Attention Deficit Hyperactivity Disorder: an overview of current advances in the field

Professor Alasdair Vance
Head, Academic Child Psychiatry
Department of Paediatrics
University of Melbourne
Royal Children’s Hospital
Outline of presentation

1. ADHD: definitional issues
2. ADHD: comorbid conditions
3. ADHD: developmental stages
4. ADHD: aetiological issues
5. ADHD: treatment issues
"Hello, Emily. This is Gladys Murphy up the street. Fine, thanks . . . Say, could you go to your window and describe what's in my front yard?"
1. **ADHD: definition**

Diagnostic nosology-some comments:

DSM-IV definition of a mental disorder-
A mental disorder is conceptualized as

a clinically significant
*behavioural pattern* that occurs
in an individual
and
is associated with *impairment* in
one or more areas of functioning

Prof. A. Vance
1. **ADHD: definition**

Diagnostic nosology-some comments

in children and adolescents-

impairment is *developmentally inappropriate*, judged relative to children of the same age, gender and IQ in social, academic, occupational or other important areas of functioning

*multi-informant* reports required

Prof. A. Vance
1. **ADHD: definition**

Multi-informant reports required:
- parent,
- teacher
- child

Low concordance repeatedly shown

Varies between externalising and internalising disorders
- externalising: parent-teacher: increased agreement
- internalising: child-teacher: increased agreement

Prof. A. Vance
1. **ADHD: definition**

assessment within a developmental context:

symptom patterns and associated with impairment in social, academic, occupational or other important areas of functioning

need to be monitored longitudinally so the clinician can accurately assess the child

[1] within their current developmental phase and

[2] across developmental phases as each child develops

Prof. A. Vance
1. **ADHD: definition**

Attention Deficit Hyperactivity Disorder (ADHD)
**DSM-IV CRITERIA**

- six or more symptoms, at least six months duration, maladaptive/inconsistent with developmental level
- inattention dimension and/or hyperactivity-impulsivity dimension
- evident in at least two settings
- onset before seven years of age
- impairment in social, academic, occupational functioning
- symptoms not due to a PDD, Psychotic, Mood, or Anxiety Disorder

Prof. A. Vance
1. ADHD: definition

TYPES of ADHD

- combined type
- predominantly inattentive type
- predominantly hyperactive-impulsive type

Prof. A. Vance
2. **ADHD: key comorbid conditions:**

- oppositional defiant disorder/conduct disorder
- anxiety and/or depressive disorders
- tic disorders
- language learning disorders (spelling/reading/arithmetic/writing)
- speech and language disorders (articulation/grammar)
- developmental coordination disorder
NO DIAGNOSIS
85.8%

CD
0.9%

DD + CD
0.3%

ADHD, CD + DD
0.5%

DD
1.9%

ADHD
8.3%

CD + ADHD
1.3%

ADHD + DD
1.0%
3. ADHD: developmental stages

Common possible developmental pathways: all associated with educational, social, occupational under-achievement, alcohol/substance abuse/dependence disorders, altered adult personality

<table>
<thead>
<tr>
<th>Childhood</th>
<th>Adolescence</th>
<th>Adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD-CT</td>
<td>ADHD-IA</td>
<td>ADHD-IA</td>
</tr>
<tr>
<td>ADHD-CT</td>
<td>Depressive d</td>
<td>Depressive d</td>
</tr>
<tr>
<td>ADHD-CT</td>
<td>Conduct d</td>
<td>ASPD</td>
</tr>
</tbody>
</table>

Prof. A. Vance
4. **ADHD: Key biological risk factors**

- **d = 1.0**
- **d = 0.5**

- Biological risk factors
- Psychosocial risk factors

Healthy | ADHD | ADHD

Prof. A. Vance
4. ADHD: Key biological risk factors

Neuropsychology of ADHD
4. ADHD: Key biological risk factors

Cognitive neuroscience
response inhibition tasks (eg STOP tasks)
working memory tasks (eg n-back; VSWM tasks)
deficits in both implicating PFC-striatal and
PFC-striatal-parietal neural networks
comorbid conditions: association unclear
investigated as markers for medication response
in children with ADHD

Prof. A. Vance
Spatial working memory task - CANTAB
Delayed Matching to Sample task - CANTAB
Mean correct responses (number)

Delay time (seconds)

- ADHD-CT(um)
- ADHD-CT(m)
- Controls
Effect sizes before and after additional comorbid conditions
4. ADHD: Key biological risk factors

Cognitive neuroscience

working memory (Mehta et al., 2000)

