Determining Medication Treatment Response in ADHD: Does Neuropsychological Impairment Matter?

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What is ADHD?
“Cool” and “Hot” Brain Boss Circuits in Learning, Emotions, and Behaviour

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What is Attention?
“Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others, and is a condition which has a real opposite in the confused, dazed, scatterbrained state.”

Is this primary attention or executive function?
How do we separate cortical tone, primary attention, and executive attention?

Executive Function
Programming, Regulating, and Verifying Mental Activity

The Brain Manager
**Frontal-Subcortical Circuits:**
**Executive Control**

Decisions, Keeping track, Doing things quickly

Motor

Oculo-motor

Watching Things, Reading

Running, Drawing

Managing life, Completing Tasks, Writing

Controlling Own Emotions and Behaviour

Cingulate

Basal Ganglia/Thalamus

Dorsolateral Prefrontal Cortex

Caudate Nucleus

Globus Pallidus

Thalamus

Substantia Nigra

Planning, organizing, monitoring, evaluating, shifting, and modifying behaviour, including COGNITIVE response inhibition

Working memory, memory encoding, and retrieval
Orbital Circuit
“Hot” Executive Functions

Orbital Prefrontal Cortex

→ Behaviour regulation – EMOTIONAL response inhibition

→ Reward processing and theory of the mind-empathy (perception of emotional state more posterior)

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“Cool” and “Hot” Circuits and Psychopathology: The Search for Balance

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Frontal-Subcortical Circuits and Psychopathology: Are the Scales Tipped?

CHAPTER 11

Assessment and Intervention Practices for Children with ADHD and Other Frontal-Striatal Circuit Disorders

JAMES B. HALE, LINDA A. REDDY, GABRIELLE WILCOX, AMY MCCLAUGHLIN, LISA HAIN, AMY STERN, JULIE HENZEL, and ELEAZAR EUSEBIO

Most children referred for a school neuropsychological evaluation present with an attention problem, and when behavioral criteria are gathered by informant report, many will meet criteria for Attention Deficit Hyperactivity Disorder (ADHD). No longer considered just a “disruptive behavior disorder,” ADHD is now widely understood to be a frontal-subcortical circuit disorder (Castellanos et al., 2002), with affected brain regions potentially contributing to both cognitive and behavioral symptom expression (Voeller, 2001). Although this clarifies the nature and manifestation of ADHD, most frontal-subcortical circuit disorders lead to impaired attention (see Lichter & Cummings, 2001), suggesting differential diagnosis of ADHD can be difficult using only behavioral criteria (Hale, Fiorello, & Brown, 2005). In fact, the conflicting evidence regarding frontal-subcortical-executive causes of ADHD may be due to considerable population heterogeneity found when behavioral diagnostic criteria are used (Sonuga-Barke, Sergeant, Mogg, & Willcutt, 2006).

All Emotional and Behavioural Disorders Have Attention Problems!

Circuit Balance Theory

(Hale et al., 2009)

![Brain Manager Diagram]

Inattention/Distractibility  ➔  Inattention/Fixation

Impulsive Behavior  ➔  Repetitive Behavior

Hyperactivity  ➔  Hypoactivity

Circuit Underactivity  ➔  Circuit Overactivity

Regulation problem of cortical-subcortical circuits

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Balance Theory and Comorbidity

- Does one circuit problem lead to compensatory balance?
- Example: Anxiety comorbid with depression
- Decreased dorsolateral and increased amygdala in depression (Siegle et al., 2007)
- Increased orbital frontal, amygdala, and anterior cingulate in GAD (McClure et al., 2007)

→ Optimal Executive Function Requires Frontal-Subcortical Circuit Balance!

