ADHD: Shifting the paradigm to improve function and modify the natural history

Daryl Efron
Mental restlessness:

- Deficits in attention
- Occurring across situations (e.g. home & school)
- Begins early in life
- Causes impairment in learning

1798 Sir Alexander Crichton
What we know

• Kids with ADHD are at increased risk for a broad range of negative outcomes in adolescence and adult life
  • MH, educational / occupational, social, substance abuse

• Meds can really help with symptoms and daily functioning
  • Core symptoms: stimulants, (ATX, clonidine, TCAs)
  • Comorbidities: eg. anxiety – SSRIs; sleep - melatonin

• Behavioural interventions can help too
  • Aggression, internalising symptoms, parent-child relationships, reading (MTA)
People with ADHD can succeed

Vincent Van Gogh
Albert Einstein
Jim Carrey
Michael Phelps
Stevie Wonder
What we don’t know

• What are the *key impairments* at different developmental stages?
• How do *girls* do?
• What’s the additional burden of *ASD symptoms*?
• How many, which kids / families access *services*?
• Which kids get *meds*?

• Who will *remit* and who will persist?

• Which kids will do well and which will do poorly in the long run?
  • What are the *modifiable* predictors of better or worse outcomes?

• What (if anything) can make a difference to *long-term outcomes*?
  • What can parents do? Schools? Psychologists? Doctors? Others?
  • Optimal timing? Intensity?
The Children’s Attention Project (CAP)

A longitudinal study of children with and without ADHD
What is CAP?

- First Australian longitudinal cohort study of children with and without ADHD
- Overcomes limitations of previous cohort studies
  - Community-based sample (rather than clinical)
  - Includes all subtypes, comorbidities, girls and boys
  - Tight age range – developmentally sensitive
Aims

1. Document the natural history and impact of ADHD
   • Children: mental health, quality of life, social & academic functioning
   • Parents: mental health and family functioning.

2. Identify risk & protective factors associated with poor versus better outcomes
Recruitment flowchart

43 schools
Grade 1

Parent screening survey distributed
n = 6098

Parent and teacher screening surveys completed
n = 3738

- Matched
- Both parents and teachers negative

Negative screen for ADHD
n = 412

Consent to longitudinal study
n = 227

CONTROL group
Did not meet ADHD criteria
n = 212

Disc-IV with parents

Positive screen for ADHD
n = 412

Both parents and teachers positive

Consent to longitudinal study
n = 266

ADHD group
Met ADHD criteria on DISC-IV
n = 179

Subthreshold
Did not meet ADHD criteria
n = 86
Recruitment flowchart

Grade 1

- Parent screening survey distributed
  n = 6098

- Parent and teacher screening surveys completed
  n = 3738

- Matched
- Both parents and teachers negative

- Positive screen for ADHD
  n = 412

- Both parents and teachers positive

- Negative screen for ADHD
  n = 412

- Consent to longitudinal study
  n = 227

- Matched

- DISC-IV with parents

- ADHD group
  Met ADHD criteria on DISC-IV
  n = 179

- Subthreshold
  Did not meet ADHD criteria
  n = 86

- CONTROL group
  Did not meet ADHD criteria
  n = 212
# Measures on CAP

<table>
<thead>
<tr>
<th>Grade (year)</th>
<th>Wave 1</th>
<th>Wave 2</th>
<th>Wave 3</th>
<th>Wave 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (2011-12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 3-4 (2013-14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 5-6 (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 6-7 (2016-17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Child assessment     | ✓                  |                   | ✓                  | ✓ (NICAP)         |
| Parent interview (DISC-IV) | ✓                |                   | ✓                  |                   |

<table>
<thead>
<tr>
<th>Surveys</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Teacher</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Child assessment measures

- Visual perception and motor coordination
- Verbal and non-verbal cognitive functioning
- Working memory
- Language
- Attention and response inhibition

Physical assessment – height and weight
Parent surveys

- Child Behaviour
- Quality of Life
- Social skills and Autism symptoms
- Treatment history
- Socio-demographic factors
Parent surveys

- Family Quality of Life
- Parent Mental Health
- Family stress
- Parenting styles
- Couple relationship quality
Teacher surveys

- Child Behaviour
- School service use
- Student-Teacher Relationship
- Social skills & Autism Symptoms
## Response rates

