ADHD: Development and Prospects

How far have we come? Where are we going?

Getting the diagnosis
Learning the brain basis
Making treatment personal

Eric Taylor; King’s College London; no competing financial interests
ADHD: advances & obstacles

1900

History

Hundred-year perspective:
Biological foundations
Social function of disorder

Current

Diagnostic arguments
Public debate
Stigma
Evolution of ADHD

- The concept of ADHD did not spring from a single clinical description (cf. autism),
- nor from epidemiological research (cf. CD - Robins - and early-onset CD - Moffitt),
- nor from adult psychiatry (cf. MDD).
- Rather, it evolved – to identify constitutional problems – then to embody deficit theories.
“MBD” emphasised the brain basis; too simple, but returning as “NDD”

- Neurodevelopmental disorders frequently coexist
- Neurocognitive bases
- Male predominance
- Genetic influences strong
- Associations with epilepsy and brain disease
- Early onset
- Continuity over time
The early trials of stimulants

<table>
<thead>
<tr>
<th>DATE</th>
<th>AUTHOR</th>
<th>OUTCOMES RATED</th>
</tr>
</thead>
<tbody>
<tr>
<td>1963</td>
<td>Eisenberg</td>
<td>learning, disobedience, overactivity improved</td>
</tr>
<tr>
<td>1962</td>
<td>Knobel</td>
<td>hyperkinesis improved</td>
</tr>
<tr>
<td>1942</td>
<td>Bender &amp; Cottington:</td>
<td>relaxed; sociable; less aggressive</td>
</tr>
<tr>
<td>1940</td>
<td>Cutler</td>
<td>reading better; little intellectual gain</td>
</tr>
<tr>
<td>1937</td>
<td>Bradley</td>
<td>school performance better; subdued; relaxed</td>
</tr>
</tbody>
</table>

The observations of drug effects gradually converge on ADHD

(Pharma companies not responsible!)
MBD in Retrospect

- **Strengths**
  - Emphasised cognitive processes and organic cause
  - Promoted research on inhibitory & EF deficits
  - Pointed to similarities in ‘neurodevelopmental’

- **Weaknesses**
  - Inferred physical causes from the behaviour
  - Over-emphasised a deficit model
  - Encouraged perseveration on unitary models
ADHD: Four “crucial concepts”

- ADHD is...
  1. A descriptive diagnosis from behaviours and impairment
  2. A ‘spectrum condition’ - the behaviour problem is at the extreme end of distribution
  3. Heterogeneous
  4. A syndrome with various causes and risk factors
Longitudinal research finds dimensions rather than diagnoses for ADHD, which includes:

**ADHD**
- Inattentive
- Impulsive

**Oppositional**
- Headstrong
- Irritable

Leading to:
- education failure
- antisocial
- mood disorder

... be clear about the goals.
Continuing Problems in Diagnosis

- Cut-off uncertain
- Adapting by age, gender and developmental level
- Understanding “comorbidity” and how other conditions can masquerade
- Reliable application in practice
- Relation of “symptoms” to impairment
HA, Imp, IA cluster together in a continuum of behaviour; diagnosis therefore depends on presence of disability.

A continuum of risk: % with HA behaviour at 17

Distribution of scores of 3,107 7-yr-old boys on a teacher rating of hyperactivity (Taylor et al 1991)
From impairment to handicap

**Impairment**: abnormality of structure or function.

**Disability**: restriction of ability to perform an activity in the normal way.

**Handicap**: disadvantage for a given individual that limits or prevents the fulfillment of a role that is normal.

**EXAMPLE**
- Frontostriatal connection, response suppression
- Cannot ‘stop and think’
- School failure
- Peer problems
Diagnosis: detecting symptoms and disability

- Screening rating scales: Conners, CBCL, DSM-IV, SDQ
- Clinical interview with parent & child
- School information
- Observation: school observation if in doubt

Screening tests useful; but expert judgements still needed
Continuing Problems in Diagnosis

- Cut-off uncertain
- Adapting by age, gender and developmental level
- Understanding “comorbidity” and how other conditions can masquerade
- Reliable application in practice
- Relation of “symptoms” to impairment
Frequent misdiagnoses

- ADHD overactivity – or Tourette restlessness?
- ADHD impulsiveness – or impulse-ridden oppositionality?
- ADHD inattention – or incapacity?
- ADHD emotionality – or psychological trauma?
- ADHD overactivity - or hypomanic energy?