Emotional Executive Function and Self-Control
Orbital Prefrontal Circuit and Theory of Mind
Hale & Fitzer, 2015; Applied Neuropsychology: Child

• Theory of Mind – Taking the perspective of others (e.g., empathy)
• Is empathy about perception or action?
  → Parietal lobe and “mirror” neurons
  → Temporal lobe and face recognition
• But theory of mind linked to frontal systems
  → Pars opercularis and imitation
  → Medial orbital cortex and theory of mind
• Balancing orbital critical, too little or too much is a problem!
• Balancing perception and action in social relationships

Frontal-Subcortical Circuits and Psychosocial Functioning: An ALE Meta-analysis
(Lee et al., 2017)
“Cool” and “Hot” Frontal-Subcortical Circuits and Stimulant Response in ADHD

American Academy of Pediatrics
Standard of Care ADHD Medical Practice

1) Primary care physician evaluates any child with academic or behavioural problems and ADHD symptoms
2) ADHD diagnosis: DSM-V criteria, 2 settings, and multisource information
3) Coexisting conditions assessment
4) Treatment includes medications and/or evidence-based behavior therapy, both best
5) Titrate maximum medication dose with minimum adverse effects
Childhood’s Greatest “Behaviour Problem”: Persistent Academic Achievement Deficits

- ADHD is a neurodevelopmental disorder, but defined by behaviour?
- Are academic deficits the common problem in all types of attention problems?

**WHAT CAUSES ADHD ACADEMIC DEFICITS?**

- Poor Availability For Learning?
- Executive Deficits Impair Learning?

*Methylphenidate (MPH) Treatment and ADHD*

- MPH effective in 60 to 90% of children with ADHD
- Increases excitatory neurotransmitter dopamine (block DA reuptake to reduce frontal-striatal hypoactivity)
- Improves classroom behaviour and peer interactions, but not academic achievement over time
- Few serious side effects, but can cause “zombie effect”

→ Best dose for cognition appears to be **lower** than best dose for behavior in good responders

(see Arnsten & Pliszka, 2011; Berridge et al., 2006; Hale et al., 2011; Kubas et al., 2012)
Modeling the Frontal-Subcortical Circuits

Determining medication treatment effects using teacher ratings and classroom observations of children with ADHD: Does neuropsychological impairment matter?

James B. Hale, Catherine A. Fiorello & Lucy L. Brown

Abstract

Children with attention deficit hyperactivity disorder (ADHD) display developmentally inappropriate levels of attention, impulse control and motor activity that lead to both indirect and direct school-based difficulties (Landau & Horr, 1995). Diagnostic definitions differ for the disorder, with IC/10 and DSM-IV criteria the most commonly used (McKenzie & Worr, 2004), and symptoms vary in severity and pervasiveness across environments (Sheldon & Ball, 1995), but academic achievement difficulties (Hoshaw, 1999) and the substantial need for special educational needs placement (Hale, 2004) may also impact school outcomes. It remains unclear whether academic difficulties are due to neuropsychological deficits (Hale & Fiorello, 2004; Hale et al., 1998) and/or limited availability for learning (Silver, 1999). Although academic failure may be the final common pathway for many children with ADHD (Shaywitz & Shaywitz, 1986), psychostimulant medication has not been effective in improving academic outcomes for children with ADHD, despite demonstrating consistent behavioural treatment efficacy (AERA, 1995; Purdie et al., 2002; Schachter et al., 2001). Although stimulant medication is prescribed for a relatively high proportion of children with ADHD in the United States, use in the United Kingdom remains low (Hale, 2004), leading to both countries experiencing controversy about whether ADHD is under-, over- or mis-diagnosed.