PET VSWM task 10 healthy adult males 2 sessions 2W apart
MPD 40mg or placebo with scanning 90+ minutes later
↓ rCBF -left DLPFC, left SMA, left PPC
associated with improved VSWM performance
4. ADHD: Key biological risk factors

Cognitive neuroscience

selective attention/working memory
(Bush et al., 2008)

fMRI MSIT 21 adults ADHD RCT 6 weeks
OROs-MPD or placebo
↑ daMCC associated with improved performance

Prof. A. Vance
4. ADHD: Key biological risk factors

Composite z-scores
ADHD children in the low dose and high dose Condition (dex. 2.5mg/7.5mg) (Mollica et al., Human Psychopharmacology 2004)

Prof. A. Vance
4. ADHD: Key biological risk factors

Neuroimaging of ADHD
4. ADHD: Key biological risk factors

Neuroimaging
-structural MRI:
  ↓ prefrontal cortex, basal ganglia, medial temporal and inferior parietal lobes (global 3% decrease)
  ↓ primarily white matter (d=.45 cf .28 gray matter)

developmental trajectories independent of medication treatment

Prof. A. Vance
Total cerebral growth curves

Controls > ADHD

$ p < .003$

Castellanos et al., JAMA 2002
4. ADHD: Key biological risk factors

Neuroimaging
- functional MRI:
  ↓ prefrontal cortex, basal ganglia, medial temporal 
  ↓ and inferior parietal lobes

bilateral task dependent decrease in activation

post-puberty - midline activation - compensatory?
pre-puberty - not evident
N=14, CBCL inattention subscale T score: 72.23 (10.72)

Silk, Vance et al, B J Psych 2005

Greater activation for Control than ADHD group.

<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left Prefrontal</td>
<td></td>
<td>-15</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Caudate I lead</td>
<td></td>
<td>-27</td>
<td>64</td>
<td>3</td>
</tr>
<tr>
<td>Sup Frontal Gyr.</td>
<td>10</td>
<td>-30</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>Inf Frontal Gyr.</td>
<td>46</td>
<td>-18</td>
<td>12</td>
<td>-21</td>
</tr>
<tr>
<td>Right Prefrontal</td>
<td></td>
<td>-57</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Ventral Inf Frontal Gyr.</td>
<td>47</td>
<td>15</td>
<td>-84</td>
<td>33</td>
</tr>
<tr>
<td>Right Parietal</td>
<td></td>
<td>42</td>
<td>-57</td>
<td>39</td>
</tr>
<tr>
<td>Inf Parietal Lob.</td>
<td>40</td>
<td>36</td>
<td>-60</td>
<td>51</td>
</tr>
<tr>
<td>Sup Parietal Lob.</td>
<td>7</td>
<td>42</td>
<td>-24</td>
<td>30</td>
</tr>
<tr>
<td>Occipital</td>
<td></td>
<td>19</td>
<td>-12</td>
<td>42</td>
</tr>
<tr>
<td>Left Precuneus</td>
<td>19</td>
<td>15</td>
<td>-81</td>
<td>42</td>
</tr>
<tr>
<td>Right Cuneus</td>
<td>19</td>
<td>15</td>
<td>-84</td>
<td>33</td>
</tr>
</tbody>
</table>

Greater activation for ADHD than Control group.

<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial Sup Frontal Gyr.</td>
<td>10</td>
<td>-9</td>
<td>63</td>
<td>15</td>
</tr>
<tr>
<td>Posterior Cingulate Gyr.</td>
<td>31</td>
<td>18</td>
<td>-24</td>
<td>30</td>
</tr>
<tr>
<td>Left Temporal</td>
<td></td>
<td>-36</td>
<td>-27</td>
<td>6</td>
</tr>
<tr>
<td>L Sup Temporal Gyr.</td>
<td>13</td>
<td>-36</td>
<td>-27</td>
<td>6</td>
</tr>
<tr>
<td>L Mid Temporal Gyr.</td>
<td>39</td>
<td>-48</td>
<td>-80</td>
<td>9</td>
</tr>
</tbody>
</table>

Silk, Vance et al, B J Psych 2005

N=14, CBCL inattention subscale T score: 72.23 (10.72)
### Region of activation

**Control Group greater than ADHD-CT Group**

**Parieto-Occipital**
- R Precuneus: 19, C (mm) = 24-70 32, Z = 3.53
- R Cuneus: 19, C (mm) = 32-90 28, Z = 2.82

**Posterior Parietal**
- R Inf. Parietal: 40, C (mm) = 36-40 50, Z = 2.82

**Frontal/Subcortical**
- R Caudate Nucleus, Body: 18, C (mm) = -12 22, Z = 2.82

---

Vance et al, Mol Psych 2007

N=24, CBCL inattention subscale T score: 72.14 (9.43)
## Greater Activation for Control than Dysthymic Disorder