Alternative conditions may be both differentials and associated problems
### Importance of recognising full range of components

<table>
<thead>
<tr>
<th>Autism</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social anxiety</td>
<td>Emotional dysregulation</td>
</tr>
<tr>
<td>Obsessions and compulsions</td>
<td>Distinct cognitive changes</td>
</tr>
<tr>
<td>Early communication</td>
<td>Peer problems</td>
</tr>
</tbody>
</table>

More therapeutic change than in global scales?
Clinical value of recognising multiple components

- Allows debate between different schools
- Reconcile conflicting formulations
- Appreciate full range of problems
- Recognise strengths
- Recognise treatable aspects of disorder
- Clarifies “comorbidity”
Prospects for diagnostic concepts

- Efficient dimensional ordering to complement diagnosis
- Relation of “symptoms” to impairment
- Adapting by age, gender and developmental level
- Understanding “comorbidity”
- Towards pathophysiology
Learning the brain basis
“Mega-analysis” of brain volume

Multivariate pattern recognition analyses (MVPR)

Machine-based supervised learning - eg Support Vector Machine

Test data: leave-one-out, partial sample

- Individual classification
  - diagnosis/ screening: how good is good enough? 85% accuracy in research
  - predict diagnosis or mechanism?
  - personalising treatment response and prognosis

Ecker et al. 2009 GM
Effect of MP on ADHD

Placebo

MPH

MPH > Plac

Caud/GP/Put/Thal

Put/Caud/Thal
CONCLUSIONS

- MPH increased activation in task-specific frontal (stop, stroop, timing), striatal (stop) and cerebellar brain areas (reward, stop) that have previously been shown to be dysfunctional and dysmorphological in ADHD.

- MPH increased activation in neural areas reported to have a high density of dopamine receptors.
The impact of medication
ADHD: The coming of Ritalin

CIBA (1970): ‘effective for the hyperactive problem child’
Controversy and stigma

That it is too commercial and too easy …

Or produces an unnatural
ADHD medication: US v Europe

Per 1,000


N Carolina
UK
France
Germany

ADHD needing drugs?
MTA 36 month ITT analysis – Jensen et al 2007
At the 8-year follow-up of the MTA the outcome is predicted by social advantage but not by group of initial allocation: same at 16 years

All ineffective? Good self-selection after randomisation? Need for intensive work to continue to maintain benefit?
Primary Outcome of the MTA Randomized Clinical Trial
(Symptom Severity from Baseline to 16-Yr Assessment)

Assigned Treatments - Inattention

Assigned Treatments - Hyperactive/Impulsive
Use of medication falls with age

**Figure 1:** Prevalence of methylphenidate, dexamfetamine and atomoxetine in males aged 15-21 between 2001 and 2005

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence (per 1000 patient years)</th>
</tr>
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<tbody>
<tr>
<td>2001</td>
<td>13.78</td>
</tr>
<tr>
<td>2002</td>
<td>11.44</td>
</tr>
<tr>
<td>2003</td>
<td>9.88</td>
</tr>
<tr>
<td>2004</td>
<td>9.49</td>
</tr>
<tr>
<td>2005</td>
<td>7.88</td>
</tr>
</tbody>
</table>

**Predicted decrease (2005):**
- 6.54
- 5.43
- 4.51
- 0.61
Common reasons for nonadherence in 66 young people at ADHD clinic

- Forget
- Stigma
- Not real self
- Losing funny side
- Adverse effects
  - Physical; sex; tension; feared brain damage
  - Incompatible with misused substances
- Inconvenience
- Don’t need it
- Up to me
- No point
Despite extended patterns of medication use that remained constant over time for the Negligible and Consistent subgroups, the initial significant subgroup difference still dissipated by 6 years after baseline.
Medication prospects

- **Immediate**
  - Guanfacine; conjugated DA; modafinil; delivery

- **Later**
  - Stabilisers; nicotine analogues; racetams

- **Uncertain**
  - Allosterics
  - Enhancers: cognition, parenting
  - Misuse modifiers
Medication prospects

- Harm minimisation
- Combination with psychological
- Personalisation
- Use beyond diagnostic boundaries
- Strategies for refractory
  - Successive trials? Pharmacogenomics? Prediction or monitoring by neuroimaging? Combination strategies?
Introduction of new medications:

