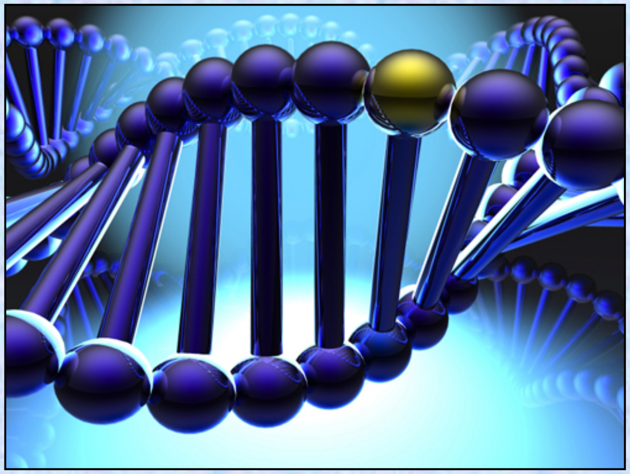
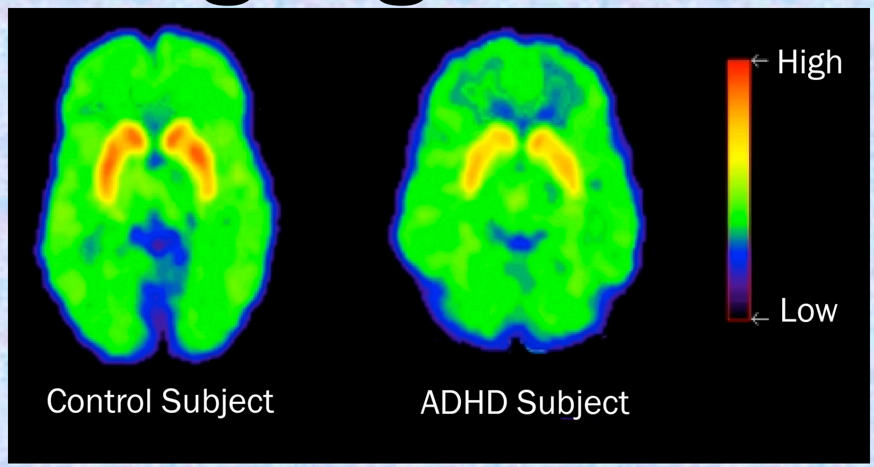
Converging methods in studying ADHD: Genes and Neuroimaging



http://www.frontsidebus.net/2011/04/gene-therapy-shows-promise-against-age-related-macular-degeneration/



http://www.bnl.gov/bnlweb/pubaf/pr/PR_display.asp?prID=06-124

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Introduction (1)

- ADHD should be diagnosed by age 7
  - Persists into adulthood in about 30%
- Impulsivity & Inattentiveness
- ADHD implicates cognitive control
- Criteria to diagnose ADHD
- Etiology (cause) of ADHD unknown
- Paper explores: genes, brain, and cognitive control in ADHD individuals, their family members, and controls

Typical Development of Cognitive Control and Frontostriatal Systems

- Cognitive control has a protracted development.
- Development coincides with structural brain development (functional changes in brain development are reflected in structural changes)

- Cortical gray matter first increases in volume -> followed by postadolescent decreases (Volume loss in primary sensorimotor areas -> in the dorsolateral prefrontal cortex.)

- **Casey et al. (1997):** associations between MRI-based prefrontal volume and specific measures of cognitive control, where developmental improvements in performance on an attention task were correlated with greater volume of the anterior cingulate gyrus.

Typical Development of Cognitive Control and Frontostriatal Systems

- **Developmental shifts in activation from diffuse to more focal patterns**(Durston, Davidson, et al., 2006): it is unclear whether such shifts reflect the functional consequences of synaptic pruning, other regressive processes, or strengthening of relevant connections.
- New imaging techniques, diffusion tensor imaging (DTI)
- **Liston & Colleagues (2006) DTI study:** Diffusion in all assessed white matter tracts became more restricted between the ages of 7 and 30 years. This shift was paralleled by an age-associated increase in efficiency in cognitive control.

