Neuroimaging and ADHD

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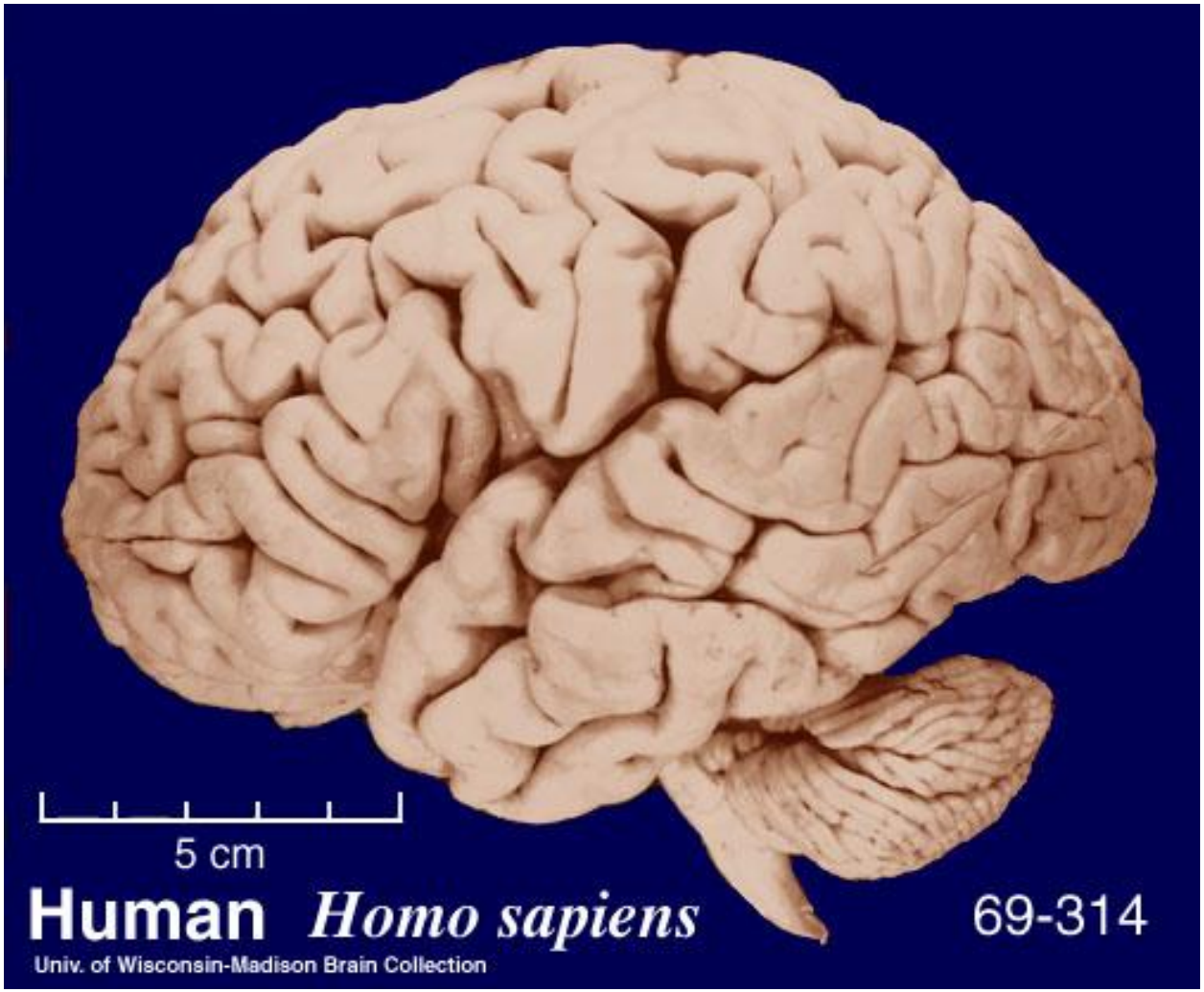
Disclosures

"Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose."

Fragile Power of the Human Brain



Background

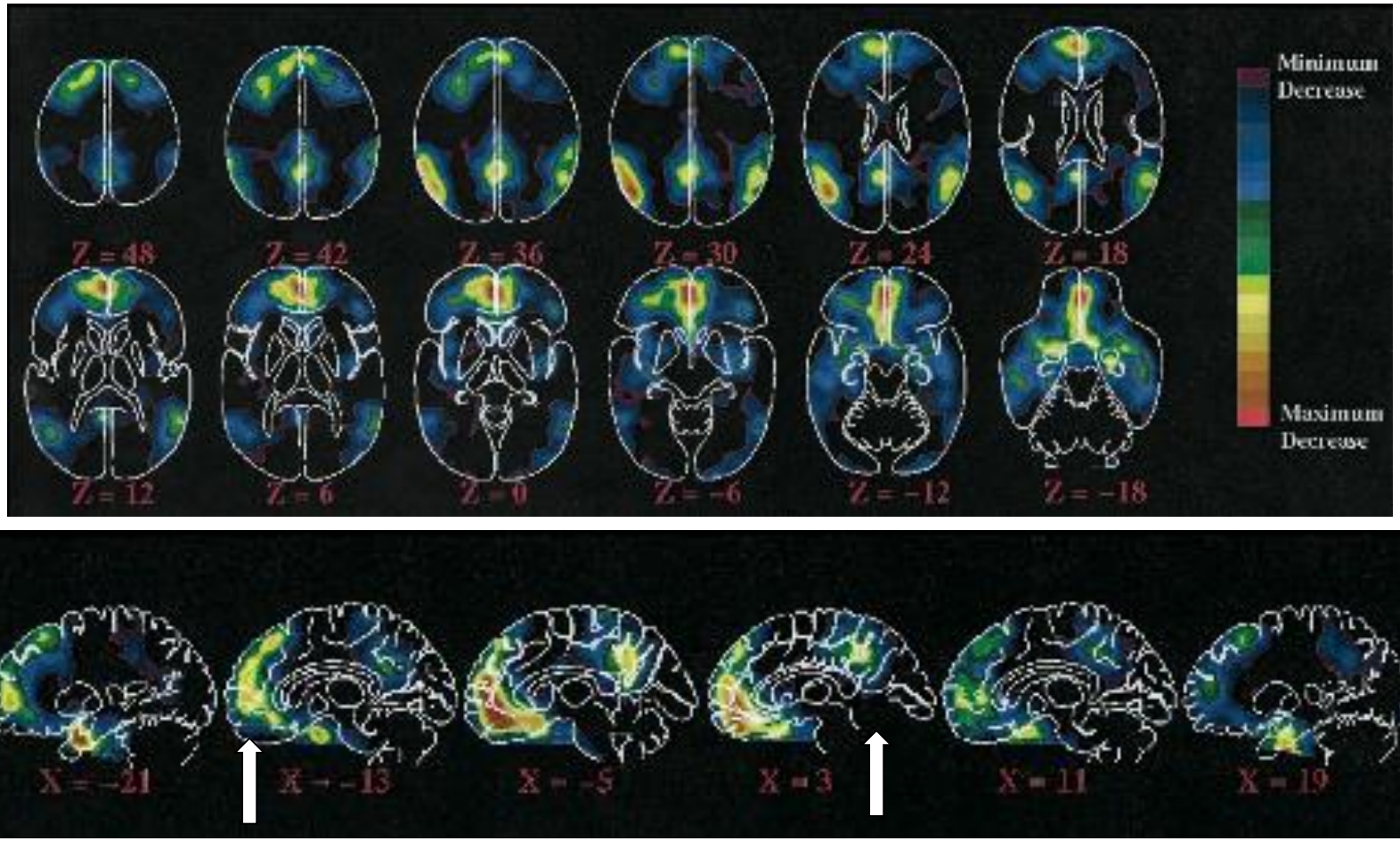
- **Default Mode Brain Network**
- **Resting State Functional Networks**

