Attention Deficit Hyperactivity Disorder: Neurodevelopmental Perspectives on Current Research and Treatment Development

Jeffrey M. Halperin, Ph.D.

Department of Psychology
Queens College, City University of New York

Department of Psychiatry
The Mount Sinai School of Medicine

Outline

- Neurodevelopmental Perspectives on ADHD
- Re-thinking the Neural Substrates of ADHD from a Lifespan Perspective
- Queens College Preschool Project (QCPP)
- Relations between neuropsychological and behavioral functioning over time
- Implications for understanding ADHD
- Implications for Treatment and Future Research

ADHD Across the Lifespan

- Adults
- Adolescents
- School-age
- Preschoolers
What Causes ADHD?

- Genetic Determinants
- Environmental Factors
- Brain Dysfunction

Hypothesized Neural Anomalies in ADHD

- Prefrontal (PFC)/Executive Impairments?
- Subcortical state regulation anomalies?
- Dopaminergic insufficiencies?
- Poor alpha 2a receptor functioning?

- Behavioral and neurocognitive heterogeneity suggest that it may not be the same in all with the disorder

- ADHD is a developmental disorder, but most models do not consider development!
ADHD is Likely Related to Catecholaminergic Innervation of the Frontal Lobe and Basal Ganglia

Developmental Considerations

- PFC and the EFs it mediates develop relatively late in ontogeny
  - Synaptic pruning: 5 – 16 years old
  - Myelination: through early adulthood
  - EFs develop into at least early adulthood

- Yet ADHD is always present in early childhood
- ADHD tends to get better with age

Developmental trajectories of behavioral deficits associated with ADHD and early frontal lobe lesions

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>Early PFC Lesion*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of Symptoms</td>
<td>Preschool</td>
<td>Later in Childhood</td>
</tr>
<tr>
<td>Present in Childhood</td>
<td>Always</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Adolescent Trajectory</td>
<td>Improve or remain the same</td>
<td>Worsen</td>
</tr>
</tbody>
</table>

*Anderson et al. 1999; Trauner et al. 2001
Corresponding trajectories for A) the remission of ADHD, B) the development of EFs, and C) the maturation of white matter in the DLPFC. Figures from A) Hill & Schoener, 1996; B) Paus, 2005; and C) Barnea-Goraly et al., 2005. Note: FA = fractional anisotropy; SSRT = Stop-signal reaction time.

A Developmental Model of ADHD

Pathophysiology*

- Distinct neural and cognitive mechanisms are involved in the etiology of and recovery from ADHD
- ADHD is due to non-cortical neural dysfunction that is present early in ontogeny and remains static throughout the lifetime
- PFC circuitry is not linked to the cause of ADHD, but is involved in recovery
- The diminution of symptoms with age is accounted for by the degree to which the development of the PFC/EFs are able to compensate through the implementation of 'top down' regulatory control.


Predictions from Model

- Improvements in behavior over time should be differentially linked to distinct types of neurocognitive functioning
  - Measures of higher cortical “recovery” mechanisms should parallel later status; effortful/goal-directed
  - Measures of subcortical “causal” mechanisms persist irrespective of later clinical status; less conscious control/stimulus-driven
Preliminary Support from Longitudinal Study of Adolescents with Childhood ADHD

- Irrespective of follow-up status, those with childhood ADHD are impaired on less consciously controlled measures (e.g., RTSD, ankle movements). 
- ADHD-persisters are most impaired on measures requiring effortful control (e.g., working memory, CPT errors, conflict resolution).
- Prefrontal activation obtained during effortful processing (i.e., conflict resolution), parallels severity of adult symptomatology.

1 Halperin et al. (2008) JCPP. 2 Schulz et al. (2005a) Neuropsychology. 3 Bedard et al. In review. 4 Schulz et al. (2005b) JAACAP.

Longitudinal Study of Urban Youth with ADHD: Baseline Assessment

- Initially recruited 1990 – 1997
- Clinically-referred sample
- Age at initial assessment 7 – 11 years
- Teacher ratings: IOWA Conners
- Parent ratings: CBCL
- Parent Interview: DISC

Comorbidity in Childhood

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N = 98</th>
</tr>
</thead>
<tbody>
<tr>
<td>% ODD</td>
<td>49.0</td>
</tr>
<tr>
<td>% CD</td>
<td>32.7</td>
</tr>
<tr>
<td>% Anxiety</td>
<td>31.6</td>
</tr>
<tr>
<td>% Mood</td>
<td>10.2</td>
</tr>
</tbody>
</table>
Adolescent Characteristics of Probands and Matched Control Group

