Homework Assignment for Week 4

NIMH Neuroimaging Primer: Found at http://www.nimh.nih.gov/health/publications/neuroimaging-and-mental-illness-a-window-into-the-brain/neuroimaging-and-mental-illness-a-window-into-the-brain.shtml)

Pay Attention: ADHD Through the Lifespan

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Week 4: Neuro-Imaging of ADHD

Homework Review

Neuro-Imaging Findings

Smaller, Less Active, Less Developed Brain Regions

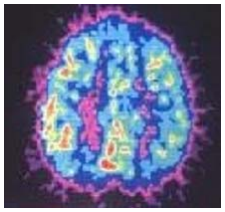
- 3-10% reduced regional volumes in these 3 regions:
  - Orbital-Prefrontal Cortex (primarily right side)
    - Genetics contributes to under-development of this region while acquired ADHD may be related to smaller inferior dorsolateral frontal region
  - Basal Ganglia (mainly striatum & globus pallidus)
  - Cerebellum (central vermis area, more on right side)
- Anterior cingulate (mostly shows underactivity)
- Size of this network is correlated with degree of ADHD symptoms, particularly inhibition
- No gender differences
- 3 year lag in brain development but achieving typical brain volumes by age 16
- Results are not due to taking stimulant medication

Never-Medicated Adults with ADHD Show Decreased Cerebral Metabolism

- Global and regional glucose metabolism by PET scan reduced in adults who have been hyperactive since childhood
- ADHD subjects showed **8.1%** decrease in cortical activity
- Largest reductions in:
  - Premotor cortex
  - Superior prefrontal cortex

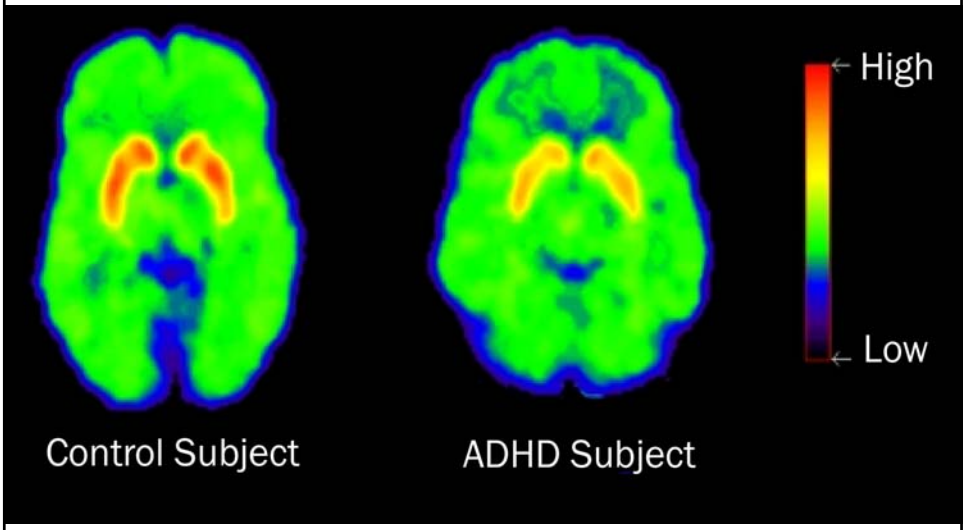
Normal

ADHD



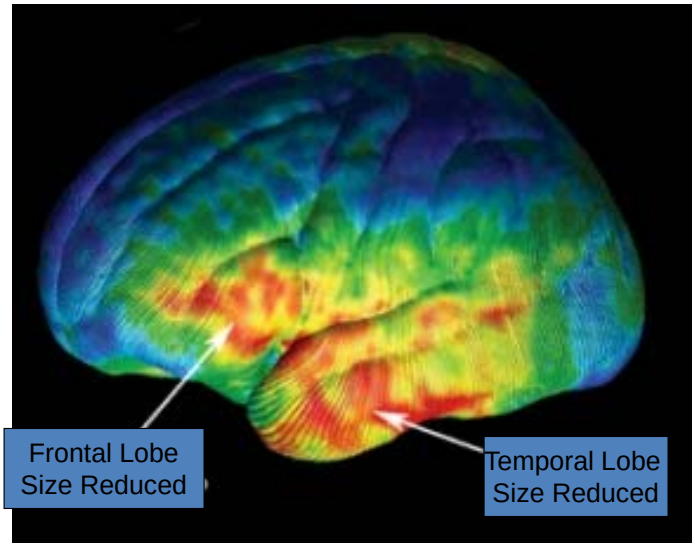
Zametkin AJ, et al. *N Engl J Med*. 1990;323:1361-6.

