Neuroscience and Neuropsychology of ADHD: Implications for Clinical Practice

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What is ADHD?

- ADHD is one of the most common behavioral disorders in children
A biological disorder?

- A biological disorder
  - Neurotransmitters in the brain cells help control behavior and attention
  - In ADHD there is an imbalance in the level of neurotransmitters
What causes ADHD?

- Neurobiological factors
- Genetic factors
- Environmental factors

Not caused by:
- Sugar
- Television
- Parenting style

Zametkin et al. 1990

Vaidya et al. 1998
Causes

- No definitive cause has been determined

Possible causes include:
- Hereditary factors
  - ADHD runs in families
- A chemical imbalance in the brain
  - Children with ADHD respond well to stimulants
  - ADHD:PI seems to respond to lower doses
ADHD: Etiology

ADHD is a heterogeneous behavioral disorder with multiple possible etiologies:

- Neuroanatomic
- Neurochemical
- Genetic origins
- CNS insults
- Environmental factors
Biological factors

- The neurobiology of ADHD
  - Abnormal gray and white matter development

- Why abnormal development?
  1. Delayed cortical maturation?
  2. Environmental toxins/exposure?
  3. Genes?

- Treatment with psychostimulant medication
  - Most common treatment
  - Prevents re-uptake of dopamine
  - “Normalizes” abnormal brain activation and behavior
  - Affects development of height and weight? (MTA Longitudinal Study; Swanson et al. 2006 & 2007)
  - Maybe brain development is altered as well?
Girls and ADHD: Research Findings

- Girls not significantly different than boys
  - Selected neuropsychological measures
  - Psychiatric family history
  - Stimulant drug response
  - Working memory, planning, and set-shifting
  - More commonly diagnosed with ADHD-PI than ADHD-C
- Seem to improve in symptomatology with age—boys don’t
- Often have more problems with adjustment and LD
Posner’s Model of Attention

- Three attentional networks:
  - Orienting/shifting: parietal lobes, thalamus, and midbrain (disengage and orient/engage attention to new stimuli)
  - Executive network: anterior cingulate and basal ganglia (detect an object and bring to conscious awareness)
  - Alerting/arousal (vigilance) network: right frontal lobe--permits maintenance of alertness
Posner’s Theory

- 3-stage model of attention and orienting
  - Disengagement of attention from its current focus
  - Movement or shifting of attention to a new location or object
  - Engagement of attention on the new location or object
FIGURE 6-4. Schematic illustrations of imaging techniques. A. The CT scan makes use of a rapidly rotating X-ray source that takes hundreds of pictures, which are fed into a computer and compiled into one image. B. PET measures gamma rays resulting from the collision of a positron and an electron. Only those rays that strike detectors opposite their source are recorded, allowing the computer to determine the line along which the positron was emitted. C. Patients must lie down for both imaging procedures, with their heads placed within the machine.
The Rise of fMRI

746 papers (2001)

Year of Publication

Number of papers (PubMed)

Slide modified from Mel Goodale
Neuroimaging of ADHD, combined type

- ADHD as a disorder of inhibitory control (Barkley, 1997)
- Brain mechanisms in inhibitory control
  - Right inferior frontal lobe
  - Anterior cingulate
- Chronic stimulant treatment vs. treatment naïve
- Gender issues
Brain mechanisms in inhibitory control

- Right inferior frontal lobe
  - Decreases in right inferior frontal lobe volume in ADHD vs. controls (Castellanos et al., 1996; Semrud-Clikeman et al., 1991; Semrud-Clikeman, 1999)
  - Healthy adults activate BA9 and BA10 in Go No Go tasks, strongly lateralized to right side (Garavan et al. 1999)
  - ERP Right frontal N200 on inhibition tasks much attenuated in ADHD children vs. controls (Pliszka et al. 2000)
Brain mechanisms in inhibitory control

- Anterior cingulate (ACC)
  - Decreased activation of ACC on Stroop in ADHD adults relative to controls (Bush et al. 1999)
  - Part of Posner’s executive attention system, recruits working memory
  - Involved in error checking/monitoring of performance
Involvement of the pre-frontal cortex is hypothesized, since problems in executive functions are thought to be at the core.

fMRI studies show low activation of the right pre-frontal cortex and basal ganglia (connected to frontal cortex – movement)
Structural Imaging Findings
Several studies have reported differences in the corpus callosum in ADHD, although some inconsistencies in regions of reported differences.