⇒ Developmental changes in brain structure and function underlie the development of cognitive control, in particular, in frontostriatal circuits.

Typical Development of Cognitive Control and Frontostriatal Systems

- **Atypical development in ADHD is due to a developmental delay or deficit?**
- A longstanding debate in the ADHD literature: behaviors associated with this disorder may be completely appropriate at one age but inappropriate at another.
- ADHD may reflect residual processes that do not necessarily diminish or change with maturity.

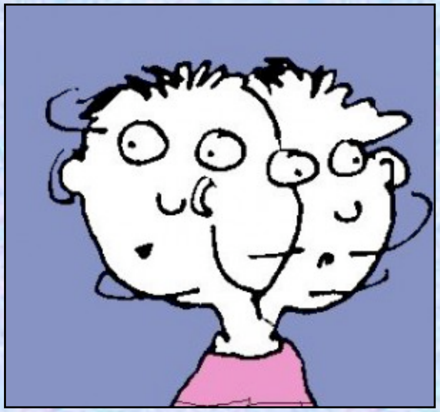
- **Shaw & Colleagues (2007):** the developmental trajectory of cortical gray matter in a longitudinal data set. (450 children with ADHD & controls)
- found that cortical gray matter in ADHD largely followed the same trajectory as in typically developing children, but lagged behind by on average 3 years. (first neurobiological evidence that ADHD associated with a developmental lag.)

Family and Genetic Studies (1)

- ADHD has a strong genetic component
- 80% of variance in phenotype accounted by genes
- Siblings of children with ADHD 3-5x more likely to develop. Risk higher for monozygotic twins
- ADHD subtypes not restricted within family
- No relationship b/w genes and specific phenotype
  - Likely to have underlying mediating factors

http://www.everydayhealth.com/adhd/living-with/help-adhd-siblings-get-along.aspx

http://cloudberryknit.blogspot.com/2009/07/adhd.html



http://trialx.com/curetalk/2011/03/list-of-schools-for-adhd-kids-in-mid-west/

Family and Genetic Studies (2)

- Genome scan vs. Candidate genes
- Genome scans somewhat inconclusive
  - Run in 4 geographically different areas
- Region of interest on chromosome 5p13
  - Next to the Dopamine transporter gene
  - Odds of linkage not very high (low odds ratio)
  - Likely reason it has been tough to replicate
- 7 candidate genes have been identified:
  - DRD4, DAT1, DRD5, DBH, SNAP-25, 5-HTT, HTR1B

Family and Genetic Studies (3)

5- "Fight or flight hormones" (i.e. dopamine)

- DRD4- post-receptor subsensitivity to dopamine
- DAT1- change in dopamine transporter activity
- DRD5- unknown-efficiency of gene transcription?
- DBH- converts dopamine to norepinephrine
- SNAP-25- alters ratio/trans. of neurotransmitters

2- Serotonin related genes

- 5-HTT- serotonin transporter-reduced transcription
- HTR1B- can change serotonin activity

ADHD is heritable but no real link has been established between risk genes and phenotype

Family and Genetic Studies (4)

- Use of endophenotypes to get a better idea
  - May shed more light on the effect of genes
- Look for comparisons to those unaffected but related to a clinically affected individual
- Unaffected siblings show similar neurobiological changes w/o clinical phenotype
- Look at ADHD from a genetic perspective, less so from clinical, and maybe this will shed light on how genes are relevant in the general population, not just in the clinical groups.