PET Scan Study of DAT



These positron emission tomography (PET) scans show that patients with ADHD had lower levels of dopamine transporters in the nucleus accumbens, a part of the brain's reward center, than control subjects.

Structural MRI Studies



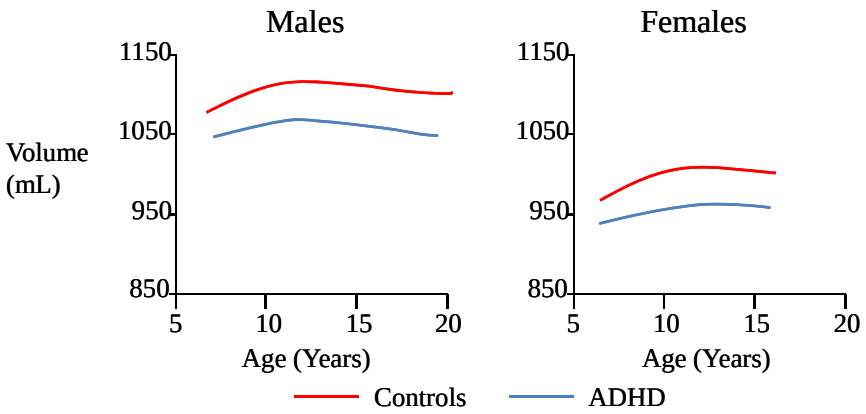
Mid-Lecture Questions

Developmental Trajectories of Brain Volume Abnormalities in Youth with ADHD

- Design: MRI case control study
- N = 152 youth with ADHD and 139 controls of both genders
- Objective: assess volumetric changes overtime in medicated vs. unmedicated youth with ADHD and controls

Castellanos, et al. *JAMA*. 2002 Oct;288(14):1740-8.

Developmental Trajectories of Brain Volumes



Stimulant treatment did not affect size of any brain structures

Castellanos FX, et al. *JAMA*. 2002 Oct 9;288(14):1740-8.

Developmental Trajectories of Brain Volume Abnormalities in Youth with ADHD

Main Findings:

- Smaller brain volumes in all regions independently of medication status
- Smaller total cerebral (-3.2%) and cerebellar (-3.5%) volumes
- Volumetric abnormalities (except caudate) persisted with age
- No gender differences
- Volumetric findings correlated with severity of ADHD

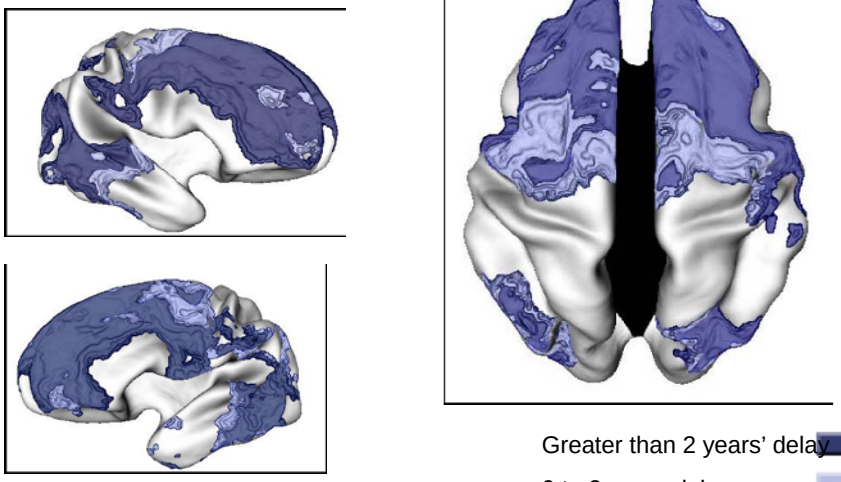
Conclusions:

- Genetic and or early environmental influences on brain development in ADHD are *fixed, nonprogressive, and unrelated to stimulant treatment*

Castellanos, et al. *JAMA*. 2002 Oct;288(14):1740-8.