<table>
<thead>
<tr>
<th></th>
<th>Childhood ADHD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>98</td>
<td>85</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>18.4</td>
<td>18.5</td>
</tr>
<tr>
<td>Mean WAIS-III FSIQ</td>
<td>93.3</td>
<td>96.8</td>
</tr>
<tr>
<td>% Male</td>
<td>88.8</td>
<td>87.1</td>
</tr>
</tbody>
</table>

Axis I Diagnoses in patients with childhood ADHD and never-ADHD controls

<table>
<thead>
<tr>
<th></th>
<th>ADHD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD (%)</td>
<td>49.5</td>
<td>0</td>
</tr>
<tr>
<td>Depression (%)</td>
<td>21.6</td>
<td>4.7</td>
</tr>
<tr>
<td>Anxiety (%)</td>
<td>18.6</td>
<td>8.2</td>
</tr>
<tr>
<td>ODD (%)</td>
<td>22.7</td>
<td>1.2</td>
</tr>
<tr>
<td>CD (%)</td>
<td>26.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Alcohol Abuse/Dep. (%)</td>
<td>15.5</td>
<td>7.1</td>
</tr>
<tr>
<td>Drug Abuse/Dep. (%)</td>
<td>44.3</td>
<td>27.1</td>
</tr>
</tbody>
</table>

Adolescents Diagnosed with ADHD During Childhood

*All groups differ, p < .05
Working Memory and ADHD Outcome

*Halperin et al. 2008*

Perceptual Inhibition

Bedard et al. In Review.

Continuous Performance Test (CPT-IP)

Errors, which reflect effortful processing, as a Function of Adolescent/Adult Status

*Controls differ from Persisters, p < .05

Halperin et al. 2008
**Less Conscious Reaction Time Measures as a Function of ADHD Persistence**

Controls | Remitters | Persisters

| Hit RT (in msec.)* | 600 | 650 | 550 | 500 |
| RT SD (in msec.)** | 200 | 250 | 150 | 100 |

*Persisters < Controls, p = .045  **Persisters = Remitters > Controls, p < .001

---

**Activity Level in Adolescents as a Function of Persistence of ADHD**

Persisters | Remitters | Controls

| Ankle* | Waist |
| 70 | 80 | 90 | 100 |

*Persisters = Remitters > Controls

Halperin et al. 2008

---

**Activation During Go/No-go Task**

Schulz et al. 2005; JAACAP
Stimulus and Response Conflict Task

 Activation During Conflict Task

The Preschooler
Queens College Preschool Project (QCPP)
Overview of Methodology
- Gather parent and teacher ADHD ratings on a large sample of 3 and 4 year-old children
- Identify “at risk” and “control” children
- Comprehensive in-lab assessment of identified children/parents
- Semi-annual parent and teacher behavior ratings
- In-lab re-evaluation annually

QCPP: Classification Criteria
- At Risk (AR) Group:
  - At least 6 Hyperactivity/Impulsivity or Inattention symptoms rated 2 or greater (0 – 3 scale) by parent, teacher, or a combination of the two
- Typically-developing (TD) Group:
  - Fewer than 3 Hyperactivity/Impulsivity and Inattention symptoms rated 2 or greater by both parent and teacher

QCPP: Sample Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TD (N=76)</th>
<th>At-Risk (N=140)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in years)</td>
<td>4.20 (.48)</td>
<td>4.36 (.46)</td>
<td>2.46</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>% Boys</td>
<td>67.1</td>
<td>75.7</td>
<td>1.84*</td>
<td>&gt; .10</td>
</tr>
<tr>
<td>WPPSI FSIQ</td>
<td>112.63 (12.0)</td>
<td>101.96 (12.8)</td>
<td>5.96</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ADHD-RS-P</td>
<td>8.74 (4.9)</td>
<td>27.6 9 (10.9)</td>
<td>17.57</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ADHD-RS-T</td>
<td>4.63 (4.3)</td>
<td>30.32 (13.5)</td>
<td>20.64</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Chi Square
ADHD and ODD Diagnoses in At-Risk Group (N = 140)

Primary Measures (for this presentation)
- Parent and Teacher Ratings
  - ADHD-RS (DuPaul et al. 1998)
  - Children’s Problem Checklist (CPC; Healey et al. 2008)
- NEPSY
  - Attention/Executive Function
  - Language
  - Sensorimotor
  - Visuospatial
  - Memory

QCPP: Solid State Actigraph Recordings

*Main Effect Group, p < .001
QCPP: NEPSY Domain Scores (Baseline)*

Typically-developing At-risk

* All p ≤ .001

NEPSY Subtest Scores in Hyperactive preschoolers

Typically-developing At-risk

*p > .05

QCPP Timeline

ADHD-RS CPC NEPSY

Time in Months
Are Changes in ADHD Severity Over Time Related to Improved Neuropsychological Functioning in At-Risk Children?