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

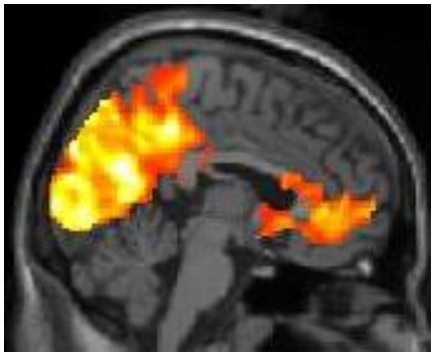
Raichle et al., 2001, *PNAS*



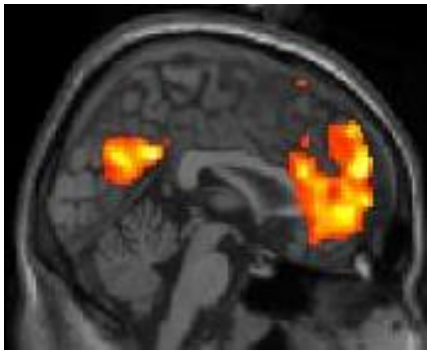
Medial prefrontal cortex (MPFC); Posterior cingulate cortex (PCC)

Default-Mode Brain Network

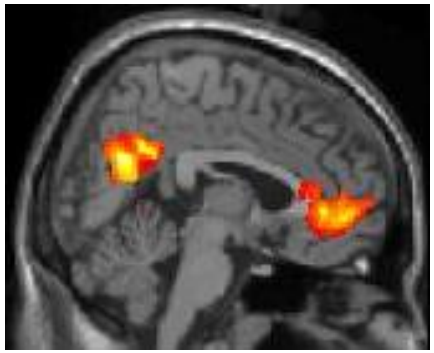
- **Default-Mode regions are *deactivated* during many tasks; *activated* during rest**
- **What *activates* Default-Mode Regions?**



Default



Self



Overlap

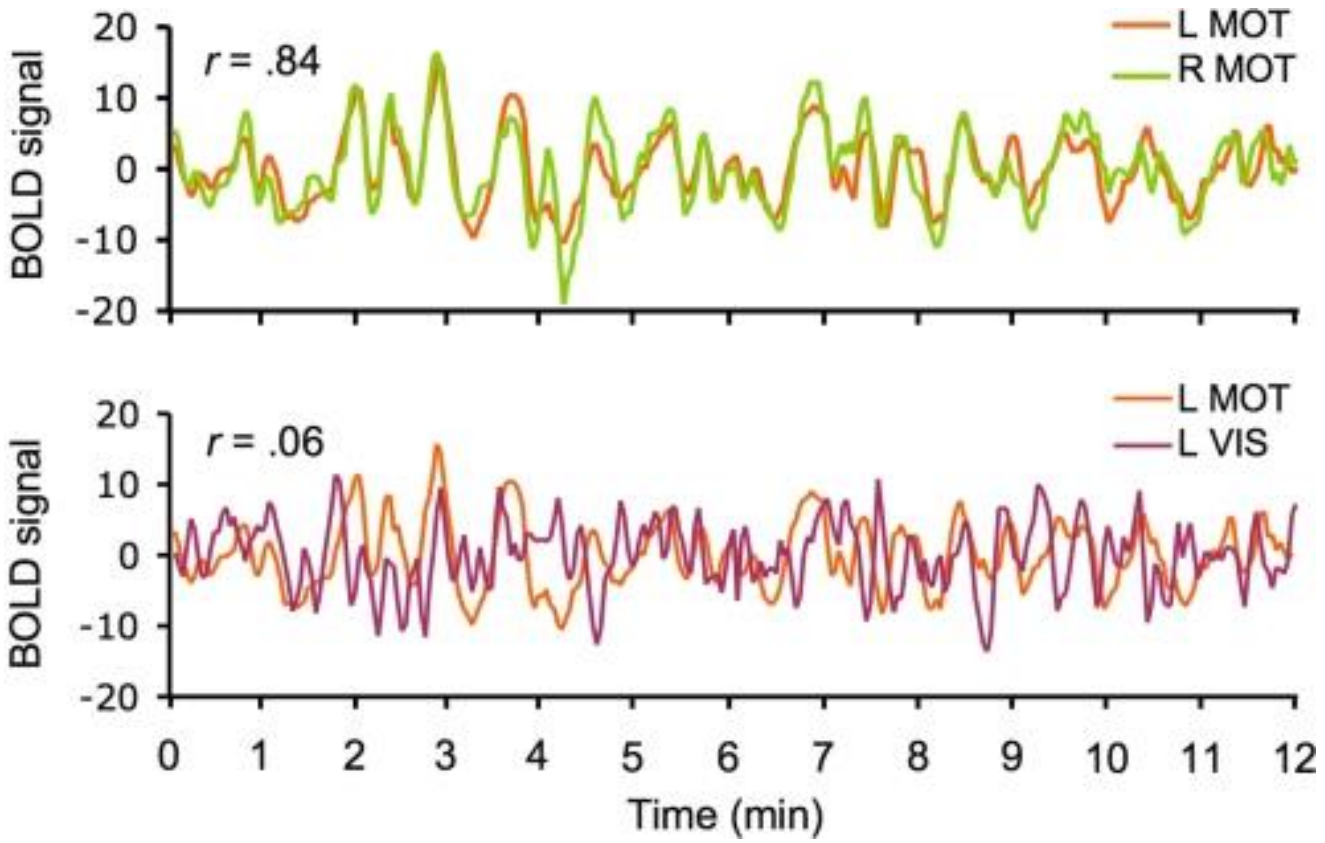
also thinking about our past, our future, other people

Resting-State Functional Networks

- **Intrinsic functional networks may be revealed by temporal correlations between fMRI (BOLD) signals in the resting brain**