Studies suggesting a structure/function link:

- ADHD: Smaller CC rated to higher ratings of hyperactive/impulsive behavior (Giedd et al., 1994)
- Links to processing speed (Jaenck & Steinmetz, 1994), sustained attention (Rueckert et al., 1994), and problem solving (Brown & Paul, 2000)
MRI Differences in ADHD

- Caudate nucleus has been found to consistently differ in ADHD (Semrud-Clikeman et al., 2000)

- Corpus Callosum differs but may be sensitive to medication response differences (Schoebelen, Semrud-Clikeman, & Pliszka, in press; Semrud-Clikeman et al., 1994)

- Consistent findings of reduced volume particularly in the right frontal region
Medication and structure

- We were also interested in the effect of medication and structure.
- Children were treated with stimulants ± 2.3 years.
- Treatment naïve ADHD equated to ADHD/Rx in severity.
<table>
<thead>
<tr>
<th></th>
<th>ADHD/Rx</th>
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<th>Controls</th>
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<tr>
<td>Parent R/I</td>
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</table>
Caudate Volumes
Anterior Cingulate Volume

Right AC  |  Left AC

ADHD/TN  |  ADHD/Rx  |  Controls
CC Findings

No difference between groups in overall volume or area of the CC

- ADHD-TN group had smallest splenium area (ADHD-TN<control, no difference between ADHD-CT and control)

- Smaller splenium associated with higher ratings of impulsivity/hyperactivity (Schnoebelen, Semrud-Clikeman, et al., 2005)
Subdivisions of CC
Do subtypes differ in volume?

- We studied 25 children in each group
  - 25 ADHD:C
  - 25 ADHD:PI
  - 25 Controls
ADHD:C, ADHD:PI, Controls

- No difference found in total volume
- No difference found in WM or GM total volume
- No difference in laterality in total volume, WM, or GM
Similar to previous studies found significant differences in caudate volume bilaterally.

- ADHD:C < Controls bilaterally
- ADHD:PI not significantly different from controls
- ADHD:C < ADHD:PI bilaterally
Caudate Volume

Graph showing Caudate Volume comparison between ADHD:C, ADHD:PI, and Controls. The graph indicates a difference in volume with the right and left sides.
Anterior Cingulate Cortex

- Significant difference was found between the groups using a MANCOVA with total volume covaried to control for age effects ($p < .0001$)
- ADHD:C significantly smaller than controls and ADHD:PI bilaterally
- No difference between ADHD:PI and controls
ACC and BASC Findings

- There was a significant finding for the relation of Right ACC volume and BASC indices of externalizing behavior ($p = .009$).
- This variable accounted for 13% of the variance in right ACC volume.
- Similarly, the left ACC approached significance in relation to externalizing behavior ($p = .09$).
Putamen Findings

- The putamen has also been implicated (McMahon, Semrud-Clikeman, et al., 2001)
- Reversed asymmetry was found (L<R) in sample of ADHD compared to controls
Cerebellum

- Treatment naïve children smaller volume in posterior vermis
- No difference in treated vs. controls

(Bledsoe, Semrud-Clikeman, et al., 2009)
Neuropsychology and Neuroimaging

- We found a significant relationship between measures of inhibition and externalizing behavior with reversed caudate asymmetry regardless of group membership (Semrud-Clikeman et al., 2000 JAACAP)

- Moreover, poorer performance on sustained attention tasks was related to smaller volume of the right frontal white matter
Casey et al. (1992) found a relationship between the right anterior region and selective attention.

