systems are atypical

- Reward system
- Sustained attention system
- Executive function system
Heterogeneity in ADHD

• Executive function system regulation/management of cognitive (& emotional) processes
  - working memory
  - reasoning
  - flexibility
  - problem solving
  - planning & execution of plan

  a core weakness in ADHD

Barkley, 1997
Heterogeneity in ADHD

• Executive function system a core weakness in ADHD
  Barkley, 1997
• but, about 50% of ADHD patients have intact executive functions (Nigg 2005; Castellanos, 2006)
• impaired executive functions tend to remain constant, and are associated with worse outcomes in ADHD (Miller, 2012; Biederman, 2004, 2006)
• can executive dysfunction be separated from ADHD?
Adult patients with childhood ADHD divided by performance on a CANTAB spatial working memory task
Intact & Impaired ADHD Groups

Mattfeld et al., *NeuroImage Clinical*, 2016
WM-Intact & WM-Impaired ADHD Groups

Persistence Across Development

Adulthood

Childhood

CANTAB Spatial Working Memory (Z-score)

WISC-R Freedom from Distractibility IQ

Control  Unimpaired ADHD  Impaired ADHD

www.mghcme.org
N-Back Working Memory Task With Increasing Demand (Load)

- **0 back**
  - Target
  - Sequence: R + W + r + F

- **1 back**
  - Target
  - Sequence: R + r + m + F

- **2 back**
  - Target
  - Sequence: r + N + R + f

- **3 back**
  - Target
  - Sequence: r + F + N + R
WM-Intact & WM-Impaired ADHD Groups

A

B

0-Back

1-Back

2-Back

3-Back

Percent Correct

Control  Intact ADHD  Impaired ADHD

Control  Intact ADHD  Impaired ADHD

n.s.

* * *
WM-Intact & WM-Impaired ADHD Groups

• Increased activation with increased WM load in fronto-parietal WM network
  \[3\text{-back} > 2\text{-back} > 1\text{-back} > 0\text{-back}\]

• Reduced activation only in WM-Impaired ADHD group

Mattfeld et al., *NeuroImage Clinical*, 2016
WM-Intact & WM-Impaired ADHD Groups

- Direct statistical comparison between groups
- Reduced activation *only* in WM-Impaired ADHD group
  - relative to Control Group & WM-Intact Group
  - no difference between Control & WM-Intact groups

Mattfeld et al., *NeuroImage Clinical*, 2016
WM-Intact & WM-Impaired ADHD Groups

Failure to recruit WM circuit with increasing WM demands

Mattfeld et al., *NeuroImage Clinical*, 2016
Dissociation Between Working Memory Impairment & ADHD

- altered fMRI activation in fronto-parietal network for N-Back in ADHD
  
  (e.g., Chantiluke et al., 2015, Cubillo et al., 2014, Fassbender et al., 2011, Ko et al., 2013, Kobel et al., 2009, Li et al., 2014, Silk et al., 2005, Valera et al., 2005, Valera et al., 2010, Vance et al., 2007)
Dissociation Between Working Memory Impairment & ADHD

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• neuroimaging studies often report activation differences without WM performance differences
  (e.g., Chantiluke et al., 2015, Fassbender et al., 2011, Ko et al., 2013, Li et al., 2014, Silk et al., 2005, Valera et al., 2005, Valera et al., 2010, Vance et al., 2007)
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• patient heterogeneity from study to study?
Dissociation Between Working Memory Impairment & ADHD

• buy why are executive functions so often compromised in ADHD?
• shared polygenic pathways?
Neurodiversity in Adult ADHD

• Does the adult definition of ADHD correspond to a neurobiological distinction? **YES**

  *Persistent vs. Remitted ADHD (state & trait) vs. (trait only)*

• Is there a neurobiological dissociation between executive function (working memory capacity/WMC) and ADHD? **YES**

  *intact vs. impaired WMC*
Neuroimaging in ADHD

• Paradox – functional (clinical) differences in ADHD are LARGE, but structural differences are often small.

• Sample size
  matters for small effects

• Noninvasive neuroimaging has poor signal-to-noise, i.e., measurement error.

• Neuroimaging is poor at detecting developmental differences.

• Neurobiology within a diagnosis is highly heterogeneous – YES (functional).
Neuroimaging of ADHD and Executive Functions

Collaborators
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