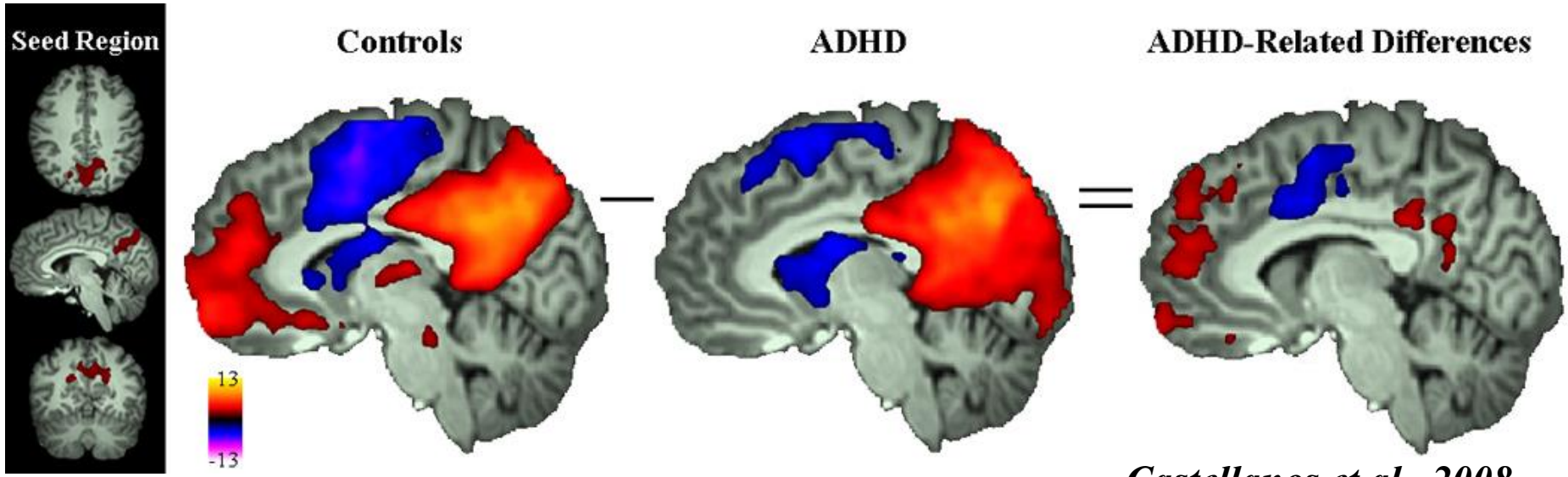
Resting-State Functional Networks

contralateral motor areas in a network



ipsilateral motor and visual areas not in a common network

Adult ADHD: Decreased Positive Correlations Between PCC-MPFC



Castellanos et al., 2008

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

Neurobiology of Persistent vs. Remitted Adult ADHD

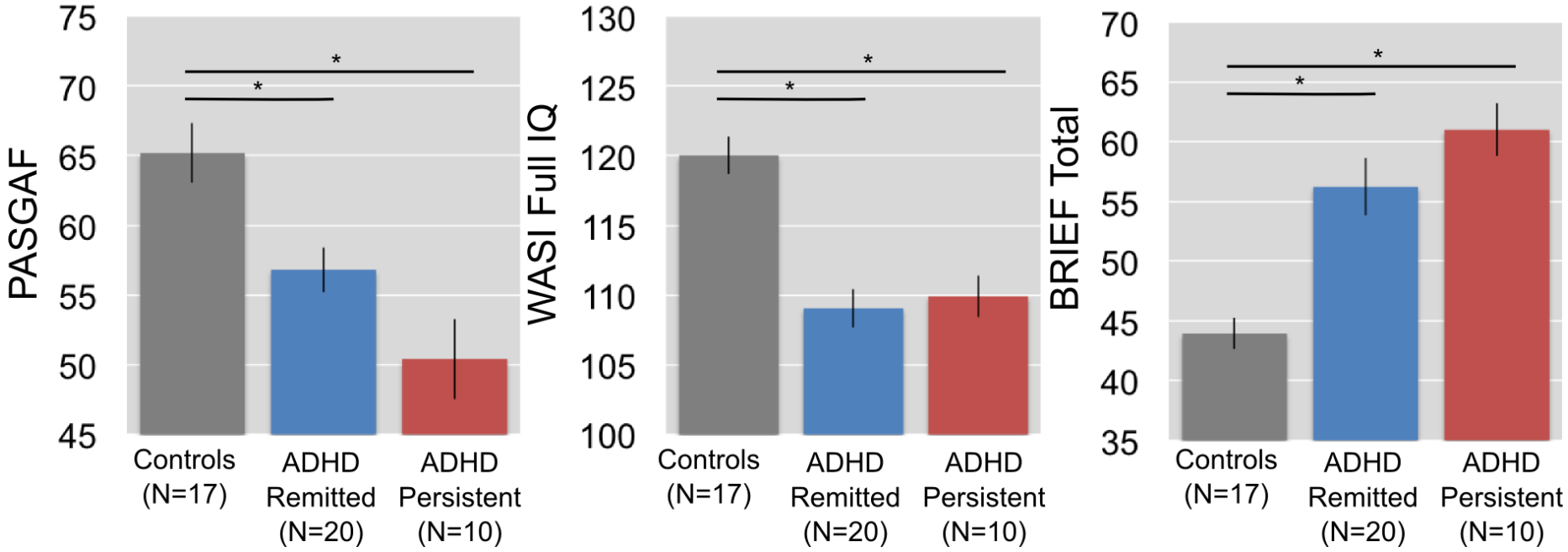
Is there a neurobiological distinction between *persistent* ADHD and *remitted* ADHD?

Neurobiology of Persistent vs. Remitted Adult ADHD

- 17 Controls (mean age = 28.7; 11 male)
- 20 Remitted ADHD (mean age = 27.5; 8 male)
- 10 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

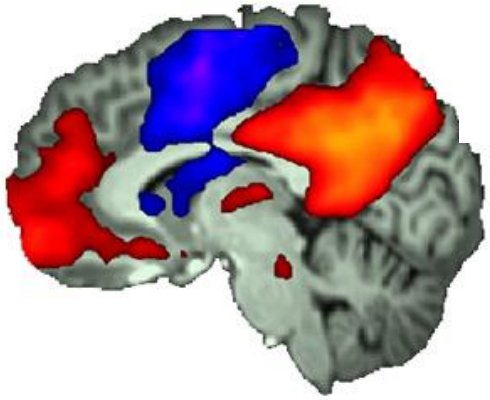


PASGAF = Past Global Assessment of Functioning Scale;
BRIEF = Behavior Rating Inventory of Executive Function

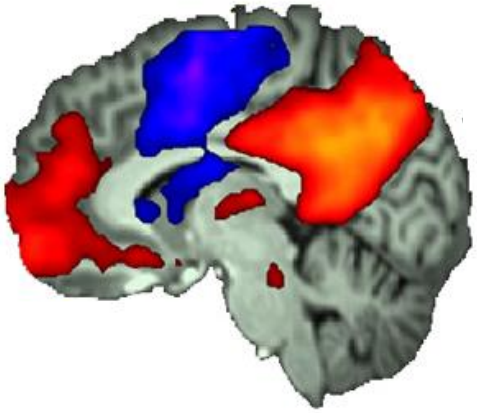
No significant differences between Persistent & Remitted ADHD on 9 other neuropsychological tests or childhood severity of ADHD

Neurobiology of Persistent vs. Remitted Adult ADHD

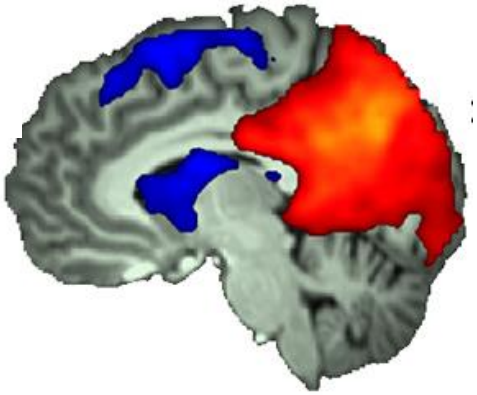
Controls



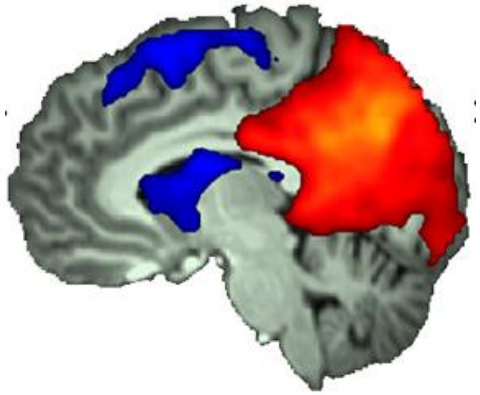
Remitted ADHD?