Castellanos et al. (1996) found the voc subtest related to total brain volume in children with ADHD.
Neuropsychological Correlates

- Giedd et al. (1994) found the rostral body of the corpus callosum to correlate negatively with scores on the Impulsivity/Hyperactivity scale of the Conner’s
Functional Neuroimaging
**MRI vs. fMRI**

- **MRI**
  - high resolution
  - (1 mm)

- **fMRI**
  - low resolution
  - (~3 mm but can be better)

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- fMRI
  - Blood Oxygenation Level Dependent (BOLD) signal
  - indirect measure of neural activity
  - ↑ neural activity ➔ ↑ blood oxygen ➔ ↑ fMRI signal

- many images
  - (e.g., every 2 sec for 5 mins)
Study

- Interested in
- Age 9 to 15, right handed, IQ > 85
- ADHD Chronically treated stimulant
  - ODD, Anxiety not requiring RX only comorbidity permitted
  - No learning disorders
- ADHD treatment naïve
  - All of above, but no history of treatment
Overall Design

- Informed Consent, DISC, rating scales
- Neuropsychological Battery
- Baseline FMRI and ERP (Stop Signal & Stroop)
- Five week double blind placebo controlled crossover study of methylphenidate. Parent and Teacher ratings obtained
- “Best dose” selected- MTA model
- ERP and MRI repeated twice- placebo and best dose
The Stop Signal Task

- The letter “A” or “B” is presented on screen
- Child must press specific button for letter
- On 25% of trials, a letter “S” is presented after the target letter
- On those trials, the child must *not* respond to the target letter
Stop Signal Task

150 ms

200-600 ms

150 ms

9.1-9.5 sec
(slow rate)
fMRI Findings

- 9 regions associated with the inhibitory process were identified
- These 9 areas included bilateral inferior frontal, anterior cingulate, bilateral insula, bilateral superior and inferior parietal lobules and bilateral occipital regions.
fMRI Findings

Healthy children showed stronger activation than children with ADHD (F[1,35]=31.05, p<.0001) across these regions
Findings

- Control children showed strong activation in the hypothesized regions of the right and left DLPC and anterior cingulate.
ACC findings

- ADHD children with a history of medication treatment did not differ from treatment naïve children ($F[1,22]=2.29$, $p<0.1$ NS).

- Previously treated ADHD children trended towards stronger ACC activation than never medicated individuals ($F[1,22]=3.41$, $p<0.07$, NS).
Findings

Healthy children showed significant activations of the anterior cingulate and right DLPFC during the inhibitory trials of the Stop signal task compared to Go trials.
ACC findings

These relatively lower activations in the ACC and DLPC were less in all children with ADHD:C compared to controls without regard to medication status.
Findings

- ADHD: treated showed right DLPC and anterior cingulate activation but not left DLPC
- ADHD Meds naïve showed activation of the right DLPC only
Findings

Controls showed more activation for unsuccessful inhibition than successful (F (1,13) = 21.99; p = 0.0003). This finding is similar to that of adults without ADHD.
Further findings

- Tamm et al. (2004) also found hypofunction in the ACC on a go/no go task with ADHD:C and controls.
Further findings

- Additional studies also found differences in the ACC (Bush et al., 1999) using the counting Stroop
Findings with medication

- Methylphenidate increased CFP and ACC activity in 21 adults with ADHD (Bush et al., 2008).

- Group on Ritalin for 6 weeks showed increased activation compared to those with placebo.
DIFFUSION TENSOR IMAGING
DTI

- Allows for examination of brain regional macrostructure and volume
- Also allows for examination of structural integrity of the region of interest
- Provides a measure of the direction and extent of diffusion of water within the brain
DTI

- Reflects the cellular or neural organization of the underlying tissue by the way it constrains water diffusion.
- Water diffusion is constrained along the direction of the axonal fibers (anisotropic diffusion).
- Fractional anisotropy (FA) is an index of the directionality of diffusion in each voxel.
DTI