Delayed brain growth in ADHD (3 yrs.)

From Shaw, P. et al. (2007). ADHD is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences, 104*, 19649-19654.



Ns: ADHD=223; Controls = 223

Delayed cortical maturation in ADHD

From Shaw, P. et al. (2007). ADHD is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences, 104*, 19649-19654.

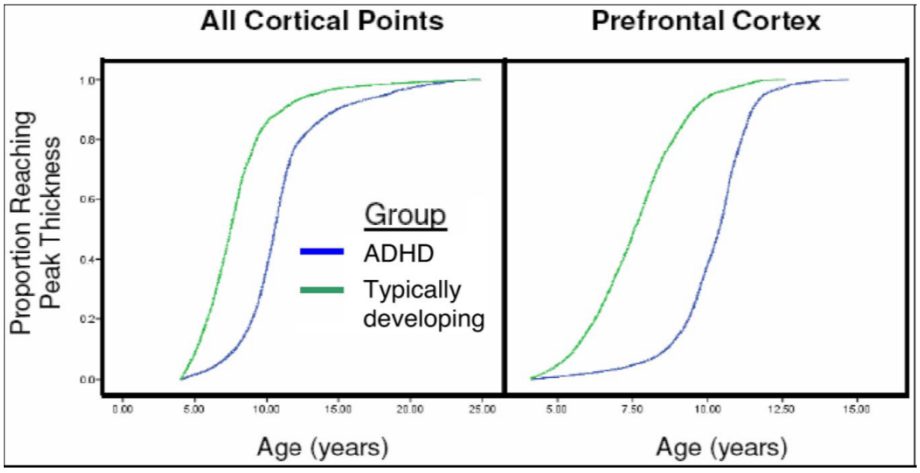


Fig. 3. Kaplan–Meier curves illustrating the proportion of cortical points that had attained peak thickness at each age for all cerebral cortical points (*Left*) and the prefrontal cortex (*Right*). The median age by which 50% of cortical points had attained their peak differed significantly between the groups

Mid-Lecture Questions

Anterior Cingulate Cortex

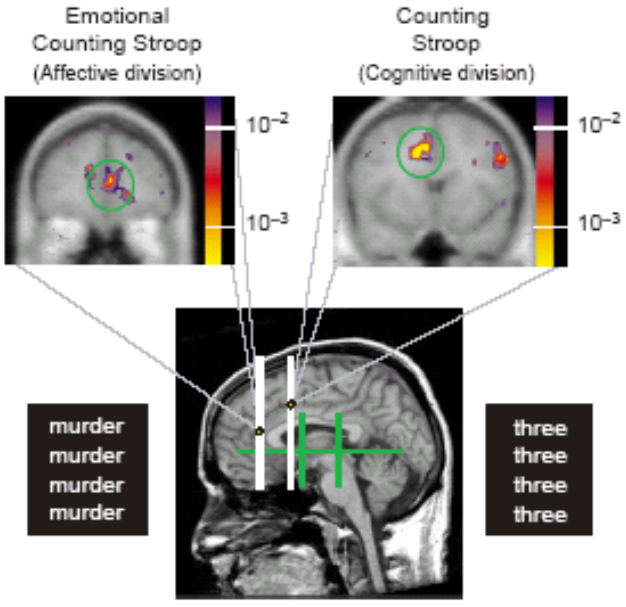
- Key part of the executive attention system
- Has 2 divisions: cognitive and emotional
- May help keep working memory on-line during cognitive tasks and monitors for errors
- Under-activity in ADHD demonstrated in numerous studies

Anterior Cingulate Cortex involved in…

- Emotion/motivation
- Anticipation/timing
- Attention: target selection/filtering (selection for action)
- Novelty
- Motor control/response selection (willed action)
- Working memory
- Pain/nociception
- Error detection
- Reward
- Competition monitoring
- Difficulty monitoring
- Autonomic control
- Prediction error
- Feedback-mediated decision-making