<table>
<thead>
<tr>
<th>Grade (year)</th>
<th>Wave 1 (n=498)</th>
<th>Wave 2 (n=493)</th>
<th>Wave 3 (n=481)</th>
<th>Wave 4 (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (2011-12)</td>
<td>99%</td>
<td>77%</td>
<td>68%</td>
<td>68%</td>
</tr>
<tr>
<td>Grades 3-4 (2013-14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 5-6 (2015)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 6-7 (2016-2017) Current*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child assessment</td>
<td>99%</td>
<td></td>
<td>75%</td>
<td>68%</td>
</tr>
<tr>
<td>Parent interview</td>
<td>99%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surveys</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent</td>
<td>94%</td>
<td>80%</td>
<td>74%</td>
<td>68%</td>
</tr>
<tr>
<td>Teacher</td>
<td>99%</td>
<td>91%</td>
<td>69%</td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td></td>
<td></td>
<td>74%</td>
<td>61%</td>
</tr>
</tbody>
</table>
FINDINGS
Baseline data
Sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>ADHD (n=179) *</th>
<th>Controls (n=212)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>7.3 (0.4)</td>
<td>7.3 (0.4)</td>
<td>.41</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>124 (69)</td>
<td>135 (64)</td>
<td>.24</td>
</tr>
<tr>
<td>Estimated FSIQ, mean (SD)</td>
<td>92 (12)</td>
<td>101 (14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Primary caregiver did not complete high school, n (%)</td>
<td>63 (38)</td>
<td>39 (19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous ADHD diagnosis , n (%)</td>
<td>31 (17)</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ASD diagnosis, n (%)</td>
<td>33 (18)</td>
<td>3 (1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ADHD medication, n (%)</td>
<td>23 (13)</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Combined 93 (52%), Inattentive 64 (36%), Hyperactive-Impulsive 22 (12%)
Sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>ADHD (n=179)</th>
<th>Controls (n=212)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>7.3 (0.4)</td>
<td>7.3 (0.4)</td>
<td>.41</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>124 (69)</td>
<td>135 (64)</td>
<td>.24</td>
</tr>
<tr>
<td>Estimated FSIQ, mean (SD)</td>
<td>92 (12)</td>
<td>101 (14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Primary caregiver did not complete high school, n (%)</td>
<td>63 (38)</td>
<td>39 (19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Previous ADHD diagnosis , n (%)</td>
<td>31 (17) *</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ASD diagnosis, n (%)</td>
<td>33 (18)</td>
<td>3 (1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ADHD medication, n (%)</td>
<td>23 (13)</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Combined type (24%), Inattentive (9%) and Hyperactive-Impulsive (14%)*
Co-existing difficulties are common (age 7)

<table>
<thead>
<tr>
<th></th>
<th>ADHD (n=179)</th>
<th>Controls (n=212)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Externalising disorder</td>
<td>54%</td>
<td>8%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Internalising disorder</td>
<td>26%</td>
<td>5%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Elevated Autism symptoms</td>
<td>21%</td>
<td>3%</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sleep problems</td>
<td>28%</td>
<td>6%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Trauma exposure</td>
<td>27%</td>
<td>16%</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

- Efron et al., 2014, *Pediatrics*
- Sciberras et al., 2014, *Pediatrics*
- Green et al., 2016, *Eur Child Adolesc Psychiatry*
- Schilpzand et al., *Under review*
Academic functioning (WRAT-IV)

Efron et al., 2014, *Pediatrics*
## Language Problems (*CELF-4, screener*)

<table>
<thead>
<tr>
<th>Language problem, n (%)</th>
<th>ADHD n=178</th>
<th>Control n=212</th>
<th>Unadjusted</th>
<th>p</th>
<th>Adjusted</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>72 (40)</td>
<td>37 (17)</td>
<td>3.2 (2.0, 5.1)</td>
<td>&lt;.001</td>
<td>2.8 (1.5, 5.1)</td>
<td>.001</td>
</tr>
</tbody>
</table>

Sciberras et al., 2014, *Pediatrics*
Relationship between Language Problems & Academic Functioning

Adjusted findings

$d = 0.7$
$d = 0.8$
$d = 0.7$

Sciberras et al., 2014, *Pediatrics*
Social functioning (*SDQ: Peer problems*)

![Bar chart showing social functioning for ADHD and control groups]

- **Parent**: 60% in clinical range for ADHD, 10% for Control (P<.001)
- **Teacher**: 50% in clinical range for ADHD, 10% for Control (P<.001)

* P<.001

Efron et al., 2014, *Pediatrics*
Girls with ADHD (compared to boys with ADHD)

- Similar profile of difficulties:
  - **Internalising disorders** (adjusted OR, 1.1; 95% CI, 0.5 to 2.4)
  - **Externalising disorders** (adjusted OR, 0.8; 95% CI, 0.3 to 1.7)
  - **Word reading** (adjusted mean difference [AMD] 1.2; 95% CI, 24.6 to 7.0)
  - **Math computation** (AMD, 4.0; 95% CI, 20.8 to 8.8)
  - **Language problems** (42% vs 40%)

- Less **parent-reported peer problems** (AMD, 0.7; 95% CI, 0.03 to 1.4; P = .04)
  - No difference by teacher report (AMD, 0.1; 95% CI, 20.16 to 0.8; P = .82).