Persistent ADHD

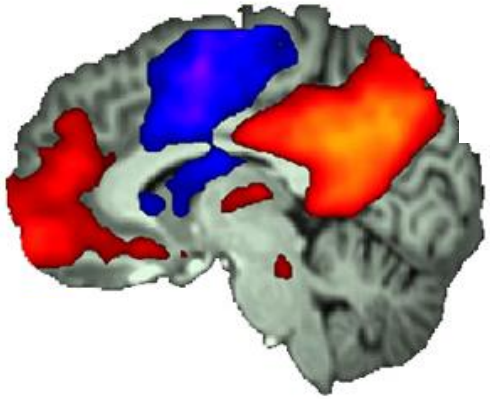


Remitted ADHD?

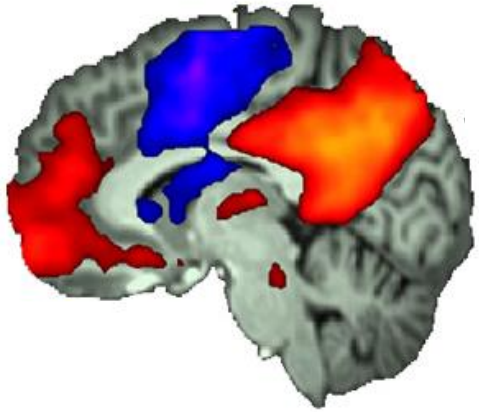


Neurobiology of Persistent vs. Remitted Adult ADHD

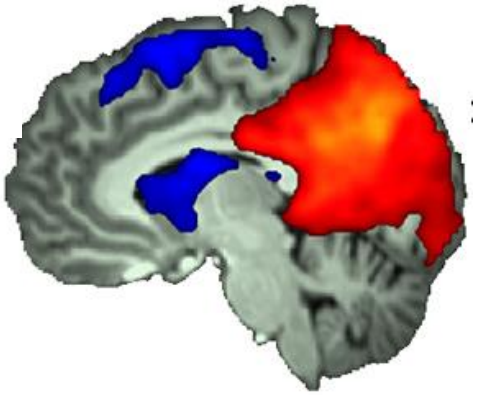
Controls



Remitted ADHD?



Persistent ADHD



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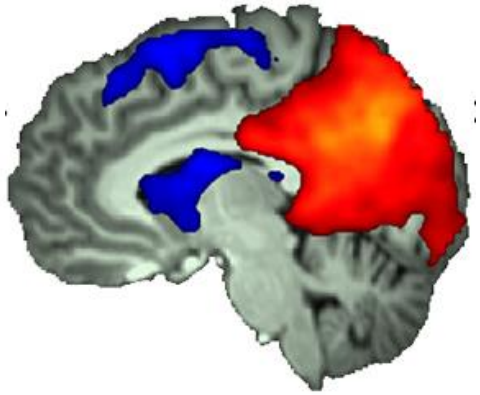
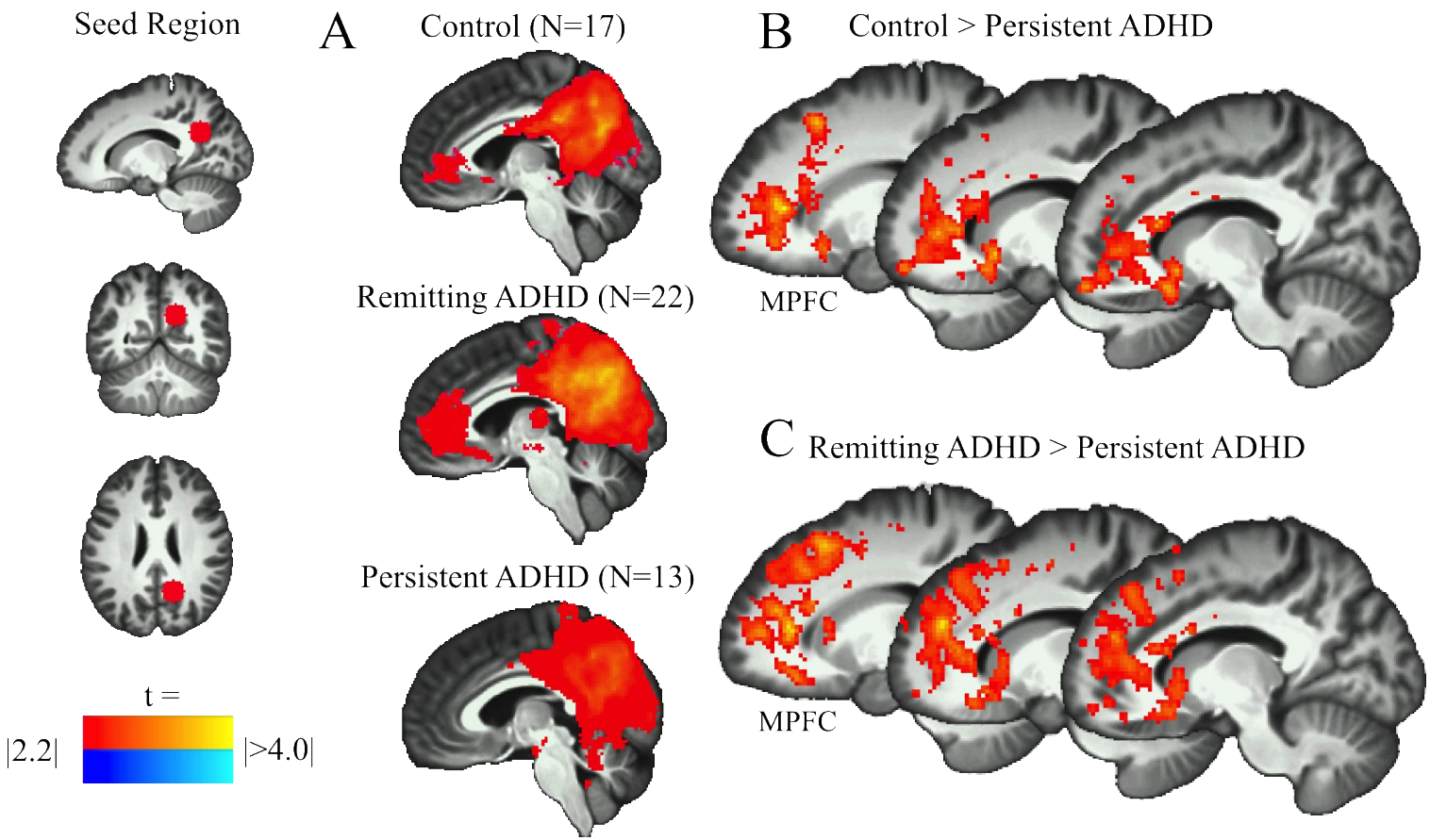
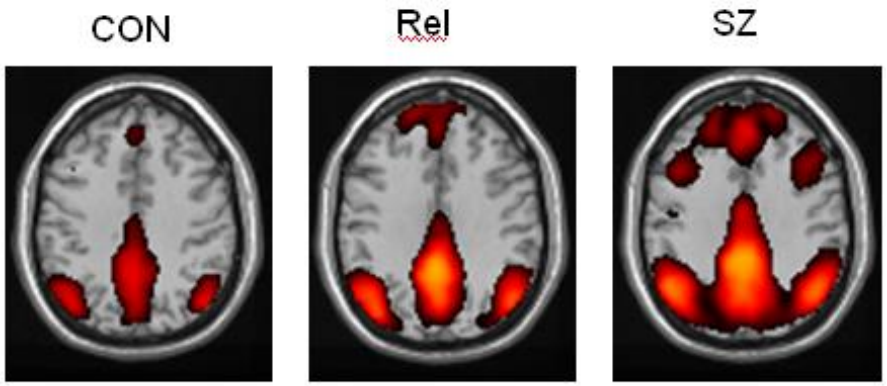