Relevance of ADHD Executive Deficits and Medication Response: Cortical-Subcortical Circuit Confirmatory Factor Analysis


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Reconsidering “Inattention” in Attention-Deficit Hyperactivity Disorder: Implications for Neuropsychological Assessment and Intervention

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Attention-deficit hyperactivity disorder (ADHD) does not exist. This explicit statement needs clarification of course given ADHD is a common neurodevelopmental disorder, but it provides a timely reminder to re-examine long-held beliefs about this condition and its treatment. Surely, there is a disorder called ADHD from which this one condition should be excluded. But the ADHD label is often applied by health professionals in a wide range of medical, psychiatric, and educational fields, which can be seen as a product of multiple interrelated brain systems. Even in the eyes of scientific research, ADHD has a rather large proportion of people diagnosed. Therefore, there is no one cause or one cure for ADHD, and treatment should be individualized. The term ‘ADHD’ is not specific enough to describe every patient with the disorder, and it is not specific enough to describe every patient with ADHD. The term ‘ADHD’ is not specific enough to describe every patient with ADHD.
**Neuropsychological Tests and DSM-V Criteria Correlations**
Carmichael et al., 2015; *Applied Neuropsychology: Child*

<table>
<thead>
<tr>
<th>Measure</th>
<th>DSM-V Criteria</th>
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<tr>
<td>Inattention</td>
<td>Hyper-Impulsive</td>
</tr>
<tr>
<td>$r$ ($r^2$)</td>
<td>$r$ ($r^2$)</td>
</tr>
<tr>
<td>HDCT Correct</td>
<td>-.15 (0.021)</td>
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<tr>
<td>SRTM Consistent Retrieve</td>
<td>.03 (0.001)</td>
</tr>
<tr>
<td>Go-No Go</td>
<td>-.08 (0.006)</td>
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<tr>
<td>CPT Omissions</td>
<td>.17 (0.030)</td>
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<tr>
<td>CPT Commissions</td>
<td>.13 (0.018)</td>
</tr>
<tr>
<td>CPT Block Change</td>
<td>.19 (0.035)</td>
</tr>
<tr>
<td>Stroop Raw</td>
<td>-.17 (0.030)</td>
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<tr>
<td>Stroop Errors</td>
<td>.01 (0.000)</td>
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<tr>
<td>TMTB Time</td>
<td>.33 (0.106)</td>
</tr>
<tr>
<td>TMTB Errors</td>
<td>.41 (0.170)</td>
</tr>
<tr>
<td>Back Digits</td>
<td>.18 (0.031)</td>
</tr>
</tbody>
</table>

Low correlations between DSM-IV and neuropsychological measures, BUT

**Neuropsychological Data, DSM-V Criteria, and MPH Response**
(Carmichael et al., in press; *Applied Neuropsychology: Child*)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Cognitive Medication Response $r$ ($r^2$)</th>
<th>Behavioural Medication Response $r$ ($r^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-IV Inattention Ratings (Parent Report)</td>
<td>.09 (0.008)</td>
<td>.03 (0.000)</td>
</tr>
<tr>
<td>DSM-IV Hyperactivity-Impulsivity Ratings (Parent Report)</td>
<td>.30* (.090)</td>
<td>.25 (0.063)</td>
</tr>
<tr>
<td>Dorsolateral-Dorsal Cingulate “Cool” Circuit Functions Factor</td>
<td>.44** (.194)</td>
<td>.33* (.109)</td>
</tr>
<tr>
<td>Orbital-Ventral Cingulate “Hot” Circuit Functions Factor</td>
<td>.45** (.203)</td>
<td>.31* (.097)</td>
</tr>
</tbody>
</table>

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Differential ADHD Dose-Response Relationships

Executive Impairment Determines ADHD Medication Response: Implications for Academic Achievement

James B. Hale, Linda A. Reddy, Margaret Semrud-Clikeman, Lisa A. Hain, James Whitaker, Jessica Morley, Kyle Lawrence, Alex Smith, and Nicole Jones