- **Current**
  - Guanfacine; conjugated DA; modafinil; delivery

- **Later**
  - S/N/DRIs; stabilisers; nicotine analogues; racetams

- **Uncertain**
  - Allosterics
  - Enhancers: cognition, parenting
  - Misuse modifiers
## Introduction of new treatments: Cognitive enhancers

<table>
<thead>
<tr>
<th>TYPE OF DRUG</th>
<th>COMPANY</th>
<th>PURPOSE</th>
<th>STATUS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREB suppressor</td>
<td>Helicon Therapeutics</td>
<td>Suppression of disturbing memories</td>
<td>Early stages of development</td>
</tr>
<tr>
<td>CREB enhancer</td>
<td>Helicon Therapeutics</td>
<td>Memory enhancement</td>
<td>Early stages of development</td>
</tr>
<tr>
<td>CREB enhancer (MEM 1414)</td>
<td>Memory Pharmaceuticals in partnership with Roche</td>
<td>Memory enhancement</td>
<td>In Phase I trials</td>
</tr>
<tr>
<td>Calcium flow regulator (MEM 1003)</td>
<td>Memory Pharmaceuticals</td>
<td>Memory enhancement</td>
<td>In Phase I trials</td>
</tr>
<tr>
<td>Ampakines</td>
<td>Cortex Pharmaceuticals</td>
<td>Memory enhancement</td>
<td>In Phase II trials</td>
</tr>
<tr>
<td>Phenserine</td>
<td>Axonyx</td>
<td>Treatment of mild to moderate Alzheimer’s</td>
<td>Phase II trials completed</td>
</tr>
<tr>
<td>Modafinil (Provigil)</td>
<td>Cephalon</td>
<td>Treatment of narcolepsy</td>
<td>On the market</td>
</tr>
<tr>
<td>Methylphenidate (Ritalin)</td>
<td>Novartis</td>
<td>Attention enhancement</td>
<td>On the market</td>
</tr>
<tr>
<td>Donepezil (Aricept)</td>
<td>Eisal/Pfizer</td>
<td>Treatment of mild to moderate Alzheimer’s</td>
<td>On the market</td>
</tr>
<tr>
<td>Rivestigmine (Exelon)</td>
<td>Novartis</td>
<td>Treatment of mild to moderate Alzheimer’s</td>
<td>On the market</td>
</tr>
<tr>
<td>Galantamine (Reminyl)</td>
<td>Janssen</td>
<td>Treatment of mild to moderate Alzheimer’s</td>
<td>On the market</td>
</tr>
<tr>
<td>Piracetam</td>
<td></td>
<td>Efficacious but unused</td>
<td></td>
</tr>
</tbody>
</table>
cAMP response element – binding protein

Rubenstein-Taybi

Fruit flies

Rats

Transmitter → receptor → cAMP → protein kinase → nucleus → CREB → gene expression
What does society think?
Results of citizen juries & focus groups

- Unprepared views; shifting attitudes; lack of trusted experience.
- Treatment v enhancement; natural v not
- 60% say enhancement unacceptable*
- Effort has intrinsic value
- Equality, Coercion, Control, Quick-fix, Robotic children, Threat to teachers

*but caffeine OK

Academy of Medical Sciences 2008
Translational impact of genetics

- Public understanding
- Genetic counselling
- High-risk for intervention
- Vulnerability counselling
  - Alcohol, parenting
- Drug decisions
Predict medication response?

- CYP2D6 polymorphisms for atomoxetine; esterase for methylphenidate
- DRD4.7 findings contradictory
- DAT 10/10 may predict nonresponsiveness*
- glutamate receptor 7 gene (GRM7) & norepinephine transporter suggested in genome scan**


Future of treatment: psychosocial

- Psychoeducation
- Extend parent training for younger children
- Manage parental ADHD
- Users ask for time w doctor & antibullying
- Develop intelligent customer role
- Overcome limitations of cognitive therapy
  - Differentiate by type of problem
  - Assess newer technologies
    - TMS, neurofeedback
Children shape their environment

Hyperactivity \(\rightarrow\) lead exposure \(\rightarrow\) pica

Inattention \(\rightarrow\) Low stimulation \(\rightarrow\) Poor achievement

Impulsive \(\rightarrow\) critical atmosphere \(\rightarrow\) Antisocial conduct
Cultural Impact

- Who are we?
- Biological basis of personality
  - Reducing over-reliance on psychoanalysis
- Understanding disability
  - Recognising adjustment to disability
  - Reducing impairment with medicine