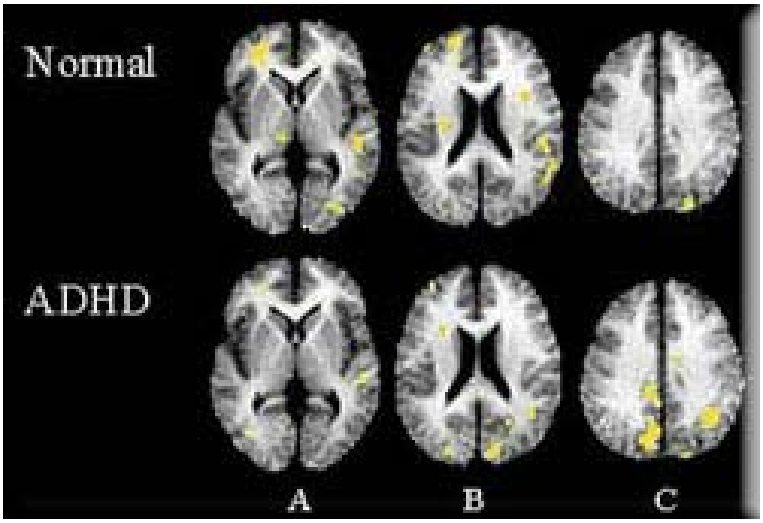
Bush et al. *Biol Psych*. 1999

A Research Paradigm for Studying ADHD Using fMRI



Failure to Activate Cingulate Gyrus During Counting Stroop Task

Bush et al, *Biol Psych* (1999)



Failure to Activate Cingulate Gyrus During Counting Stroop Task

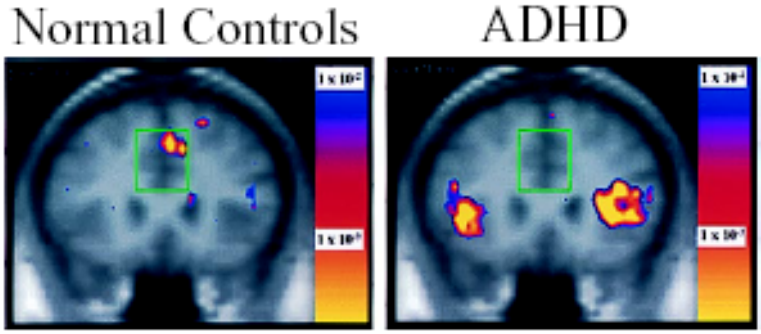
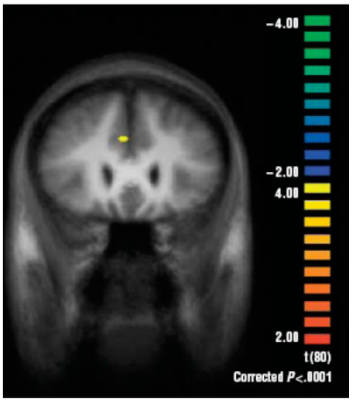


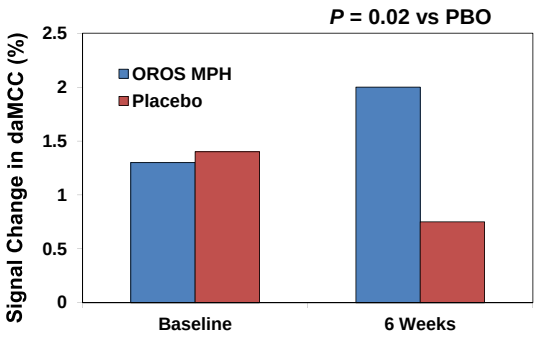
Figure 3. Anterior cingulate cognitive division activates in the normal control group but not in the ADHD group during the counting Stroop. The ACcd showed significantly higher activity in the normal control group during the interference blocks minus the neutral blocks. In contrast, while the ADHD group did display significant activity in a frontostriato–insular–thalamic network, they did not show significant activation anywhere in cingulate cortex. *Bush et al, Biol Psych 1999*

Mid-Lecture Questions

Methylphenidate Activates Dorsal Anterior Mid-Cingulate Cortex & Dorsolateral Prefrontal Cortex

