Childhood Disorders: ADHD and Autism

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ADHD
Symptoms of ADHD

Signs of hyperactivity-impulsivity are:
• Feels restless, fidgety or squirms while seated
• Runs, climbing, or leaves seat in situations where sitting or quiet behavior is expected
• Blurts out answers before hearing the whole question
• Has difficulty waiting in line or taking turns.

DSM-IV-R gives these signs of inattention:
• Easily distracted by irrelevant sights and sounds
• Fails to pay attention to details, careless mistakes
• Rarely follows instructions, loses and forgets things
• Skips from one uncompleted activity to another.
Diagnosis

- The *DSM-IV criteria define 3 subtypes of ADHD*
  - ADHD primarily of the inattentive type (ADHD/I, meeting at least 6 of 9 inattention behaviors)
  - ADHD primarily of the hyperactive-impulsive type (ADHD/HI, meeting at least 6 of 9 hyperactive-impulsive behaviors)
  - ADHD combined type (ADHD/C) - meeting at least 6 of 9 behaviors in both the inattention and hyperactive-impulsive lists
ADHD

• ADHD is a neurobehavioral disorder characterized by pervasive inattention and/or hyperactivity-impulsivity.

• 4.4 million youth ages 4-17 have been diagnosed with ADHD by a healthcare professional.

• 2.5 million youth ages 4-17 are currently receiving medication treatment for the disorder.
FIGURE 1. Percentage of children aged 4–17 years ever diagnosed with ADHD,* by age, sex, and medication treatment status — United States, 2003

*Attention-deficit/hyperactivity disorder.
\(^\d\) Confidence interval.
WHAT DO WE KNOW ABOUT THE BIOLOGY OF ADHD

Highlight findings from recent neuroimaging and genetic studies of ADHD that may inform biologically-targeted treatments.
CIRCUITRY IMPLICATED IN ADHD

Casey & Durston 2006 American J Psychiatry
Magnetic Resonance Imaging (MRI) of the Developing Human Brain

Structural MRI to track changes in size and shape of neuroanatomical structures with development

Functional MRI (fMRI) to track changes in brain and behavior with development

Diffusion Tensor Imaging (DTI) to track strengthening of connectivity of fiber tracts with development

Casey et al 2005 Current Opinions in Neurobiology
Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation

P. Shaw†,‡, K. Eckstrand†, W. Sharp†, J. Blumenthal†, L. Clasen†, A. Evans§, J. Giedd†, and J. L. Rapoport†

Fig. 1.

The age of attaining peak cortical thickness in children with ADHD compared with typically developing children. (A) Dorsal view of the cortical regions where peak thickness was attained at each age (shown, ages 7–12) in ADHD (Upper) and typically developing controls (Lower). The darker colors indicate regions where a quadratic model was not appropriate (and thus a peak age could not be calculated), or the peak age was estimated to lie outside the age range covered. Both groups showed a similar sequence of the regions that attained peak thickness, but the ADHD group showed considerable delay in reaching this developmental marker. (B) Right lateral view of the cortical regions where peak thickness was attained at each age (shown, ages 7–13) in ADHD (Upper) and typically developing controls (Lower). Again, the delay in ADHD group in attaining peak cortical thickness is apparent.
Cerebellum, NOT Prefrontal Cortex, differs in siblings with & without ADHD


<table>
<thead>
<tr>
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<th>Comparison</th>
<th>Unaffected Siblings</th>
<th>Affected Siblings</th>
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<tr>
<td><strong>Prefrontal Cortex</strong></td>
<td>155</td>
<td>150</td>
<td>145</td>
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<tr>
<td><strong>Cerebellum</strong></td>
<td></td>
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<td>n=90</td>
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Magnetic Resonance Imaging (MRI) of the Developing Human Brain

- Structural MRI to track changes in size and shape of neuroanatomical structures with development
- Functional MRI (fMRI) to track changes in brain and behavior with development
- Diffusion Tensor Imaging (DTI) to track strengthening of connectivity of fiber tracts with development

Casey et al 2005 Current Opinions in Neurobiology
NIMH Imaging Study of MTA ADHD Parent-Child Dyads

Recruitment Sites: Berkeley, Columbia and Duke

Imaging Sites: Cornell, Duke, and Stanford

Sample: 30 parent-child dyads (n = 60)
20 with ADHD (n = 40)
10 without ADHD (n = 20)

Methods: Go/Nogo Task (impulse control)
MRI, fMRI, DTI
NIMH Multi-site Study of ADHD Parent-Child Dyads

Greater frontostriatal activity in controls relative to ADHD

Epstein, Casey et al. 2007
JCPP
Most Robust Area discriminating Children with and without ADHD

Vaidya et al 1999, PNAS, Epstein et al 2007 JCPP

Striatum

Important in picking up on regularities within the environment (i.e., learns what to expect).
NIMH Randomized, Double-Blind Crossover Ritalin-Placebo Challenge in ADHD Parent-Child Dyads

Epstein, Casey et al. 2007 JCPP
Note: Similar finding reported by Vaidya et al 1998 *PNAS*. 
Effects of Stimulants

- Inhibit reuptake of dopamine (and norepinephrine) by blocking DAT
- Enhance the activity of neurotransmitter systems
- Reduce symptoms of ADHD
Clinically Relevant Doses of Methylphenidate Significantly Occupy Norepinephrine Transporters in Humans In Vivo

Jonas Hannestad, Jean-Dominique Gallezot, Beata Planeta-Wilson, Shu-Fei Lin, Wendol A. Williams, Christopher H. van Dyck, Robert T. Malison, Richard E. Carson, and Yu-Shin Ding
Methylenidate blocks DAT in striatum