Abstract

Methylphenidate (MPH) often ameliorates attention-deficit/hyperactivity disorder (ADHD) behavioral dysfunction according to indirect informant reports and rating scales. The standard of care behavioral MPH titration approach seldom includes direct neuropsychological or academic assessment data to determine treatment efficacy. Documenting “cool” executive-working memory (EWM) and “hot” self-regulation (SR) neuropsychological impairments could aid in differential diagnosis of ADHD subtypes and determining cognitive and academic MPH response. In this study, children aged 6 to 16 with ADHD inattentive type (IT, n = 19) and combined type (n = 33) hyperactive-impulsive type (n = 4) (CT) participated in double-blind placebo-controlled MPH trials with baseline and randomized placebo, low MPH dose, and high MPH dose conditions. EWM and behavior ratings/behavioral observations were ranked separately across conditions, with nonparametric randomization tests conducted to determine individual MPH response. Participants were subsequently grouped according to their level of “cool” EWM and “hot” SR circuit dysfunction. Robust cognitive and behavioral MPH response was achieved for children with significant baseline EWM and SR impairment, yet response was poor for those with adequate EWM and SR baseline performance. Even for strong MPH responders, the best dose for neuropsychological functioning was typically lower than the best dose for behavior. Findings offer one possible explanation for why long-term academic MPH treatment gains in ADHD have not been realized. Implications for academic achievement and medication titration practices for children with behaviorally diagnosed ADHD will be discussed.

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Moderate and Severe Frontal-Subcortical Impairment
And Statistical Medication Response

What Neuropsychological Functions Are Most Impaired on High Dose Stimulants? Working Memory

CLINICAL FOCUS: ADHD, DEPRESSION, PAIN, AND NEUROLOGICAL DISORDERS

The Effects of Methylphenidate on Cognitive Function in Children with Attention-Deficit/Hyperactivity Disorder

Abstract: Focusing on behavioral criteria for attention-deficit/hyperactivity disorder (ADHD) diagnosis leads to considerable neuropsychological profile heterogeneity among diagnosed children, as well as variable response to methylphenidate (MPH) treatment. Documenting “cold” executive working memory (EWM) or “hot” self-regulation (SR) neuropsychological impairments could aid in the differential diagnosis of ADHD subtypes and may help to determine the optimal MPH treatment dose. In this study, children with ADHD inattentive type (n = 19), combined type (n = 33), and hyperactive-impulsive type (n = 4) underwent randomized controlled MPH trials; neuropsychological, behavioral, and observational data were collected to evaluate the children’s responses. Those with moderate or significant baseline EWM or SR impairment showed robust MPH response, whereas response for those with lower baseline impairment was equivocal. Implications for medication use and titration, academic achievement, and long-term treatment efficacy are examined.

Keywords: attention-deficit/hyperactivity disorder; methylphenidate; frontal-subcortical circuits; executive function; achievement
Neuropsychological Impairment, Behavioural Diagnosis, and ADHD Medication Response

What Can A Busy Clinician Do? Use DSM-V, Behavioural Ratings, and Screen for Executive Deficits

Development and validation of an attention-deficit/hyperactivity disorder (ADHD) executive function and behavior rating screening battery

James B. Hale, Linda A. Reddy, Scott L. Decker, Rebecca Thompson, Julie Henzel, Annemarie Tedodi, Elizabeth Forrest, Eleazar Eusebio, and Martha Bridge Denckla

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3Georgia State University, Atlanta, GA, USA
4Temple University, Philadelphia, PA, USA
5Kennedy Krieger Institute, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Attention problems are ubiquitous in clinical practice, commonly found in many childhood learning and behavior disorders. Practitioners need cost- and time-effective methods for determining whether children have attention problems due to attention-deficit/hyperactivity disorder (ADHD) or numerous other conditions. This study examined the utility of a 13-minute ADHD screening battery designed to differentiate ADHD (including inattentive, IT, and combined, CT, subtypes), specific learning disability (SLD), and typical child samples. Results for the 368 children (age 6 to 12 years) revealed that the Trail Making Test–Part B (Time/Errors), Hale–Denckla Cancellation Test (Time/Correct), and Child Attention Profile (Inattention/Overactivity) teacher ratings discriminated between typical and ADHD groups (87% correct classification; sensitivity = .64; specificity = .92) and differentiated between IT, CT, and SLD groups (86% correct classification; IT sensitivity = .82, and specificity = .96; CT sensitivity = .84, and specificity = .82). Discriminant function and Bonferroni post hoc results revealed different neuropsychological and behavioral patterns among groups.
Double-Blind Placebo Biphentin Protocol