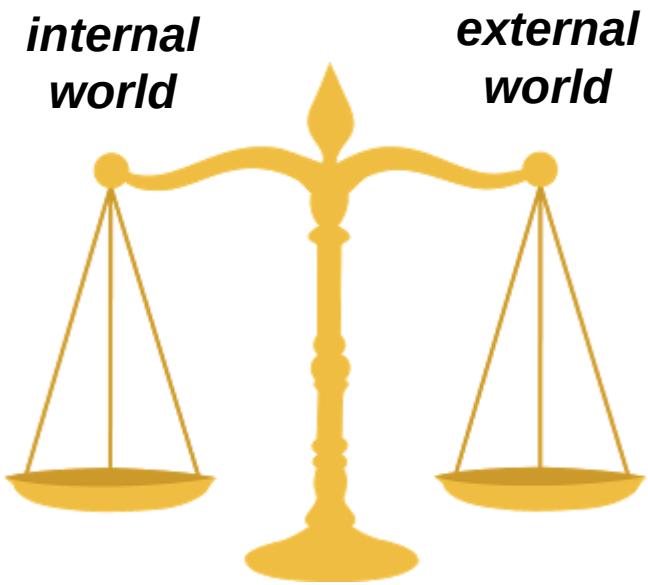
Reduced MPFC-PCC Coupling Reflects Current Diagnostic State of ADHD



Neurobiology of Persistent vs. Remitted Adult ADHD

- **Persistent ADHD –** ↓ **DMN connectivity**
- **Schizophrenia –** ↑ **DMN connectivity**





