Cognitive Impairment and the Effects of Medication in ADHD

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Talk Overview

1) What is the cognitive profile of ADHD?

2) Does medication improve cognitive functioning?
   - Can cognitive function predict response to treatment?

3) Does cognitive impairment improve over time?
   - Does cognitive improvement predict clinical improvement?
Core symptoms and high rate of comorbidity impact the child and family.

**Symptom domains**
- Hyperactivity
- Inattention
- Impulsivity

**Psychiatric comorbidities**
- Anxiety and mood disorders
- Disruptive behavioural disorders (conduct disorder and oppositional defiant disorder)

**Lead to**

**Child**
- Low self-esteem
- Accidents and injuries
- Smoking
- Substance abuse
- Delinquency
- School/work
  - Academic/learning difficulties
  - Underachievement

**Family/Home**
- Family stress/burden
- Parenting difficulties
- Parental mental health

**Social**
- Poor peer relationships
- Socialization deficit
- Relationship difficulties

Barkley’s “single cause” model of ADHD

Genetic factors → Dopaminergic and Noradrenergic abnormalities in Fronto / striatal pathways → 1º Behavioural Inhibition deficits → 2º Broader Executive Dysfunctions e.g. Working memory, planning → ADHD Symptoms

- Biological
- Cognitive
- Behaviour
Multiple Genetic Factors

Multiple Environmental Factors

Mesolimbic reward circuits

Fronto Cerebellar circuits

Behavioural Inhibition deficits

Delay aversion

Timing deficits

Working Memory Deficits

ADHD Symptoms

Dopaminergic and Noradrenergic abnormalities in Fronto / striatal pathways

Temporal lobe, amygdalo / hippocampal circuits

Non-Executive Memory Deficits

Acetylcholine
ADHD is associated with significant deficits in both executive and non-executive aspects of working memory.

Rhodes, Coghill and Matthews 2004, 2005
ADHD is associated with significant deficits in both executive and non-executive aspects of working memory. However these deficits were not associated with altered response speed or inhibitory control.

These data present a strong challenge to the primacy of inhibition deficits in ADHD.
ADHD is associated with significant deficits in both executive and non-executive aspects of working memory

Rhodes, Coghill and Matthews 2004, 2005
ADHD is associated with significant deficits in both executive and non-executive aspects of working memory. These contribute to the executive deficits and are not mediated by inhibitory problems.

These are non-executive deficits are very similar in type and severity to individuals with temporal lobe of amygdale/hippocampal damage.

These data present a strong challenge to the primacy of frontal lobe executive function deficits in ADHD.
<table>
<thead>
<tr>
<th>Task Description</th>
<th>Effect Size (d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial Working Memory</td>
<td>0.75 0.70</td>
</tr>
<tr>
<td>• BSE</td>
<td></td>
</tr>
<tr>
<td>• Strategy</td>
<td></td>
</tr>
<tr>
<td>Tower of London (Planning, working memory)</td>
<td>0.38</td>
</tr>
<tr>
<td>ID/ED Attentional Set Shifting</td>
<td>0.46</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>0.71</td>
</tr>
<tr>
<td>Spatial Span</td>
<td>0.60</td>
</tr>
<tr>
<td>Delayed Matching to Sample</td>
<td>0.92</td>
</tr>
<tr>
<td>Pattern Recognition</td>
<td>0.89</td>
</tr>
<tr>
<td>Spatial Recognition</td>
<td>0.72</td>
</tr>
<tr>
<td>PAL</td>
<td>0.47 0.58</td>
</tr>
<tr>
<td>• Tot errors</td>
<td></td>
</tr>
<tr>
<td>• Tot trials</td>
<td></td>
</tr>
</tbody>
</table>
Delay aversion

• Choose between a small immediate reward and a large delayed reward
• Under most conditions ADHD and control children perform similarly
• However when the child is able to choose between shortening the trial (for a smaller reward) and maximising the reward (but taking longer)
  – Control children will maximise reward
  – ADHD children will minimise the duration
ADHD and Timing

Several groups have identified that those with ADHD have specific problems with timing tasks known to be dependent on intact cerebellar functioning.
Interim Conclusion

• Impairment in executive functions such as working memory but inhibition is not the primary deficit

• Range of impairments in short- and long-term memory that involve storing information in memory

• Cognitive profile is broad
Gene factors

Dopaminergic and Noradrenergic abnormalities in Fronto/striatal pathways

Environmental factors

Mesolimbic reward circuits

Fronto Cerebellar circuits

Dopaminergic and Noradrenergic abnormalities in Fronto/striatal pathways

Temporal lobe, amygdalo/hippocampal circuits

Acetylcholine

ADHD Symptoms and Impairments

Behavioural Inhibition deficits

Working Memory Deficits

Delay aversion

Timing deficits

“Hot” EF Deficits

Model simplified by excluding variability and other executive deficits e.g. planning, set shifting
Talk Overview

2) Does medication improve cognitive function?