- With development have more white matter (myelination) and FA increases with age.
- Given differences in caudate volume, FA was thought to differ in children with ADHD.
DTI findings with BG

- Study using 15 children with ADHD:C and controls
- Looked at caudate, putamen, and thalamus using DTI
- Increases in connectivity found with age for putamen and thalamus for both groups
Caudate

- Caudate did not show same changes
- Changes in the ADHD group are more similar to early adolescents in the control group
- Not similar to older adolescents
- Developmental changes are different for the groups indicating a developmental lag—may normalize at later age
CORTICAL THICKNESS
Findings from our recent study
(Bledsoe, Semrud-Clikeman et al., submitted for publication)

1. Is region-specific cortical thinning related to ADHD?
2. Does long-term medication treatment affect cortical thickness?
3. Is there a relationship between ADHD symptoms, response inhibition, and cortical thickness?
   1. Brain-behavior
   2. Is the density of neurons in region related to behavioral outcomes
Methods

Participants

- ADHD
  - n = 32 (21m/11f)
  - Age 11.71 (+/- 1.80)
  - 18 Treated (treated 2.4 +/- .4 years), 14 Not-Treated
  - No comorbid psychiatric/psychological disorders

- Control
  - n = 15 (11m/4f)
  - Age 11.11 (+/- 2.01)
## Brain and behavior (R.Rostral ACC)

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<th>ΔR²</th>
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<th>B (unstd)</th>
<th>F</th>
<th>p-Value</th>
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<td>.000</td>
<td>.009</td>
<td>.000</td>
<td>.003</td>
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</table>
Discussion

ADHD-C and the ACC
- Reduced right rostral ACC thickness in ADHD-C
  - No reductions in PFC or parietal cortex
  - Most robust anatomical finding in ADHD-C
- What is the role of the ACC?
- May explain inattention and problems maintaining goal-directed behavior

Effects of long-term psychostimulant treatment
- No effect of medication (almost)
- Does medication affect brain development? If so, how and why?

Brain and behavior
- Parent report and teacher report predict ~40% variance in right rostral ACC
- No relationship for response inhibition
  - EF not specific or necessary impairment in ADHD
- Neuroimaging endophenotypes
  - Brain structure/function may predict genetic risk
Discussion

- Clinical implications
  - Interventions that target activation of ACC (ATT, ANT) (Posner et al., Fan et al., & McCandliss et al.)
  - May “normalize” brain developmental trajectories
  - May allow for learning and changes in behavior that, over time, change brain structure and function
  - EF subtypes of ADHD?
  - Multi-method assessments
    - Multiple domains
    - Multiple contexts
    - Multiple informants
Discussion

Future directions

- ADHD subtypes
- The many roles of the ACC
- Neuronal density and development
  - Is more or less good, and when?
- Structural and functional
  - Does structure predict function?
ERP RESULTS
Conclusions

- ADHD children under activated AC region during inhibition trials. These differences do not seem to be secondary to medication effects, as differences between previously treated and treatment naïve were insignificant.
Conclusions

- Although healthy children show AC activation patterns similar to those found in healthy adults (relatively greater AC for unsuccessful vs. successful trial). ADHD children do not show this difference and even trend towards the opposite.
- Neither group shows a significant effect for the DLPC
Summary

- Imaging has found differences in the ACC, DLPC, basal ganglia, cerebellum and to a lesser extent parietal lobe.
- Make up the cingulo-frontal-parietal (CFP) cognitive-attention network (Bush, 2011).
CURRENT FINDINGS IN OUR STUDY WITH NEUROIMAGING AND ADHD
Goal of the Study

- Children with ADHD engage in high-risk behaviors
- Problems with inhibition may be related to problems with modulation of response to reward or risk
- ADHD-C show problems with inhibition independent of level of reward
- ADHD-PI respond to high but not to low rewards for inhibition
Reward Delay Problems in ADHD

- May be due to disturbance in motivational processes and a deficit in multiple neural networks.
- Seems to be related to parts of the brain including the orbital and medial prefrontal cortices.
Inhibitory control