Mapping Family and Genetic Effects on the Brain (1)

- Smaller brain volume in ADHD than CTL
- 3 specific areas identified as smaller:
  - Caudate nucleus
  - Pre-frontal cortex (PFC)
  - Cerebellum (specifically the vermis)
- Cognitive control implicated
  - Frontostriatal pathway compromised

Mapping Family and Genetic Effects on the Brain (2)

- DRD4 & DAT1 associated with decreased frontostriatal volumes (gray matter volumes)
- Risk genes can impact neurobiology without requiring a clinical phenotype to be present
  - Can impact those w/o ADHD, neurobiologically
  - Most obvious differences in PFC & striatum
- DAT1 shown to correlate with different brain activation patterns in those who have familial risk of ADHD (i.e. affected and unaffected sibs)
  - Differences in striatum in At Risk vs. Controls
- Cerebellum spared from familial ADHD effects

Functional Neuroimaging Approaches to Understanding ADHD

- Studies with tasks that tax cognitive control have shown that differences in cognitive control between subjects with and without ADHD are associated with differences in brain activation patterns (e.g., Bush et al., 1999)

- Reduced activation in prefrontal and striatal regions during paradigms that require subjects to suppress prepotent tendencies as part of the task, such as go/no-go or Stroop paradigms (Booth et al., 2005 etc.)

- Go/no-go tasks, Stroop paradigm(Classic/Several variations on this classic task)
- The pattern of decreased activation in prefrontal and striatal areas in cognitive control tasks has led investigators to suggest that deficits in these regions may be central to ADHD (for a review, see Bush, Valera, & Seidman, 2005)

Functional Neuroimaging Approaches to Understanding ADHD

- Other studies investigate other aspects of behavior(e.g. attention, mental rotation paradigms, and motivated behavior) again, have shown deficits in striatal and prefrontal activation have been found, as well as changes in activation in parietal areas.

- Importance of frontostriatal networks in ADHD as deficits in this network have now been associated with a wide range of tasks.

- **Casey, Epstein, et al., 2007:** A recent study used DTI
- Reduced frontostriatal activation during a go/no-go task was related to reduced white matter integrity in both children with ADHD and their affected parents. (Disruption of frontostriatal white matter tracts may contribute to a familial form of the disorder.)

Converging Methods Suggest New Directions in ADHD Research

Frontocerebellar loops in the etiology of ADHD

- **Mostofsky & Colleagues(2006):**

 - Neural correlates of simple motor movements in ADHD
 - Reduced activation in parietal and primary motor cortex only.
 - Frontostriatal involvement is specific to the cognitive and motivational deficits.

- **Durston et al., 2007:**

 - Children & adolescents with ADHD not able to benefit from trials being predictable
 - Task: a variation of a go/no-go task. (expected/unexpected stimuli presented at expected/unexpected times)
 - Children and adolescents with ADHD had increased variability in reaction times
 - Decreased benefit in reaction time when events were predictable.
 - Behavioral changes accompanied by decreases in frontostriatal and cerebellar activation. (Prefrontal: unpredictable, stimulus identity violated, Cerebellum: timing violated.)

Converging Methods Suggest New Directions in ADHD Research

A role for striatal reward circuitry in treating ADHD?

- **Scheres et al., 2007; Strohle et al., 2008:** Reduced activation in ventral striatum in ADHD on tasks where subjects anticipated, in addition to striatal dysregulation in cognitive control tasks. (functional imaging studies)
- **New directions for intervention:** “improve cognitive control in ADHD by using reward strategies.”
- **A biological basis:** ventral frontostriatal circuits involved in reward processing project to more dorsolateral networks. (Haber, 2003)
- Reward may enhance activation in ventral striatum, boosting more dorsolateral networks and lead to improvements in cognitive performance.

Converging Methods Suggest New Directions in ADHD Research

A role for striatal reward circuitry in treating ADHD?

- **Durston et al., ??** : the effect of reward on cognitive control in ADHD. Reward parametrically manipulated in the context of a go/no-go task

  - In both children and adolescents(with & without ADHD), performance on go trials improved with reward
  - No evidence that reward improved cognitive control or activation in frontostriatal circuits.
  - No behavioral improvement on no-go trials in either sample, no effect on fMRI signal on no-go trials. (Surprising given reports of cognitive improvements with reward in ADHD)
  - Behavioral programs using small, predictable rewards, limited utility in ADHD. (larger or unexpected rewards may still be of use)

THE END

Questions?