- Can neuropsych predict response to treatment?
Genes → Brain Structure and Function → Cognition
Cognition → Symptoms

Methylphenidate REDUCES Symptoms

Environmental Factors → Genes → Brain Structure and Function
Environmental Factors → Cognition
<table>
<thead>
<tr>
<th>Time</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>4 weeks</td>
</tr>
<tr>
<td>ADHD</td>
<td>Baseline</td>
<td>0.3mg/kg</td>
<td>0.3mg/kg</td>
<td>0.6mg/kg</td>
<td>placebo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6mg/kg</td>
<td>0.6mg/kg</td>
<td>placebo</td>
<td>0.3mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>placeholder</td>
<td>placeholder</td>
<td>0.3mg/kg</td>
<td>0.6mg/kg</td>
</tr>
<tr>
<td>Control</td>
<td>Baseline</td>
<td>No further follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 70</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Patterns of “full” clinical response to methylphenidate

“Full” response = \( \text{T score} \leq 65 \) and Reliable change index > 1.96 on 10 item Connors’ Global Impact (Parent)

The results for response defined only by reliable change or by clinically significant change are similar.
<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>Effect of chronic methylphenidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spatial Working Memory</td>
<td>No significant effect of MPH on any measure</td>
</tr>
<tr>
<td>Stockings of Cambridge</td>
<td>No significant effect of MPH on any measure</td>
</tr>
<tr>
<td>ID/ED (attentional set-shifting)</td>
<td>No significant effect of MPH on any measure</td>
</tr>
<tr>
<td>Spatial Span</td>
<td>No significant effect of MPH on any measure</td>
</tr>
<tr>
<td>Delayed Matching to Sample</td>
<td>0.3 &amp; 0.6mg/kg MPH improved performance on simultaneous &amp; delay conditions</td>
</tr>
<tr>
<td>Pattern Recognition</td>
<td>0.3 &amp; 0.6mg/kg MPH improved performance</td>
</tr>
<tr>
<td>Spatial Recognition</td>
<td>0.3 &amp; 0.6mg/kg MPH improved performance</td>
</tr>
<tr>
<td>Paired Associates Learning</td>
<td>No significant effect of MPH on any measure</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>No significant effect of MPH on any measure</td>
</tr>
</tbody>
</table>

Coghill, Rhodes & Matthews (2007) Biological Psychiatry
DMtS: Acute Challenge with methylphenidate
(including baseline for comparison)

% correct

Baseline ADHD
Baseline Control
Acute Placebo
Acute MPH 0.6 mg/kg

delay

sim 0 sec 4 sec 12 sec
Spatial Working Memory

between search errors

placebo  0.3mg/kg  0.6mg/kg

drug condition
So what does medication do?

• Stimulant medication improves symptoms in 70% of children

• Medication improves the ability to hold information in memory over a delay

• Executive function impairments still evident when children are medicated
DOES THE BASELINE COGNITIVE PROFILE HELP PREDICT RESPONSE TO TREATMENT?
Cognitive, sociodemographic and clinical predictors of methylphenidate response (Linear Regression)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Predictors of clinical response</th>
<th>Predictors of clinical response</th>
<th>Predictors of clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Reliable Change index” for Connors’ Global Index - Parent</td>
<td>Poor Baseline Short and Long Term Memory</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Restless/Impulsive Subscale</td>
<td>Poor Baseline Short and Long Term Memory</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>CPRS ADHD Subscale</td>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Emotional Lability Subscale</td>
<td>Poor Baseline Short and Long Term Memory</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>CPRS Cognitive Subscale</td>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Predictors of Clinical Response (Logistic Regression)</td>
<td>Low Dose Methylphenidate (0.3 mg/kg)</td>
<td>High Dose Methylphenidate (0.6 mg/kg)</td>
<td>Either or Both Doses of Methylphenidate (0.3 mg/kg or 0.6 mg/kg)</td>
</tr>
<tr>
<td>-----------------------------------------------------</td>
<td>--------------------------------------</td>
<td>----------------------------------------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Connors’ Global Index (Total Score)</td>
<td><strong>Poor Baseline Working Memory and Planning</strong></td>
<td>BPVS Percentile Rank</td>
<td>None</td>
</tr>
<tr>
<td>Connors’ Global Index (Restless/Impulsive subscale)</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Connors’ Global Index (Emotional Lability subscale)</td>
<td>Poor Baseline Working Memory and Planning, CPRS Cognitive Subscale</td>
<td>Poor Baseline Working Memory and Planning, CPRS Hyperactivity Subscale, BPVS Percentile Rank</td>
<td>Poor Baseline Working Memory and Planning, CPRS Cognitive Subscale</td>
</tr>
</tbody>
</table>