- Barkley suggest related to disinhibition in ADHD-C but not ADHD-PI
- This disinhibition is related to generalized problems with executive functioning.
- In contrast inattention and disorganization seen in ADHD-PI are related to problems with working memory
Our Study

- **Stimuli for fMRI**
  - **Balloon Analogue Risk-Taking Task (BART)**
    - Child holds down the button while the balloon inflates
    - If the balloon bursts before the child lets go of the button, he/she loses money
    - If it doesn’t burst, he/she wins money
    - Blue balloons pay less but lose less
    - Red balloons pay more but lose more
<table>
<thead>
<tr>
<th>Brain regions involved</th>
<th>ADHD subtype</th>
<th>Gender</th>
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</thead>
<tbody>
<tr>
<td>Right Frontal volume or area</td>
<td>ADHD-C</td>
<td>Males</td>
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<tr>
<td>Splenial measure of the corpus callosum</td>
<td>ADHD-C</td>
<td>Males</td>
</tr>
<tr>
<td>Caudate</td>
<td>ADHD-C</td>
<td>Males</td>
</tr>
<tr>
<td>Anterior Cingulate (ADHD-C&lt;C)</td>
<td>ADHD-C</td>
<td>Males</td>
</tr>
<tr>
<td>Vermis of the cerebellum (ADHD-C &lt; C)</td>
<td>ADHD-C</td>
<td>Males</td>
</tr>
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Our Study Hypotheses

1a Children with ADHD-C will respond differently to a risk-taking task

1b Response inhibition and working memory findings will be related to difficulties in delaying rewards and higher risk-taking behaviors.

1c Lower scores on the BART will be related to higher levels of risk-taking outside of the laboratory
Study Participants

- 60 total children: 20 children in each group—ADHD-C, ADHD-PI, and controls
- 10 girls and 10 boys in each group
- All right-handed
- No comorbid diagnoses
- All responders to stimulant medication
- No one on medication the day of testing and scanning
Findings

- ADHD-C have increased activation to high-risk compared to low risk situations
- ADHD-PI and Controls have similar activation for high and low risk
- High vs low-risk difference in the ADHD-C group is due to activation for the lose condition
CO-MORBID CONDITIONS
AUTISTIC SPECTRUM DISORDERS
ASD

- Intense circumscribed interests and behaviors
- Compulsions & rituals
- Disinterest in social interaction at early ages
ASD

Symptoms include:

• Failure to develop normal social relations
• Impaired communication skills
• Lack of imagination
• Apparent self-absorption
• Fascination with objects
• Often begins at age 3 after relatively normal development
Autistic Spectrum Disorders

- Boys are more affected 3:1
- Often show tactile defensiveness
- Eye contact is poor
- Frequently mentally retarded but can be average to gifted
- Often have echolalia
- Show stereotyped movements
- Some have isolated skills
Autism

• Causes:
  • Most believe are biological in nature
  • 2 to 3% of siblings of autistic individuals are also autistic
  • Twin studies show concordance rate for monozygotic twins to be 96%—no such rate for dizygotic twins
Can ASD and ADHD co-occur

- DSM indicates that ADHD does not co-occur with ASD
- Our study and others have found about a 25% incidence of ADHD in children with ASD
Brain Activation Differences

- Studies have found that autistic individuals have activation patterns in posterior brain regions with significant differences from unaffected persons in:
  - Broca’s area
  - Sensorimotor areas
  - Temporal regions
Brain Activation Differences

- Research has led to the hypothesis that autism involves dysfunction of the cortical-limbic-reticular system.
- Different from ADHD which is thought to be a disorder in frontal and basal ganglia systems.
Fusiform Face Gyrus

Initial failure to activate fusiform face gyrus (Pierce et al. 2001)

People with ASD ‘See’ faces with different neural system

A reciprocal relationship between social interaction and wiring of these synapses?

