Neuroimaging of ADHD and Executive Functions

John Gabrieli
Department of Brain and Cognitive Sciences & Martinos Imaging Center at the McGovern Institute for Brain Research, MIT
Disclosures

“Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose.”
Fragile Power of the Human Brain
Neuroimaging in ADHD

• Neurodiversity in adult ADHD
  
  *two fMRI experiments*

• What can neuroimaging contribute to help people with ADHD?
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?
Neurobiology of Persistent vs. Remitted Adult 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

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

Controls

Persistent ADHD

Remitted ADHD?

Remitted ADHD?
Neurobiology of Persistent vs. Remitted Adult ADHD

Controls

Remitted ADHD

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

Seed Region

A  Control (N=17)

B  Control > Persistent ADHD

Remitting ADHD (N=22)

C  Remitting ADHD > Persistent ADHD

Persistent ADHD (N=13)

MPFC

t = 2.2

|>4.0|
Neurobiology of Persistent vs. Remitted Adult ADHD

- Persistent ADHD – DMN connectivity
- Schizophrenia – DMN connectivity

CON  Rel  SZ

internal world  external world
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 (and 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

Controls → Intact ADHD

Intact ADHD → Impaired ADHD

Mattfeld et al., *NeuroImage Clinical*, 2016

Controls

Intact ADHD

Impaired ADHD
WM-Intact & WM-Impaired ADHD Groups

Persistence Across Development

Adulthood

Childhood

CANTAB Spatial Working Memory (z-score)

E

WISC-R Freedom from Distractibility IQ

Control Unimpaired ADHD Impaired ADHD

n.s. **
N-Back Working Memory Task With Increasing Demand (Load)

0 back

Target

R + W + r + F

1 back

Target

R + r + m + F

2 back

Target

r + N + R + f

3 back

Target

r + F + N + R
WM-Intact & WM-Impaired ADHD Groups

A

CANTAB Spatial Working Memory (z-score)

B

0-Back

1-Back

2-Back

3-Back

Percent Correct

Control  Intact ADHD  Impaired ADHD

Control  Intact ADHD  Impaired ADHD

Control  Intact ADHD  Impaired ADHD

Control  Intact ADHD  Impaired ADHD

www.mghcme.org
WM-Intact & WM-Impaired ADHD Groups

• Increased activation with increased WM load in fronto-parietal WM network
  3-back > 2-back > 1-back > 0-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
Failure to recruit WM circuit with increasing WM demands

Mattfeld et al., *NeuroImage Clinical*, 2016
• 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

• 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)

• 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)
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)

- 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)

- 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

- Neurodiversity in ADHD
  *two fMRI experiments*

- What can neuroimaging contribute to help people with ADHD?
ADHD Publications (PubMed)

- ADHD & MRI - 1353
- ADHD & EEG - 1285
- ADHD & PET - 138
- ADHD & SPECT - 140
- ADHD & MEG - 31
- ADHD & DTI - 69
- ADHD & MRS - 51

Total 3067
Neuropsychiatry & Neuroimaging & Genetics
Neuroimaging in ADHD

• What can neuroimaging contribute to help people with ADHD?
  - *early identification & prevention*
  - *individualized treatment selection*
Neuromarkers can predict who will benefit from a treatment connectomic measures at baseline accounted for 60% of variance in CBT effectiveness for social anxiety vs. 10% of scale measure of initial severity; 80% individual accuracy for responder/non-responder (brain measures can outperform scale measures)

DTI & resting-state fMRI

Whitfield-Gabrieli et al., Molecular Psychiatry, 2016
Neuroimaging in ADHD

- What can neuroimaging contribute to help people with ADHD?
  - *individualized treatment selection*

- Which patient should get which treatment(s)?
  - current – trial & error
  - evidence – about half of children benefit substantially more from either methylphenidate or amphetamine, about 30% do not respond to one, over 10% do not respond to either

(Winsberg et al., 1974; Arnold et al., 1978; Pelham et al., 1990; Elia et al., 1991; Efron et al., 1997; Sharp et al., 1999; Stein et al., 2011; Ramtvedt et al., 2013)
Neuroimaging of ADHD and Executive Functions

Collaborators
Aaron Mattfeld
Joseph Biederman
Thomas Spencer
Susan Whitfield-Gabrieli
Ariel Brown