“Full Response” = T score ≤ 65 and Reliable change index > 1.96 on 10 item Connors’ Global Impact (Parent)
Genes → Environmental Factors → Brain Structure and Function → Cognition → Symptoms

Methylphenidate

IMPROVES

REDUCES
WM TRAINING CAN IMPROVE WM IN THOSE WITH WM DEFICITS AND WITH ADHD

Figure 1  Impact of training on working memory.

Holmes et al., 2009

Holmes et al., 2010
Interim SUMMARY

Does medication improve cognitive functioning? YES, but medication does not improve executive functions, it does improve short-and long-term memory

Can cognitive function predict clinical response to treatment? YES, poor baseline memory and executive functions can predict response to treatment
Talk Overview

3) Does cognitive impairment improve over time?
   - Does cognitive improvement predict clinical improvement?
Developmental theory (Halperin & Schulz)

- Development of executive functions across adolescence accounts for reduction in symptoms over time for those whose ADHD symptoms improve into adulthood

Executive Function improves = ADHD reduces
• Bedard et al. (2010) Halperin et al. (2008)

• Remission of ADHD was associated with superior executive functions

• No clinical measures available at follow up
  – Did remitters and non-remitters differ on executive functions?
Followed up ADHD and control boys 4 years later

N=17 each group (representative of larger group at Time 1 on clinical and neuropsychological measures)

Both cognitive and clinical measures at both time-points
Clinical Profile Time 2

• At Time 2 10/17 met criteria for ADHD
  - 3 combined type
  - 4 Inattentive type
  - 3 Hyperactive impulsive type

• Seven participants no longer met criteria for any form of ADHD
3) Does cognitive impairment improve over time?

YES

• Some aspects of cognitive function ‘catch up’
• Some improve but don’t ‘catch up’
• Some remain impaired
Some aspects of cognition ‘catch up’

• ADHD adolescents had ‘caught up’ with their peers on a number of long-term memory tasks
Some improve but don’t ‘catch up’

• ADHD adolescents improved but didn’t catch up with their peers on executive function tasks
Some aspects remain impaired

- ADHD adolescents remained impaired at Time 2 in delayed short-term memory (biggest deficit at Time 1)
- Also remained impaired in executive attention set-shifting
ADHD and Control

Spatial Working Memory

Set Shifting

Paired Associates Learning

Delayed Matching to Sample

Pattern Recognition

Spatial Recognition

Time 1  Time 2

ADHD  Control
3) Does cognitive impairment improve over time?

YES

• Some aspects of cognition ‘catch up’
• Some improve but don’t ‘catch up’
• Some remain impaired
Improvement over time

• Data suggests all participants improved over time

• ADHD children ‘catch-up’ with their peers on some measures – non executive aspects of cognitive function

• Baseline performance in attention set-shifting predicts clinical improvement

• Clinical improvement seems unrelated to improvements in executive functions and does not support Halperin and Schulz (2006)
DOES BASELINE COGNITIVE PROFILE PREDICT THE COURSE OF ADHD?
Is there an association between clinical change and neuropsychological performance at baseline (Time 1)?

Baseline performance on the **ID/ED set shifting task**, but not any of the other executive or non-executive tasks, was associated with greater total symptom reduction of between Times 1 & 2.
IS THERE AN ASSOCIATION BETWEEN COGNITIVE CHANGE AND CLINICAL CHANGE?
Is there an association between clinical change and change in neuropsychological performance between Times 1 and 2?

“Non-executive tasks”
Delayed Matching to Sample
(delayed short-term memory)

Improved performance on the Delayed Matching to Sample task was associated with a greater improvement in Total symptoms
Conclusions: ADHD and development

• Children with ADHD ‘catch-up’ on some cognitive aspects of functioning, but most areas show improvement rather than ‘catch-up’, some still impaired relative to peers

• Baseline attention set-shifting predicted clinical improvement 4 years later

• Clinical improvement seems unrelated to executive function improvements, again delayed short-term memory functioning is key
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