What if that interaction were interrupted?
ASD Neural Findings

- The fusiform face area problem is probably part of a larger neurological problem in the brain.
  - Increased whole-brain volume, presumed poor pruning.
  - Smaller, denser packed cells.
  - Abnormalities in frontal lobe, corpus callosum, amygdala, cerebellum and other brain structures.
Structural findings

- Children with ASD have not been found to show significantly different caudate volumes.
- Differences have been found in ASD vs. controls in the bilateral volume of the ACC.
- A subsample of children with ASD with ADHD show smaller caudates.
Study

- Our study also included children with NVLD
- These children frequently also have ADHD
How Does NVLD Present?

- Aspects of NVLD

  - Gross Motor
  - Fine Motor
  - Visual Perception
  - Visual-Motor Integration

  - Emotional Regulation
  - Working Memory (visual)
  - Working Memory (verbal)
  - Flexibility/Fluency

  - Mathematics
  - Reading
  - Humanities
  - Reasoning

  - Academic

  - Social

  - Executive

  - Friendship quality
  - Conversational
  - Reciprocity
  - Personal Space
  - Colloquial Language (idioms)
NVLD

- Frequently see comorbid ADHD—particularly ADHD:PI
- Poor organization
- Poor motor planning
- Difficulty with insight/big picture
- Poor regulation of emotion
- Poor working memory
Caudate and ACC

- While we didn’t have a group of children with ADHD, we did find differences in the caudate and ACC.
- Approximately 75% of the children with NVLD had ADHD and 25% of AS.
Differences in ASD and Controls

- Our study of children with ASD found that differences were present in the amygdala and hippocampus.
- We also had a group of children diagnosed with NLD (to be discussed shortly).
Amygdala and Hippocampus

Bar chart showing comparisons between different groups for Right (R) and Left (L) Amygdala and Hippocampus:

- Controls
- NVLD
- AS

Statistics:

- R Amygdala: p < .0001
- L Amygdala: p = .03
- R Hippo: p = .01
- L Hippo: p = .02
LEARNING DISABILITIES
Types of LD

- Common types are:
  - Reading disability
  - Nonverbal learning disability

- ADHD is comorbid in approximately 25-75% of children

- ADHD:PI appears to more related to learning problems than ADHD:C
Types of LDs

- Language LDs (2) Reading Disorder
  - 3-10% of Western populations (phonetic languages)
    - 17% in US
    - 1%-5% in Asian countries (?)
  - Heterogeneous presentation
    - decoding (auditory/visual)
    - fluency
    - comprehension
Models for RD (English)

- **Phonological awareness deficit** (Goswami, Snowling, Torgeson)
  - poor detection of small sound units of words

“say ‘bring’... now say ‘bring’ without the /b/”
Models for RD (English)

- **Rapid automatic naming** (Catts, Wolf, Semrud)
  - slow translation of symbol-to-sound
Models for RD

- **Double deficit**
  - children who have both phonological and RAN deficits
Model emphasizes multiple pathways at the genetic and neuro-developmental level as well as interaction with environment to produce complex behavioral disorders.
Models of LD and why they’re important

Pennington’s multi-dimensional model helps think in terms of:

- multiple genes
- brain development
- environment
- cognition
- behavioral symptoms
RD Neurological Models

Phonological and word form systems are used in skilled readers:
- Phonological (slower) for sounding out
- Word-form (faster) for whole-word recognition

Non-impaired reader: fMRI activation
Most activity encapsulated in left hemisphere

Adapted from SE Shaywitz (2003)
Readers with RD fail to develop left occipito-temporal word-form region.

Non-impaired and impaired readers fMRI activation in left hemisphere

Adapted from SE Shaywitz (2003)
RD Neurological Models

At the macroscopic level, the size of brain structures found related to reading

Reverse or lack of asymmetry (larger or equal right in dyslexics)
planum temporale (posterior temporoparietal)

Thinner corpus callosum at the midbody (primary auditory; Fine, Semrud-Clikeman, et al. 2007)


Additional Readings


Additional Readings


Additional Readings


DISCUSSION