<table>
<thead>
<tr>
<th>Region</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right Frontal Lobe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>9</td>
<td>42</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>46</td>
<td>44</td>
<td>42</td>
<td>14</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>46</td>
<td>40</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Middle Frontal Gyrus</td>
<td>10</td>
<td>34</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Inferior Frontal Gyrus</td>
<td>44</td>
<td>50</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td><strong>Right Parietal Lobe</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>40</td>
<td>40</td>
<td>-58</td>
<td>44</td>
</tr>
<tr>
<td>Superior Parietal Lobule</td>
<td>7</td>
<td>36</td>
<td>-74</td>
<td>44</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>39</td>
<td>48</td>
<td>-62</td>
<td>40</td>
</tr>
<tr>
<td>Superior Parietal Lobule</td>
<td>7</td>
<td>30</td>
<td>-74</td>
<td>44</td>
</tr>
<tr>
<td>Precuneus</td>
<td>19</td>
<td>34</td>
<td>-66</td>
<td>36</td>
</tr>
<tr>
<td>Inferior Parietal Lobule</td>
<td>40</td>
<td>42</td>
<td>-44</td>
<td>44</td>
</tr>
</tbody>
</table>

N=14, CBCL inattention subscale T score: 70.88 (9.75)

Prof. A. Vance
4. **ADHD: Key biological risk factors**

Molecular genetics of ADHD
4. ADHD: Key biological risk factors

Genetics:

- heritability estimates 65%-90% phenotypic variance in population

<table>
<thead>
<tr>
<th>Studies</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=14</td>
<td>1.13</td>
</tr>
<tr>
<td>N=13</td>
<td>1.45</td>
</tr>
<tr>
<td>N=3</td>
<td>1.33</td>
</tr>
<tr>
<td>N=5</td>
<td>1.19</td>
</tr>
<tr>
<td>N=3</td>
<td>1.44</td>
</tr>
</tbody>
</table>
4. ADHD: Key biological risk factors

- Cognitive deficits in ADHD are associated with these key candidate genes:

Healthy children:

DAT1 3’ VNTR 10-repeat allele
DAT1 intron 8 VNTR 3-repeat allele → R spatial inattention
DAT1 3’ UTR VNTR 10-repeat allele (\(\eta^2 = .07/.08/.08\))

- this 10/3DAT1 haplotype – ADHD (OR 2.58)
Epigenetics has arrived.....
D = Deoxyribose (sugar)
P = Phosphate
Hydrogen Bond
The two main components of the epigenetic code

DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the ‘tails’ of proteins called histones. These alter the activity of the DNA wrapped around them.
They Are What She Ate

Scientists have found that certain nutrients consumed during pregnancy can change the way genes are activated in the offspring of laboratory mice, without affecting their underlying DNA.

**NORMAL DIET**
One strain of mice tends to have fat, yellow pups that are prone to cancer, diabetes and other diseases.

Most pups are fat and yellow because the "agouti" gene that determines coat color and appetite control goes into overdrive when an adjacent segment of genetic material interferes with it.

The segment, called a transposon, is the remnant of a past viral infection. Transposons act like on or off switches for genes.

**MODIFIED DIET**
(Adding vitamin B12, folic acid, choline and betaine)

Transposons are powered by compounds, called methyl groups, from food.

When pregnant mice were fed extra methyl groups found in supplements like folic acid, both the transposon and agouti gene were silenced. Most of their pups were brown and had normal appetites.

Source: Dr. Randy L. Jirtle, Department of Radiation Oncology, Duke University
Epigenetics

-Gene functional activity not structure (DNA sequence) changed

-parental care affects stability genes: stress responsiveness, neural development, neural reproduction

-tactile stimulation/nurture (week 1)

\[ \text{GH} \uparrow \quad \text{IGF} \uparrow \quad \text{glucocorticoids} \downarrow \]
-tactile stimulation/nurture

CRF gene

CRF mRNA

glucocorticoid receptors – eg hippocampus

serotonin protective effects blocked by

absence of NGF1-A mRNA

NGF1-A a transcription factor – binds to exon 1 GR and increases GR expression
The structure of a typical human protein coding mRNA including the untranslated regions (UTRs)
-regulatory regions turn on/off coding areas

Exon 7 binding site for NGF1-A

Exon 7 3’ 5’