- Less likely to be **diagnosed**:

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Boys</th>
<th>Girls</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (age 7)</td>
<td>31/179</td>
<td>28/124</td>
<td>3/55</td>
<td>5.2</td>
<td>1.6-17.5</td>
<td>.007</td>
</tr>
<tr>
<td></td>
<td>(17%)</td>
<td>(22%)</td>
<td>(5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 years (age 10)</td>
<td>49/130</td>
<td>41/91</td>
<td>8/39</td>
<td>3.3</td>
<td>1.3-8.4</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>(38%)</td>
<td>(45%)</td>
<td>(21%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Autism Spectrum Disorders

• Children with ADHD had more ASD symptoms than controls (AMD = 4.0, 95% CI 2.8; 5.3, p < 0.001)

• Greater ADHD symptom severity assoc with greater ASD symptom severity (regression co-efficient = 1.6, 95% CI 1.2; 2.0, p < 0.001).

• Boys with ADHD had greater ASD symptom severity than girls with ADHD (AMD = 2.9, 95% CI 0.8; 5.2, p = 0.01)

• No differences by ADHD subtype.

• ASD symptoms associated with increased internalising (OR 1.8), externalising (OR 1.5), & sleep problems (OR 1.5), and decreased QoL

Green et al Arch Dis Child 2016
Service use

• Have you sought professional help for concerns about your child’s learning, behaviour or emotions in last 12 months?
  • GP
  • Paediatrician
  • Psychologist
  • Psychiatrist
  • Speech path,
  • OT
  • educational specialist

• child & family predictors
  • univariate and multivariate logistic regression

Efron et al Arch Dis Child 2016
Service use

• 37% had not received professional services in past 12 months

• Services used
  • Paediatrician 35%
  • Psychologist 26%
  • GP 22%
  • Speech path 21%
  • OT 11%

• Predictors
  • Age
  • Impact of behaviour on family
  • (academic failure – fell out in adjusted analyses)

Efron et al Arch Dis Child 2016
3 year data
## Comorbidities, academic function

<table>
<thead>
<tr>
<th></th>
<th>Age 7</th>
<th></th>
<th>p</th>
<th>Age 10</th>
<th></th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADHD</td>
<td>Control</td>
<td></td>
<td>ADHD</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Externalising disorder</td>
<td>54%</td>
<td>8%</td>
<td>&lt; .001</td>
<td>51%</td>
<td>9%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Internalising disorder</td>
<td>26%</td>
<td>5%</td>
<td>&lt; .001</td>
<td>26%</td>
<td>7%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>&lt;25&lt;sup&gt;th&lt;/sup&gt; percentile reading or maths</td>
<td>53%</td>
<td>17%</td>
<td>&lt; .001</td>
<td>69%</td>
<td>28%</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Outcomes did not differ by medication status or gender
ADHD persistence

- 67% of children with ADHD met full ADHD criteria 3 years later.
  - Boys more likely to persist than girls (74% vs 50%; OR: 3.4; 95% CI 1.3, 8.4, p=0.01)
  - Persistent ADHD more likely to have (cf remitted):
    - Externalising disorder (57% vs 33%; p=0.008)
    - Mood disorder (8% vs 0%; p=0.04)
    - Better word reading (MD 5.5; 95% CI 0.2, 10.8; p=0.04)
Development of externalising disorders in ADHD (n=131)
Development of internalising disorders in ADHD (n=131)

<table>
<thead>
<tr>
<th>Age</th>
<th>Internalising disorder</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 7</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 (58%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 (14%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 10</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14 (42%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>84 (86%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Predictors of medication use

<table>
<thead>
<tr>
<th></th>
<th>Clinical diagnosis</th>
<th>ADHD med prescribed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (age 7)</td>
<td>31/179 (17%)</td>
<td>21/179 (13%)</td>
</tr>
<tr>
<td>3 years (age 10)</td>
<td>49/144 (38%)</td>
<td>35/144 (26%)</td>
</tr>
</tbody>
</table>

Predictors (adjusted analyses):

- **ADHD symptom severity (Conners ADHD Index, parent report)**
  - Baseline (OR 1.25, 95%CI 1.06-1.47, \( p = .01 \))
  - 3 yrs (OR 1.17, 95%CI 1.05-1.30, \( p = .004 \))

- **Socio-economic status (SEIFA)**
  - Baseline (OR 0.51, 95%CI 0.30-0.85, \( p = .01 \))
  - 3 yrs (OR 0.65, 95%CI 0.37-1.12, \( p = .12 \))

Not academic performance, gender, comorbidities, social problems, maternal MH
Other CAP work

- Anxiety
- Health problems (obesity, injuries, sleep problems)
- Disruptive Mood Dysregulation Disorder
- Parenting (relation to child function)
- Maternal ADHD symptoms (relation to child function)
- Peer victimization
- Global self-worth
- Influence of age at school entry on rate of ADHD medication use
- Chronic tics / Tourette
- Quality of Life