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**

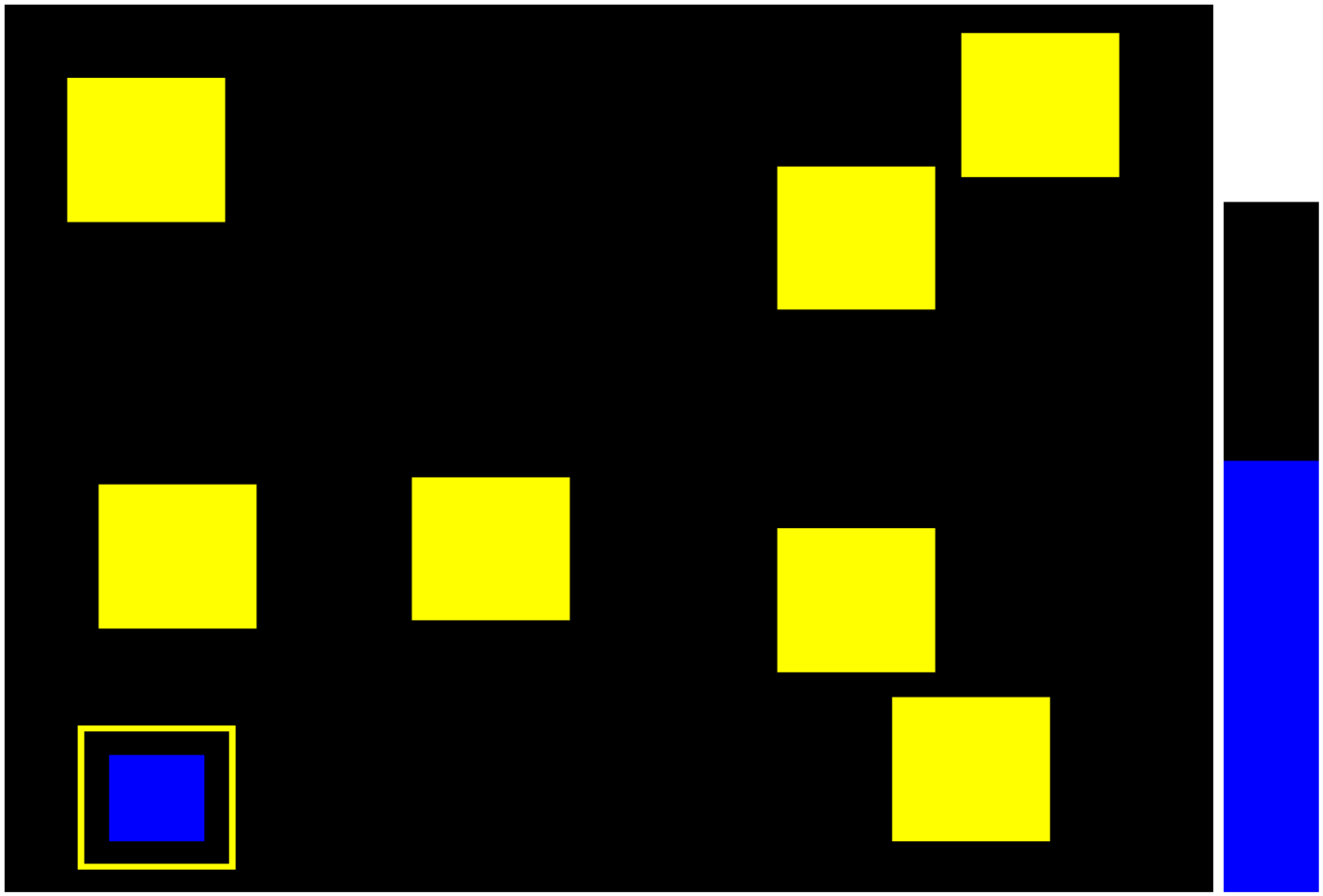
a core weakness in ADHD

Barkley, 1997

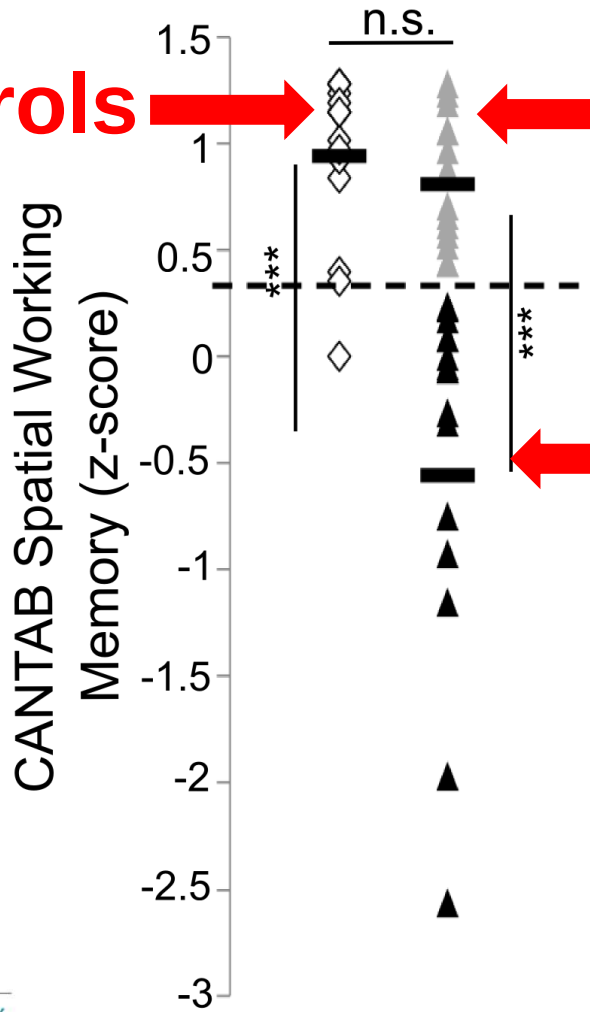
Heterogeneity in ADHD

- **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



Controls

Intact ADHD

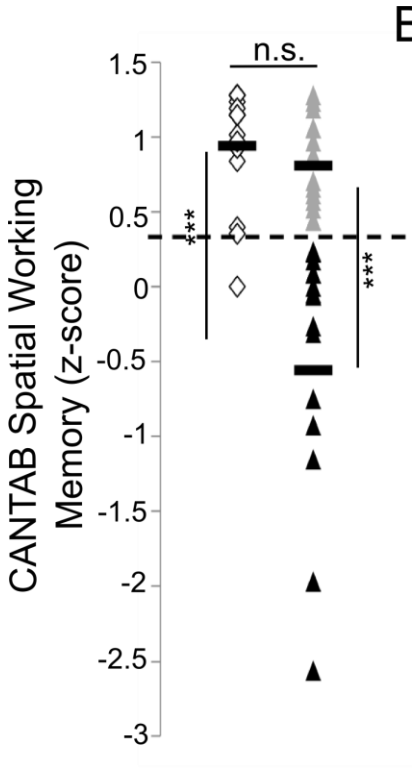