↓ ↓ ↓ ↓

- maternal care

↑

demethylation 5’ and histone deacetylation

open up chromatin and increase binding translational factors

Prof. A. Vance
- High stimulation  ↓  low stimulation  →  1st 24 hours

↓ NGF1-A  Exon 7  5’ methylation and histone acetylation

↑ CRF

↑ Glucocorticoid receptors – eg hippocampus

- This process can be reversed by dietary methionine (a histone deacetylase inhibitor) in adult rats

Prof. A. Vance
4. ADHD: Key biological risk factors

Summary

- biological factors important
- large effect: CogNS constructs
- brain structural/functional changes
developmental stage-independent deficits compensatory changes post-puberty
- small effect: candidate genes - symptoms
- medium effect: candidate genes - CogNS measures;
- medication changes non-specific currently
- epigenetics emphasizing importance of biological and psychosocial factors being in synergy

Prof. A. Vance
4. ADHD: Key psychological risk factors

Summary
- parental psychopathology: alcohol/depressive/anxiety disorders
- marital functioning:
- family functioning:
- peer group functioning:

“empathy/attunement/sensitivity/responsiveness”

“flexibility/adaptiveness/regulation of affect/problem solving”

sociocultural context affects the character of these aspects and their detection

Prof. A. Vance
Seminal research study

Conclusion: Protective factors can make a more profound impact on the life course than a specific risk factor

Individual coping styles
- Social Competence
- Problem Solving Skills
- Autonomy
- Sense of purpose, belief in a bright future

Environmental factors
- Caring Relationships
- High Expectations
- Opportunities for participation

Prof. A. Vance
### Risk factors

<table>
<thead>
<tr>
<th>Child factors</th>
<th>Family factors</th>
<th>School context</th>
<th>Life events</th>
<th>Community and cultural factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low self esteem</td>
<td>Family violence</td>
<td>School failure</td>
<td>Divorce and family breakup</td>
<td>Neighbourhood violence and crime</td>
</tr>
<tr>
<td>Poor social skills</td>
<td>Poor supervision</td>
<td>Bullying</td>
<td>Death of a family member</td>
<td>Lack of support services</td>
</tr>
<tr>
<td>Poor problem solving</td>
<td>Harsh or inconsistent discipline</td>
<td>Peer rejection</td>
<td></td>
<td>Social or cultural discrimination</td>
</tr>
<tr>
<td>Difficult temperament</td>
<td>Lack of warmth and affection</td>
<td>Poor attachment to school</td>
<td></td>
<td>Community norms concerning violence</td>
</tr>
<tr>
<td>Lack of empathy</td>
<td>Abuse and neglect</td>
<td>Deviant peer group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homelessness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early school leaving</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Protective factors

<table>
<thead>
<tr>
<th>Child factors</th>
<th>Family factors</th>
<th>School context</th>
<th>Life events</th>
<th>Community and cultural factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social competence</td>
<td>Supportive caring parents</td>
<td>Positive school climate</td>
<td>Meeting significant person</td>
<td>Access to support services</td>
</tr>
<tr>
<td>Attachment to family</td>
<td>Family harmony</td>
<td>Prosocial peer group</td>
<td>Moving to new area</td>
<td>Community networking</td>
</tr>
<tr>
<td>Empathy</td>
<td>Secure and stable family</td>
<td>Sense of belonging</td>
<td>Opportunities at critical turning points</td>
<td>Attachment to the community</td>
</tr>
<tr>
<td>Problem solving</td>
<td>Supportive relationship with other adult</td>
<td>Opportunities for some success at school and recognition of achievement: School norms re violence</td>
<td></td>
<td>Participation in community group</td>
</tr>
<tr>
<td>Optimism</td>
<td>Strong family norms and morality</td>
<td></td>
<td></td>
<td>Community/cultural norms against violence</td>
</tr>
<tr>
<td>School achievement</td>
<td></td>
<td></td>
<td></td>
<td>Strong cultural identity/ethnic pride</td>
</tr>
<tr>
<td>Easy temperament</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good coping style</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
"Our psychopharmacologist is a genius."
I worry about the decreased polarization of our society.
"All right, Billy, you just go right ahead! . . . I've warned you enough times about playing under the anvil tree!"
"Rub his belly, Ernie! Rub his belly!"
5. A model for intervention

-assessment and treatment focuses on delineation of risk factors and resilience factors—biologically (eg, executive function deficits; good arousal regulation) psychologically (eg, externalise blame; balanced critical self-reflection) and socially (eg, hostile critical interpersonal environment; confiding, nurturing consistent interpersonal environment)

-monitoring of these risk and resilience factors and their response to treatment through developmental phases

Prof. A. Vance
5. **A model for intervention**
-a practical approach

[A] psychological and social treatment approach implemented for 4-6 weeks (may take 6 months of new habit formation before sustained behavioural change)