- Mulraney et al 2015, *Eur Child Adolesc Psychiatry*
- Sciberras et al 2016, *Child Care Health Dev.*
- Mulraney et al., 2016, *J Atten Disord*
- Bhide et al., 2017, *J Atten Disord*
- Sciberras et al 2017, *MJA* (letter)
- Efron et al, *under review*
- Wijaya et al, *under review*
Neuroimaging of the Children’s Attention Project (NICAP)  
Dr Tim Silk
NICAP

• Aim: To investigate trajectories in brain structure and function for children with and without ADHD
  - associations with academic, cognitive, social and mental health outcomes

• Longitudinal multi-modal MRI
  - ages 11, 12.5, 14

• Scans completed
  - Wave 1: 180 of 206 (87%)
  - Wave 2: 146 of 160 (90%) to date

Silk et al, 2016, BMC Psychiatry
Summary

• CAP will help us understand the natural history of ADHD and the factors influencing outcomes
  • important information for health and education professionals, families and policy makers

We wouldn’t be able to do this research without the support of families, schools and teachers
CAP Staff

Investigator Team
Dr Emma Sciberras MCRI, RCH
Dr Daryl Efron RCH, MCRI
Prof Jan Nicholson La Trobe, MCRI
Prof Vicki Anderson MCRI, RCH
Dr Tim Silk MCRI
Prof Philip Hazell SSWAHS, USYD
Dr Brad Jongeling CDS, UWA
Dr Obioha Ukoumunne PenCLAHRC
Ms Karen Underwood DEECD

Current Project Team
Alisha Gulenc Project Coordinator
Lilli Nonneman Research Assistant
Charles Malpas Post-Doctorate
Helena Brace Intern

Current Students
Sampada Bhide MPSYCH/PhD
Hannah Korrel MPSYCH/PhD
Sila Genc PhD
Kate Stephens PhD
Howard Chiu MPSYCH
Phoebe Thomson Honours
William Poh Scholarly selective
Australian paediatric practice: Assessment

• Multi-site audit paediatric practice
  • 24 paediatricians: Vic and WA, private and public
  • 137 patients, 77% male, mean age 8.1 yrs

• Questionnaire use: Parent 88%, teacher 85%
• Comorbidities identified:

Efron et al J Paed Child Health 2016
Australian paediatric practice: Assessment

• Multi-site audit paediatric practice
  • 24 paediatricians: Vic and WA, private and public
  • 137 patients, 77% male, mean age 8.1 yrs

• Questionnaire use: Parent 88%, teacher 85%

• Comorbidities identified:

<table>
<thead>
<tr>
<th></th>
<th>Internalising (%)</th>
<th>Externalising (%)</th>
<th>Sleep problems (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediatrician</td>
<td>18</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Parent (SDQ)</td>
<td>51</td>
<td>66</td>
<td>39</td>
</tr>
</tbody>
</table>

Efron et al *J Paed Child Health* 2016
Children Attending Paediatricians Study (CAPS)

- 2-week audit
  - Nov 2013
- N=185
- 7514 consultations
**CAPS 2013: Medications prescribed**

<table>
<thead>
<tr>
<th>Medication group</th>
<th>Proportion of consultations in which medication prescribed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotropic</td>
<td>27</td>
</tr>
<tr>
<td>Laxatives</td>
<td>5</td>
</tr>
<tr>
<td>Asthma medications</td>
<td>4</td>
</tr>
<tr>
<td>Melatonin</td>
<td>4</td>
</tr>
<tr>
<td>Acid-suppressing agents</td>
<td>3</td>
</tr>
<tr>
<td>Eczema medications</td>
<td>2</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>1</td>
</tr>
<tr>
<td>Enuresis medications</td>
<td>1</td>
</tr>
<tr>
<td>Specialised infant formula</td>
<td>0.5</td>
</tr>
<tr>
<td>Other</td>
<td>12</td>
</tr>
</tbody>
</table>

Efron et al *J Paed Child Health* In Press
### CAPS 2013: Psychotropics

<table>
<thead>
<tr>
<th>Medication group</th>
<th>Proportion of consultations in which medication prescribed (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotropic any</td>
<td>27</td>
</tr>
<tr>
<td>Stimulants</td>
<td>17</td>
</tr>
<tr>
<td>SSRI/SNRI</td>
<td>4</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>3</td>
</tr>
<tr>
<td>Clonidine</td>
<td>2</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>1</td>
</tr>
<tr>
<td>Tricyclics</td>
<td>0.5</td>
</tr>
<tr>
<td>Anti-epileptic drugs</td>
<td>4</td>
</tr>
</tbody>
</table>

Efron et al *J Paed Child Health* In Press