- Children diagnosed by physician and psychologist, consent, and random assignment
- Standard of Care control group = baseline, best dose, 6 months; open trial
- Experimental group = baseline, randomized placebo, low dose, high dose, best dose, 6 months, blinded trial
- Neuropsychological tests, academic tests, and parent/teacher behaviour ratings
- Data rank ordered across conditions with nonparametric randomization to judge response
- Graphic and statistical response reported to physician/parent for clinical decision-making
Drug Trial Example: Lisa

- 11 year, 7 month-old friendly and outgoing girl with love for adventure and being outdoors
- Academic and social concerns:
  - Inattentive, easily distracted, fidgety
  - Frequently off-task
  - Poor writing skills
  - Noncompliant behaviour
  - Limited social skills
- Comprehensive evaluation revealed Lisa had ADHD
- Pediatrician then referred Lisa to our medication trial

Lisa’s Neuropsychological Response to Stimulant Medication

<table>
<thead>
<tr>
<th>Subtest</th>
<th>Baseline No Medication</th>
<th>Week 2 Placebo</th>
<th>Week 1 10 mg</th>
<th>Week 3 20 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Auditory-Verbal Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WSRT Long-term Storage</td>
<td>72 (3)</td>
<td>73 (1.5)</td>
<td>73 (1.5)</td>
<td>65 (4)</td>
</tr>
<tr>
<td>WSRT Consistent LT Retrieval</td>
<td>72 (2)</td>
<td>56 (3)</td>
<td>73 (1)</td>
<td>39 (4)</td>
</tr>
<tr>
<td>WSRT LTS-CLTR Ratio</td>
<td>100% (1.5)</td>
<td>77% (3)</td>
<td>100% (1.5)</td>
<td>60% (4)</td>
</tr>
<tr>
<td>Go-No Go Correct (30 Possible)</td>
<td>25 (4)</td>
<td>28 (2.5)</td>
<td>28 (2.5)</td>
<td>30 (1)</td>
</tr>
<tr>
<td>WISC-IV-I Digit Span Backward</td>
<td>20 (4)</td>
<td>33 (1)</td>
<td>28 (2)</td>
<td>26 (3)</td>
</tr>
<tr>
<td>D-KEFS Inhibition Time</td>
<td>85&quot; (4)</td>
<td>66&quot; (3)</td>
<td>63&quot; (2)</td>
<td>52&quot; (1)</td>
</tr>
<tr>
<td>D-KEFS Inhibition # of Errors (raw)</td>
<td>8 (4)</td>
<td>2 (3)</td>
<td>1 (1.5)</td>
<td>1 (1.5)</td>
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<tr>
<td><strong>Visual-Motor Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hale-Denckla Cancellation (Correct)</td>
<td>26 (4)</td>
<td>30 (2)</td>
<td>30 (2)</td>
<td>30 (2)</td>
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<tr>
<td>Hale-Denckla Cancellation (Time)</td>
<td>87&quot; (2)</td>
<td>99&quot; (3)</td>
<td>71&quot; (1)</td>
<td>130&quot; (4)</td>
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<tr>
<td>WISC-IV-I Spatial Span Backward</td>
<td>43 (2)</td>
<td>23 (4)</td>
<td>28 (3)</td>
<td>44 (1)</td>
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<tr>
<td>Trail Making Test-Part B Errors</td>
<td>1 (3.5)</td>
<td>1 (3.5)</td>
<td>0 (1.5)</td>
<td>0 (1.5)</td>
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<td>Trail Making Test-Part B Time</td>
<td>30&quot; (3.5)</td>
<td>30&quot; (3.5)</td>
<td>19&quot; (1)</td>
<td>20&quot; (2)</td>
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<tr>
<td>CPT-II Omissions</td>
<td>47 (2)</td>
<td>49 (4)</td>
<td>47 (2)</td>
<td>47 (2)</td>
</tr>
<tr>
<td>CPT-II Commissions</td>
<td>50 (3)</td>
<td>49 (2)</td>
<td>47 (1)</td>
<td>56 (4)</td>
</tr>
<tr>
<td>CPT-II Reaction Time</td>
<td>57 (3)</td>
<td>58 (4)</td>
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<td>55 (1)</td>
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<tr>
<td>CPT-II Reaction Time Standard Error</td>
<td>47 (1)</td>
<td>55 (4)</td>
<td>48 (2)</td>
<td>49 (3)</td>
</tr>
<tr>
<td>CPT-II Hit Reaction Time Block Change</td>
<td>54 (4)</td>
<td>45 (2.5)</td>
<td>42 (1)</td>
<td>45 (2.5)</td>
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<tr>
<td>CPT-II Hit Reaction Time ISI Change</td>
<td>48 (3)</td>
<td>55 (4)</td>
<td>43 (1)</td>
<td>45 (2)</td>
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<tr>
<td><strong>AVERAGE COGNITIVE RANK</strong></td>
<td>2.97</td>
<td>2.97</td>
<td></td>
<td>2.42</td>
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Lisa's Behavioural Response to Stimulant Medication