Volkow et al. J Neuroscience 2001
DAT1 gene, a variable nucleotide tandem repeat (VNTR) in the 3’ untranslated region has been implicated (e.g. Cook et al., 1995). The 9- and 10-repeat (9R and 10R) alleles are the most common alleles of this polymorphism and the 10R has been associated with ADHD.
Fig. 2.6. Number (per 5000 μm²) of dopamine axon varicosities in deep layer 3 of monkey PFC area 9. Data are presented as values (mean of triplicate measures) for individual animals (a) and as mean (±SD) values for the same animals clustered into six groups defined by chronological age (b). In (b), groups not sharing the same letter are significantly different at p<0.05. (Adapted from Rosenberg and Lewis 1995.)
FIGURE 1. Percentage of children aged 4–17 years ever diagnosed with ADHD:
United States, 2003

*Attention-deficit/hyperactivity disorder.
†Confidence interval.
Frontostriatal connectivity correlated with frontostriatal activity, especially in the striatum.
Frontostriatal connectivity in correlated with how well the individuals with ADHD performed the go/nogo task.
In ADHD parents - as frontostriatal connectivity increased - performance approached that of parents w/o ADHD.
Traditionally, the focus of biological research on ADHD has been on neurotransmitters within prefrontal circuitry like dopamine and norepinephrine.

The findings highlight the need to also consider genetic and environmental factors that may alter myelin and axonal migration (e.g. neurotrophin factors and white matter injury).
Computerized Training of Working Memory in Children With ADHD—A Randomized, Controlled Trial
Recap on ADHD

- ADHD is characterized by impulsivity/hyperactivity and inattention

- Frontostriatal and frontocerebellum circuitry implicated in ADHD

- Primary treatment of ADHD are stimulants that inhibit reuptake of dopamine and norepinephrine by blocking DAT

- New behavioral interventions are being tested.
Understanding AUTISM?
Autism- Prevalence and Symptoms

• Autism is a serious, lifelong developmental disability
• Prevalence of approximately 1/1000 (4:1 males, females)
• Characterized by significant impairments in:
  - reciprocal social interactions (joint attention);
  - communication skills (language delays); and
  - restricted/repetitive pattern of interests and/or behaviors
DIAGNOSIS OF AUTISM

1) a thorough caregiver interview (Autism Diagnostic Interview-Revised [ADI-R; Lord et al., 1994].
2) an interactive assessment of the affected Child (the Autism Diagnostic Observation Schedule [ADOS; Lord et al., 1989].); and
3) experienced clinical judgment.

ADI-R and ADOS, require training to administer and score and are the “gold standard” for diagnosis.

Children under 2 years are most difficult to diagnose.
Prevalence of Autism

Number of Cases
[U.S. School Years 1992 - 2003]

Graph Source: www.fightingautism.org  Data Source: www.idea.data.org and www.cdc.gov/nchs/
Analogous to broad syndromes such as mental retardation, autism has many etiologies and should be considered not as a single disorder but, rather, as 'the autisms'.

Geshwind & Levitt 2007 CON
Biology of Autism

- The etiology of autism is unknown and treatments vary
- No single lesion or gene can explain complex symptoms
- Refined phenotypes are helping characterize the biology
Possible Etiologies

- An excess of neurons causing local overconnectivity in key brain regions
- Disturbed neuronal migration during early gestation
- Unbalanced excitatory-inhibitory networks
- Abnormal formation of synapses and dendritic spines (atypical neurxin modulation, or synthesis of synaptic proteins) Disrupted synaptic development may contribute to epilepsy in some cases.
Treatment of Autism

Behavioral Interventions (social and communication skills)
- Applied behavioral analysis (ABA are grounded in basic principles of learning theory)

Pharmacological Treatments (outbursts, emotions, stereotypies)
- Risperdal - blocks dopamine and serotonin receptors (self injurious behavior and tantrums)
- Haldol - dopamine blocker (stereotypies)
- Clomipramine & fluoxetine (prozac) - serotonin reuptake inhibitor SSRI (repetitive thoughts, aggression)
Imaging of Autism
Imaging Studies of Autism
Imaging Studies of Autism: Examining Most Basic Aspect of Social Interactions ("reading faces")
Imaging of Autism

Less amygdala and fusiform activity to emotional faces.
Adults with Autism do not show typical neural response to faces

Typical Volunteer

“Face Area”

Autism

Little to no “Face Area”

_Schultz et al., 2000_
Adults with Autism do not show typical neural response to faces.

Schultz et al., 2000

Wang et al., 2004
Defining and Quantifying the Social Phenotype in Autism
(Orange: Autism Spectrum Disorder, Yellow: Typically developing)

Importance of Eye Gaze in Processing Emotion

Whalen et al 2004 Science
Importance of Eye Gaze in Processing Emotion

Adapted from Dalton et al 2005 Nature Neuroscienc
Looking at the eyes of a face results in activity in face-sensitive areas in the brain of individuals with Autism.

Focus on the MOUTH

Focus on the EYES

Tottenham et al., Weill Cornell
Recap on Autism

-Autism is characterized by:
  a) reciprocal social interactions (joint attention);
  b) communication skills; and
  c) restricted/repetitive pattern of interests/behaviors

- Prevalence is 1/1000 w/ 4:1 male to female ratio

-The etiology of autism is unknown and treatments vary

-No single lesion or gene can explain complex symptoms

-Refined phenotypes are helping characterize the biology