Impaired ADHD

Mattfeld et al., *NeuroImage Clinical*, 2016

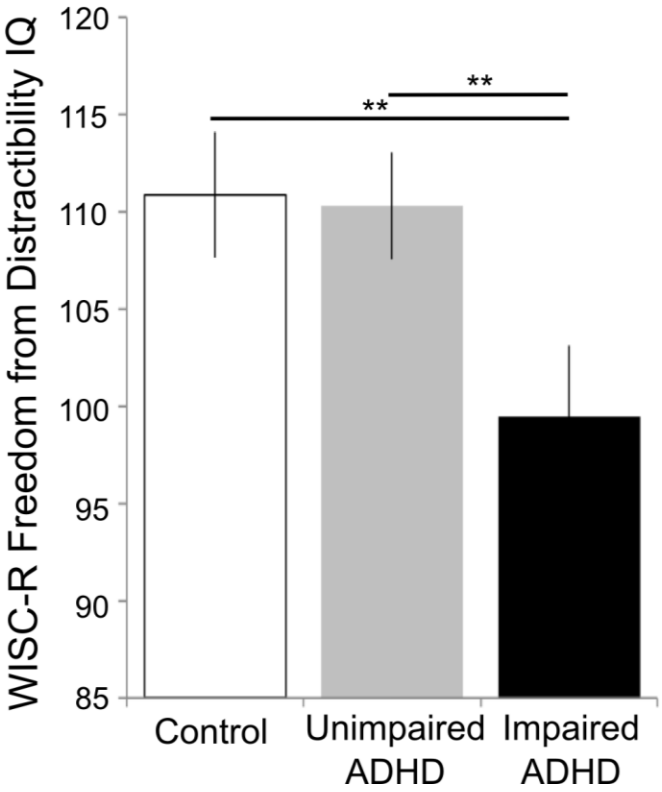
WM-Intact & WM-Impaired ADHD Groups

Persistence Across Development

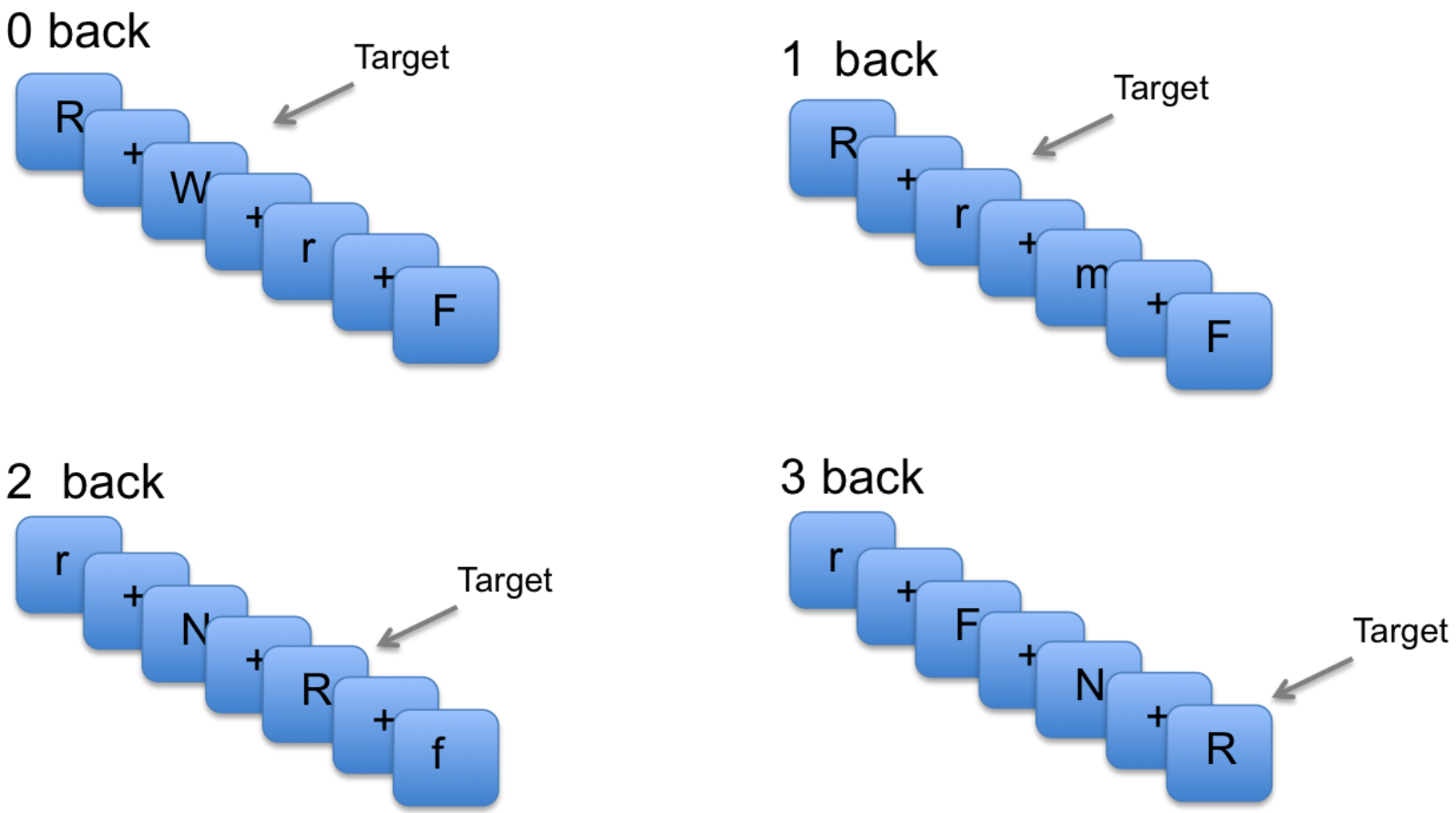
Adulthood



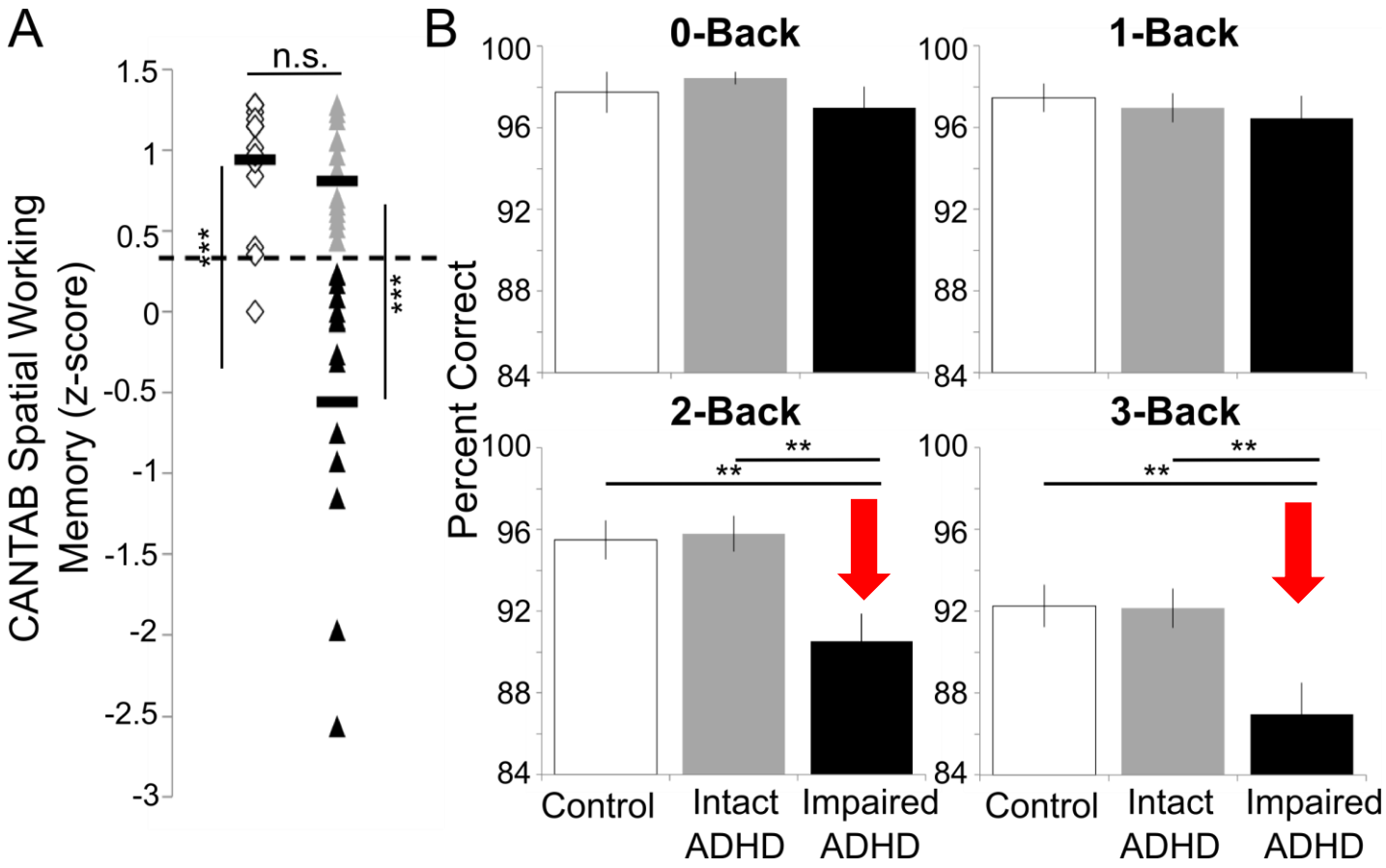
Childhood



N-Back Working Memory Task With Increasing Demand (Load)