Bush et al, *Arch Gen Psych* (2008)

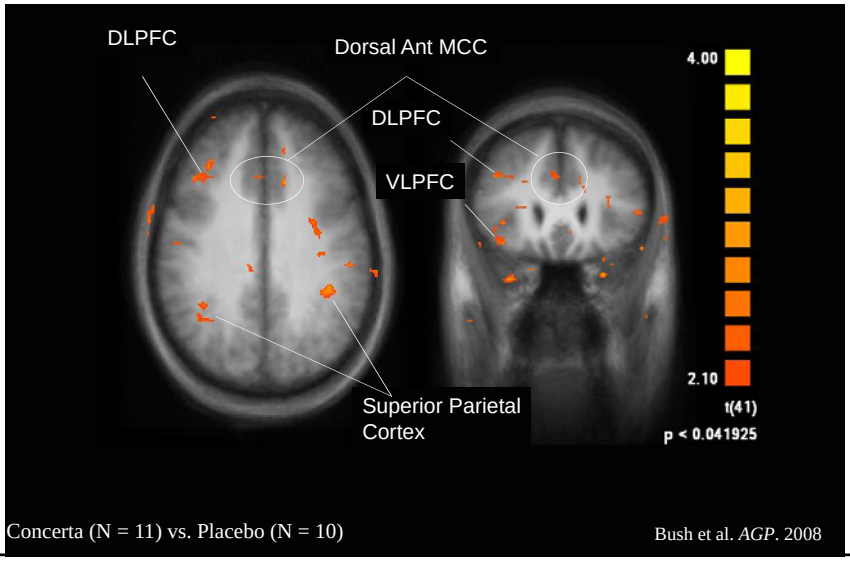




- fMRI at baseline and again at week 6
- OROS MPH group showed higher daMCC activation at 6 weeks vs placebo
- N=21 adults with ADHD; dosing to 1.3 mg/kg/day OROS MPH or placebo

Methylphenidate Activates Dorsal Anterior Mid-Cingulate Cortex and Dorsolateral Prefrontal Corex

Bush et al, *Arch Gen Psych* (2008)



Concerta (N = 11) vs. Placebo (N = 10)

Bush et al. *AGP*. 2008

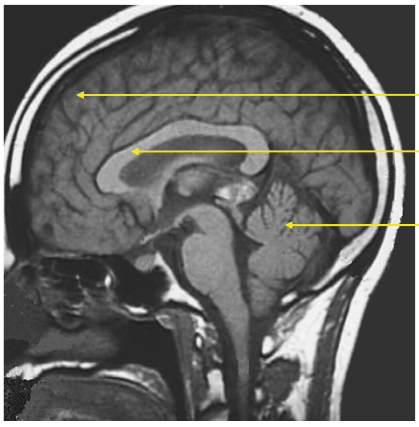
Summary of ADHD MRI Studies

- Frontal lobes (rich in dopamine receptors)
- Basal ganglia (striatum)
- Cerebellum

All three found to be smaller in individuals with ADHD compared with controls

Structural MRI studies
~10% decrease in size of ADHD-associated areas

Functional imaging studies
Decreased striatal perfusion in ADHD subjects



Swanson JM et al. *Lancet.* 1998;351:429–433. Castellanos FX et al. *Arch Gen Psychiatry.* 2001;58:289–295.

ADHD NeuroImaging Studies
Summary

- Neuroimaging studies *confirm* that ADHD is associated with abnormalities in frontal-subcortical networks with some involvement of the cerebellum and the parietal cortex
- Neuroimaging techniques are **not** valid tools for ADHD diagnosis; imaging measures are not sensitive or specific enough to be used for diagnostic purposes

Bush G, Valera EM, Seidman LJ. Biol Psychiatry. 2005;57:1273-1284.

Future Directions of ADHD Neuroimaging Research

- Diffusion Tensor Imaging
- Resting State Imaging
- Gene x Functional Studies
- Clinical Intervention Strategies

Homework Assignment for Week 5

READING: Surgeon General on ADHD 1999
(Namely pages 142-150) Found at
http://profiles.nlm.nih.gov/ps/access/NNBBJB.pdf

Quiz Questions