*key elements are the interpersonal and the intra-individual milieu*

**interpersonal:** positive reinforcement, response cost, token economy, contingency planning (turn taking, active listening, active ignoring, empathy skills, etc), making and keeping friends

**intra-individual:** controlled breathing, muscle biofeedback, guided visual imagery

Prof. A. Vance
5. **A model for intervention**

- a practical approach

[B] key other vulnerabilities addressed – vision, hearing, specific verbal and/or visuospatial learning difficulties, developmental coordination difficulties, speech and language difficulties

Prof. A. Vance
5. A model for intervention

A practical approach

[C] medication use to facilitate availability of the young person to learn from the psychological and social interventions through better arousal regulation, better mood regulation, better executive functioning

Prof. A. Vance
5. A model for intervention

**Summary**

- medication can aid a child’s ability to invest in a psychosocial treatment program and learn from this program

- can take 6 months of practice before new habits are formed

- biological and psychosocial treatments maximize resilience and minimize risk factors through shared effects on the brain and the mind

Prof. A. Vance
5. A medication approach (Australian perspective)

- stimulant medication is the first line treatment

short-acting forms: methylphenidate, dexamphetamine
long-acting forms: OROS-methylphenidate, LA-methylphenidate

clear and substantial evidence for methylphenidate efficacy up to a dose of 60mg daily for treatments periods of approximately 12 months

methylphenidate and dexamphetamine similar efficacy and adverse effects profile although individual preferences manifest
5. A medication approach (Australian perspective)

- **Stimulant medication benefits**
  
  decrease core symptoms of ADHD  
  decrease aggression  
  increase quality of social interactions  
  increase compliance  

- **Stimulant medication indications**

  ADHD diagnosis and psychosocial interventions insufficient
5. A medication approach (Australian perspective)

- Stimulant medication adverse effects

initial insomnia,
appetite suppression

nervousness, restlessness, dysphoria,
easy crying, agitation, depressive symptoms, stomach ache
headache, dizziness, rash, motor tics, mannerisms

in overdose: delirium, sweating, tremor, twitching, vomiting

Prof. A. Vance
5. A medication approach (Australian perspective)

- Stimulant medication adverse effects

  growth retardation (MTA 3y f/u: 2cm ↓2.7kg ↓)
  weight loss

  epileptic seizures
  psychotic episodes
  abuse potential

  not adverse effects but careful monitoring needed in vulnerable patients

Prof. A. Vance
5. A medication approach (Australian perspective)

- Atomoxetine is the second line treatment

  specific potent noradrenaline re-uptake inhibitor indicated when stimulant medication ineffective, associated with significant adverse effects

  common adverse effects: nausea, drowsiness, initial insomnia, appetite suppression

Prof. A. Vance
5. A medication approach (Australian perspective)

- **Imipramine** is a third line treatment tricyclic compound similar to atomoxetine (a phenylpropanolamine derivative) but with less specific noradrenaline effect and significant cardiac adverse effects.

- **Clonidine** is a third line treatment central $\alpha$-2 noradrenergic agonist significant effect; primarily hyperactivity/impulsiveness significant drowsiness, hypotensive and cardiac adverse effects gradual withdrawal because of rebound hypertension and tics

Prof. A. Vance
5. A medication approach (Australian perspective)

- Neuroleptic medication is a third line treatment
  atypical neuroleptic medication: eg risperidone / aripiprazole
  low doses (up to risperidone 1.5mg daily equivalent)
  severe aggression, affective lability, PDD, ID

  typical neuroleptic medication: eg pericyazine - thioridazine
  equivalent (now withdrawn)

  third line treatments only used with careful monitoring
  and involvement in a treatment-resistant unit

Prof. A. Vance
5. A medication approach (Australian perspective)

Conclusion

- start low, go slow, finish slow, although ensure optimal doses are used

- medication facilitates each child’s ability to learn in the classroom, playground and home environment: new habits can take 6 months to evolve

- Comprehensively assess and treat with approved medication and/or psychosocial treatments all comorbid conditions

Prof. A. Vance
5. We need an adequate evidence base for medication treatment, psychosocial treatment and their combination....
In the context of careful systematic comprehensive training...
TRANSLATIONAL CLINICAL SCIENTISTS

From laboratory bench, social/cultural factors to clinical practice
Tools for Translation: 2009

WGAS Sequencing Transgenics Epigenetics Databases
Electrode Arrays Zebrafish PET fMRI DTI Databases
Web 2.0 Knowledge management

Repositories – Data Sharing - Integration