### Parent Behavior Ratings

<table>
<thead>
<tr>
<th>Scale/Subscale</th>
<th>Baseline</th>
<th>Placebo</th>
<th>10 mg</th>
<th>20 mg</th>
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</thead>
<tbody>
<tr>
<td>BRIEF Inhibit</td>
<td>86 (3)</td>
<td>84 (2)</td>
<td>89 (4)</td>
<td>68 (1)</td>
</tr>
<tr>
<td>Emotional Control</td>
<td>83 (3)</td>
<td>85 (4)</td>
<td>71 (2)</td>
<td>61 (1)</td>
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<tr>
<td>Initiate</td>
<td>73 (2.5)</td>
<td>73 (2.5)</td>
<td>76 (4)</td>
<td>66 (1)</td>
</tr>
<tr>
<td>Working Memory</td>
<td>74 (2)</td>
<td>82 (3.5)</td>
<td>82 (3.5)</td>
<td>62 (1)</td>
</tr>
<tr>
<td>Plan/Organize</td>
<td>84 (4)</td>
<td>66 (2)</td>
<td>80 (3)</td>
<td>62 (1)</td>
</tr>
<tr>
<td>Organization of Materials</td>
<td>70 (3.5)</td>
<td>70 (3.5)</td>
<td>67 (2)</td>
<td>55 (1)</td>
</tr>
<tr>
<td>HSQR Number of Problems</td>
<td>9 (1.5)</td>
<td>13 (4)</td>
<td>9 (1.5)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Mean Severity</td>
<td>5.89 (3)</td>
<td>5.92 (4)</td>
<td>5.67 (2)</td>
<td>2.27 (1)</td>
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### Teacher Behaviour Ratings