ADHD severity assessed via a single latent variable

Individual Trajectories for ADHD Severity in At-Risk Children
Change in Neuropsychological Functioning
Assessed via a Single Latent Variable
(Baseline to 24 Month)

Distribution of NEPSY Change Scores

Change in NEPSY Associated with improved ADHD trajectory
Percentage of Cases Meeting Criteria for ADHD at 24-month Follow-up as a Function of Change in NEPSY Score

Chi Square = 11.18, p = .025

Do Changes in ADHD Severity Over Time Precede or Follow Changes in Neuropsychological Functioning?

At-risk children

Attention Deficit & Impairment Baseline

Neuropsychological Functioning Baseline

Psychological Functioning at Time 2

Psychological Functioning at Time 3

At-risk children
Summary of Preschool Data

- Behavioral impairment related to ADHD symptoms is clearly apparent during the preschool years.
- Behavioral difficulties are accompanied by a wide array of cognitive deficits.
- Improved behavioral functioning is related to and may be preceded by improved neuropsychological functioning.

Implications for Conceptualizing ADHD

- ADHD is a lifespan disorder that must be conceptualized within the context of a developmental framework.
- Within the framework of our model, ADHD might have a unitary cause; behavioral and cognitive heterogeneity should increase with age.
- Although we might not be able to “cure” ADHD, the trajectory should be susceptible to positive and negative influences.
Implications for Treatment

- If ADHD is due to subcortical disorder that is relatively permanent, can we develop lasting treatments?
- Must take advantage of early cortical neurodevelopment, that may be linked to clinical/behavioral improvement across the lifespan.
- Perhaps, environmental manipulations targeted at facilitating experience-dependent neurodevelopmental processes such as synaptic pruning, dendritic arborization and myelination could be employed to facilitate recovery.

TEAMS

Training Executive, Attention and Motor Skills

TEAMS is based on these ideas:

1) ADHD is associated with deficient neural networks that:
   • affect a wide array of neurocognitive and behavioral processes
   • may not be identical in all children with the disorder;
2) Neurodevelopment is sensitive to and can be positively affected by appropriate environmental influences;
3) Effective environmental stimulation will be best achieved within a social context;
4) Core activities of the treatment must be intrinsically rewarding (i.e., fun) rather than extrinsically reinforced (e.g., parental praise or tokens). This will:
   • facilitate self-imposed continuation of the intervention
   • lead to generalization over time and across settings.
How Do We Think TEAMS Will Work?

- ‘Exercise the brain’ using game-like activities which employ neurocognitive and motor skills.
- Small group setting (4-5 children)
- Parent education about ADHD and support
- Encourage parents to engage their children in these game-like and exercise activities at home.

Directions for Future Research

- Need to develop and apply better measures of stimulus-driven or “bottom-up” processes
- Need to add neuroimaging to the mix in developmental studies
  - Does cognitive/behavioral improvement relate to measurable changes in brain structure and function?
- Do genes moderate ADHD trajectory?
- Development of interventions to alter the trajectory over the lifespan

Acknowledgements

Preschool Studies
- David Marks, Ph.D.
- Dione Hader, Ph.D.
- Olga Secord, Ph.D.
- Elizabeth Kern, Ph.D.
- Amrita Saha, Ph.D.
- Chrys Gopin
- Agnieszka Misiurcka
- Beth Babenrouz
- Kamila Skaheza
- Michelle Babnik
- Karin Crozifi
- Bipasha Basu

Adolescent Studies
- Jeffrey Nuechter, M.D.
- Carin Miller, Ph.D.
- Joey Turella
- Virginia Fontallo
- Seth Harry
- Tobey Bunch
- Dana Harnack

Neuroimaging
- Kurt Schulz, Ph.D.
- Jin Fan, Ph.D.
- Chuck Yong, Ph.D.
- Suzanne Clifton, Ph.D.

NIMH
- ROI MH66098
- ROI MH66286
- 1R21MH085898

Dana Barowsky
Thank you.