WM-Intact & WM-Impaired ADHD Groups

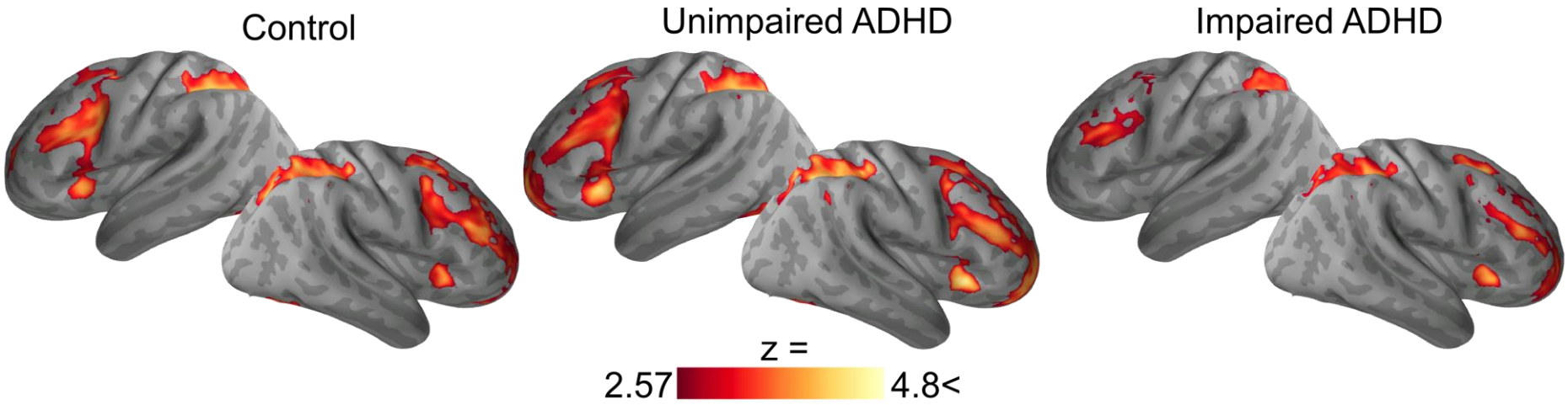


WM-Intact & WM-Impaired ADHD Groups

- **Increased activation with increased WM load in fronto-parietal WM network**

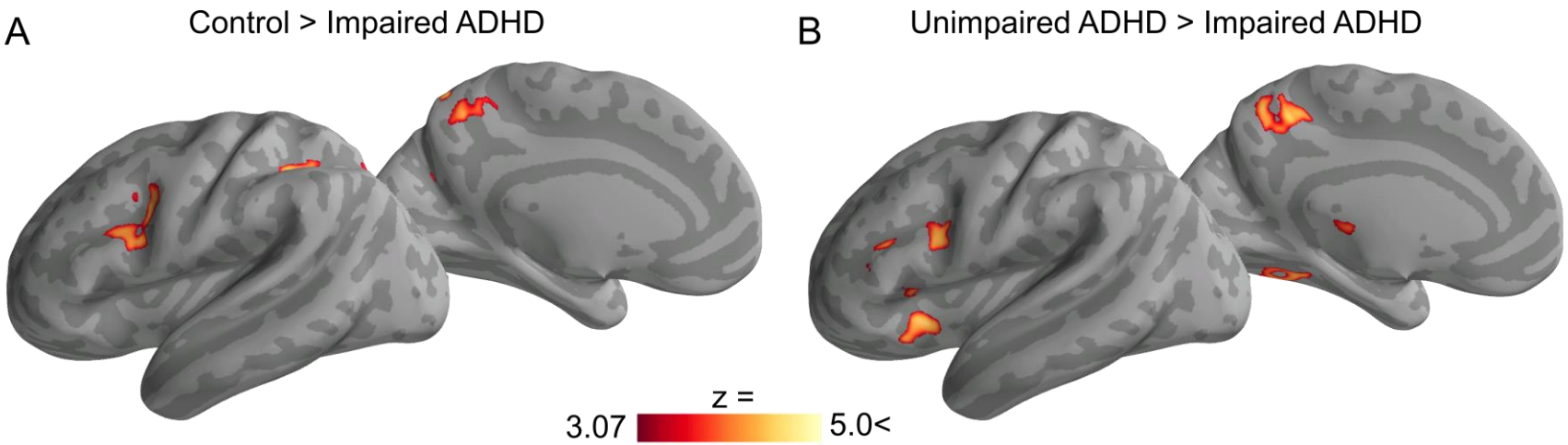
3-back > 2-back > 1-back > 0-back

- **Reduced activation only in WM-Impaired ADHD group**



Mattfeld et al., *NeuroImage Clinical*, 2016

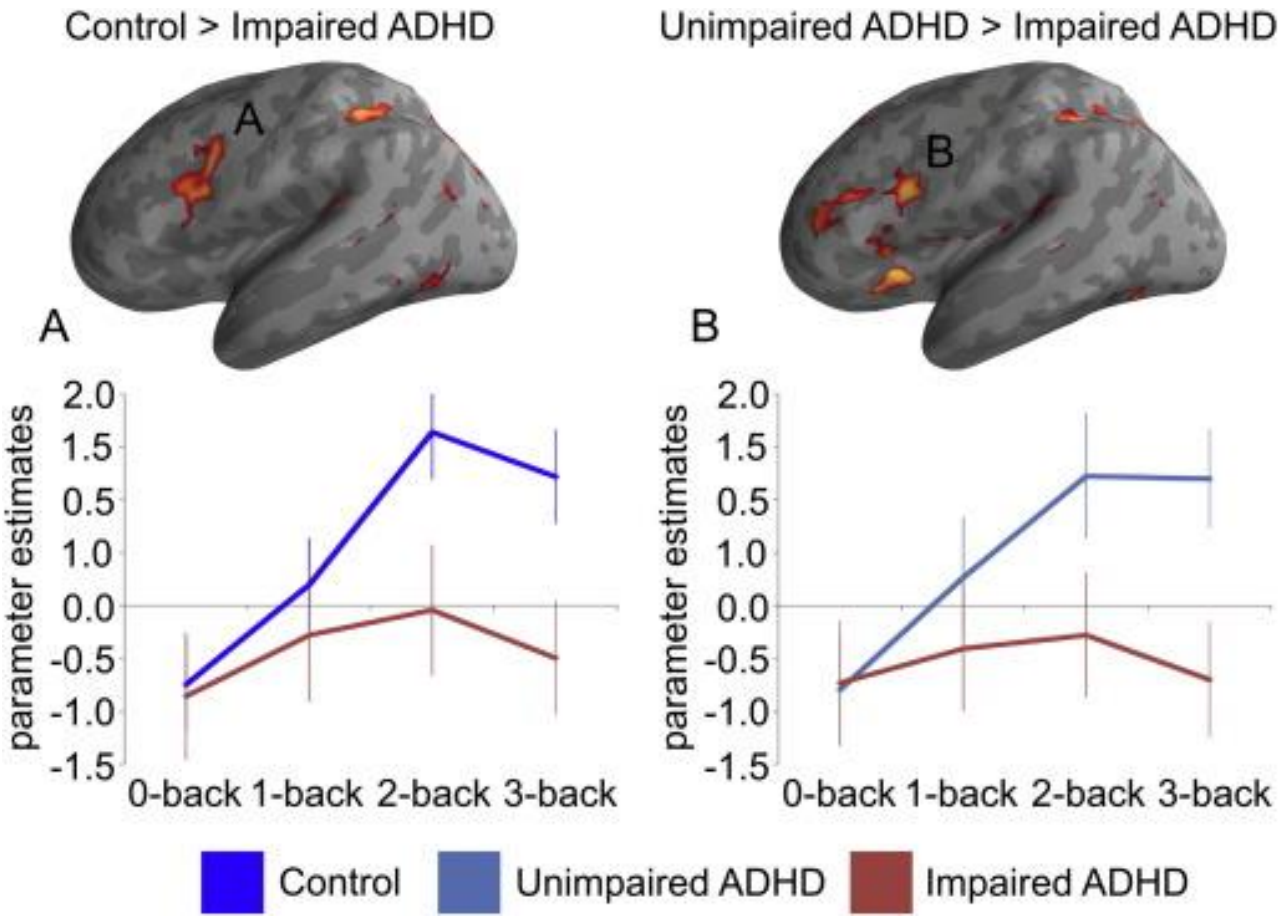
WM-Intact & WM-Impaired ADHD Groups



- **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

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)

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- **neuroimaging studies often report activation differences without WM performance differences**

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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

Collaborators

- **ADHD**
  - **Joseph Biederman**
  - **Aaron Mattfeld**
  - **Thomas Spencer**
  - **Ariel Brown**
  - **Elana Kagan**
  - **Susan Whitfield-Gabrieli**