<table>
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<th>Scale/Subscale</th>
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<th>Placebo</th>
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<th>20 mg</th>
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<tbody>
<tr>
<td>BRIEF Inhibit</td>
<td>53 (4)</td>
<td>49 (2.5)</td>
<td>49 (2.5)</td>
<td>45 (1)</td>
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<tr>
<td>Emotional Control</td>
<td>46 (2.5)</td>
<td>46 (2.5)</td>
<td>46 (2.5)</td>
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<tr>
<td>Initiate</td>
<td>65 (3.5)</td>
<td>58 (2)</td>
<td>65 (3.5)</td>
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<tr>
<td>Working Memory</td>
<td>60 (4)</td>
<td>61 (2)</td>
<td>65 (3)</td>
<td>54 (1)</td>
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<tr>
<td>Plan/Organize</td>
<td>70 (3.5)</td>
<td>58 (2)</td>
<td>70 (3.5)</td>
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<tr>
<td>Organization of Materials</td>
<td>69 (3)</td>
<td>69 (3)</td>
<td>57 (4)</td>
<td>69 (3)</td>
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<td>SSQR Number of Problems</td>
<td>3 (1.5)</td>
<td>2 (1.5)</td>
<td>3 (1.5)</td>
<td>2 (1.5)</td>
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<tr>
<td>Mean Severity</td>
<td>1.7 (3)</td>
<td>2.0 (4)</td>
<td>1.0 (1.5)</td>
<td>1.0 (1.5)</td>
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<td>APRS Learning</td>
<td>14 (4)</td>
<td>17 (1)</td>
<td>16 (2.5)</td>
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<td>Impulse Control</td>
<td>18 (3.5)</td>
<td>18 (3.5)</td>
<td>20 (1.5)</td>
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<tr>
<td>Academic Performance</td>
<td>21 (3.5)</td>
<td>21 (3.5)</td>
<td>24 (2)</td>
<td>25 (3)</td>
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<tr>
<td>Social Interest</td>
<td>16 (4)</td>
<td>18 (2)</td>
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</table>

<table>
<thead>
<tr>
<th>Classroom Observation - Restricted Academic Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAT Off Task</td>
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<tr>
<td>Fidgeting</td>
</tr>
<tr>
<td>Vocalization</td>
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<tr>
<td>Plays with Objects</td>
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<td>Out of Seat</td>
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### Classroom Observation - Restricted Academic Task

<table>
<thead>
<tr>
<th>Classroom Observation - Restricted Academic Task</th>
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<tbody>
<tr>
<td>RAT Off Task</td>
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<tr>
<td>Fidgeting</td>
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<tr>
<td>Vocalization</td>
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<td>Plays with Objects</td>
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<td>Out of Seat</td>
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### Average Behavioural Rank

- **Baseline:** 3.18
- **Placebo:** 2.78
- **10mg MPH:** 2.44
- **20mg MPH:** 1.60

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**Contrasting Lisa’s Neuropsychological and Behavioural Response to Stimulant Medication**

![Graph showing cognitive and behavioural response]

- **Note:** Lower Ranks = Better performance and behaviour.
- **Order of conditions =** Baseline, Low Dose, Placebo, High Dose

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Structure: Cortical Thickness/Regional Brain Volumes

Structure: Diffusion Tensor Imaging
Is Cognitive or Behavioural MPH Response More Relevant for Academic Achievement? fMRI Tasks

- *Momentary Incentive Delay Task* (Helfinstein, Kirwan, Benson, Hardin, Pine, Ernst, Fox)
- *Multi-Source Interference Task* (Bush, Shin)

Is “Dopamine Insufficiency” Insufficient? Neuropsychological Medication Response and Glutamate

- **Left Striatum**
  - Standard of Care: Behavioral Titration
  - Experimental Group: Neuropsychological Titration

- **Right Prefrontal**
  - Standard of Care: Behavioral Titration
  - Experimental Group: Neuropsychological Titration
Discussion

- Academic achievement deficits due to poor availability or executive deficits?
- Medication trials detect neuropsychological and behavioral response
- Children with executive impairment and ADHD-Combined Type show robust medication response
- Children with low impairment and ADHD-Inattentive Type less likely to respond
- Differential “brain boss” executive circuits could explain why best dose for cognition lower than best dose for behaviour
- Using combination of medicine and other interventions could optimize both academic and behavioural outcomes

Questions? Comments?

Were YOU paying attention? 😊

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