Biological Underpinnings of ADHD and the Progression over time

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The following short quiz consists of 4 questions and will tell whether you are qualified to be a professional.

The questions are not difficult.
1. How do you put a giraffe into a refrigerator

A. Open the door, put the giraffe in, close the door.

This question tests whether you tend to do simple things in an overly complicated way.
2. How do you put an elephant into a refrigerator?

A. Open the refrigerator, put in the elephant and close the refrigerator.
   Correct answer: Open the refrigerator, take out the giraffe, put in the elephant and close the door.

This tests your ability to think through the repercussions of your previous actions.
3. The Lion King is hosting an animal conference. All the animals attend except one. Which animal doesn't?

A. The elephant. He is in the refrigerator.

This tests your memory.

OK, even if you did not answer the first three questions correctly, you still have one more chance to show your true abilities.
4. There is a river you must cross. But it is inhabited by crocodiles. How do you manage it?

A. You swim across. All the crocodiles are attending the Lion King's Animal Meeting.

This tests whether you learn quickly from your mistakes.
• According to Anderson Consulting, around 90% of the professionals got all questions wrong.

• But many preschoolers got several correct answers.

• This disproves the theory that most professionals have the brains of a 4 year old.
Brain Development

Research has now determined that, contrary to long-held ideas that the brain was mostly fully "formed" by the end of childhood, considerable changes continue to take place through the second decade of life.
Fig. 1. Sequence of events in brain maturation.
OVERPRODUCTION AND PRUNING

Brain development occurs in 2 basic stages—growth spurts/overproduction of neurons and pruning.

Overproduction

3 critical phases: in utero 0-3 years 10-13 years

Results in significant increase in the number of neurons and synapses

Exuberant growth during these 3 phases gives the brain enormous potential

Pruning

These 3 critical phases are quickly followed by a process in which the brain prunes and organizes its neural pathways.
Learning

A process of creating and strengthening frequently used synapses the brain discards unused synapses and keeps only the most efficient and “strongest” synapses.

Children/teens need to understand that they decide which synapses flourish and which are pruned away.

How they use their time seems to be crucial to brain development since their activities guide the structure of the brain.

“USE IT OR LOSE IT”— Reading, sports, music, video games, x-box, hanging out—whatever a child/teen is doing—these determine which neural synapses will be retained.
Fig. 3. Total cerebral volume (TCV) by age for 224 females (375 scans) in red and 287 males (532 scans) in blue.
Fig. 1. Mixed-model regression plots at regions of interest over the cortical surface. The following regions were selected for analyses in each hemisphere: A, precentral gyrus and primary motor cortex; B, superior frontal gyrus, posterior end near central sulcus; C, inferior frontal gyrus, posterior end; D, inferior frontal sulcus, anterior end in the ventrolateral prefrontal cortex; E, inferior frontal sulcus in the dorsolateral prefrontal cortex; F, anterior limit of superior frontal sulcus; G, frontal pole; H, primary sensory cortex in postcentral gyrus; I, supramarginal gyrus (area 40); J, angular gyrus (area 39); K, occipital pole; L-N, anterior, middle, and posterior portions of STG; O-Q, anterior, middle, and posterior points along the inferior temporal gyrus anterior end. All quadratic, cubic, or linear terms were significant with $P < 0.05$. Age of peak GM is shown for B-D, I, and J. x-axis values are ages in years, and y-axis values show GM volumes.
Fig. 5. Frontal GM, parietal GM, and temporal GM volumes: 243 scans from 145 subjects (scans acquired at approximately 2-year intervals). The arrows indicate peak volume. (I need to remove the WM figure from this panel as I show it in Fig. 8. I am reacing these measures on the updated sample so that all will be consistent.)
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Elaboration of pyramidal cell dendritic arbor and dopamine inputs in postnatal development of the primate prefrontal cortex.
Red indicates more gray matter, blue less gray matter. Gray matter wanes in a back to front wave as the brain matures and neural connections are pruned. Areas performing more basic functions mature earlier; areas for higher-order functions (emotion, self-control) mature later. The prefrontal cortex, which handles reasoning and other "executive" functions, emerged late in evolution, and is among the last to mature.
Red indicates more gray matter, blue less gray matter. Gray matter wanes in a back to front wave as the brain matures and neural connections are pruned. Areas performing more basic functions mature earlier; areas for higher-order functions (emotion, self-control) mature later. The pre-frontal cortex, which handles reasoning and other "executive" functions, emerged late in evolution, and is among the last to mature.
ADHD is associated with delay in brain maturation

Maturation of the brain, as reflected in the age at which a cortex area attains peak thickness, in ADHD (above) and normal development (below). Lighter areas are thinner, darker areas...

Shaw et al PNAS (2007)
What causes ADHD?
What causes ADHD?
What causes ADHD?
What causes ADHD?
Faraone et al 2005

Heritability

Mean ADHD 0.76
## Significant pooled odds ratios for gene variants examined in three or more case-control or family-based studies

<table>
<thead>
<tr>
<th>Gene</th>
<th>Study Design</th>
<th>Pooled OR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Dopamine D4 Receptor (exon III VNTR, 7 repeat)</td>
<td>Family</td>
<td>1.16</td>
<td>1.03-1.31</td>
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<tr>
<td>Dopamine D4 Receptor (exon III VNTR, 7 repeat)</td>
<td>Case-control</td>
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<td>1.27-1.65</td>
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<td>Dopamine D5 Receptor (CA repeat, 148bp)</td>
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<td>1.12-1.38</td>
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<tr>
<td>Dopamine Transporter (VNTR, 10-repeat)</td>
<td>Family</td>
<td>1.13</td>
<td>1.03-1.24</td>
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<tr>
<td>Dopamine β-Hydroxylase (TaqI A)</td>
<td>Case-control</td>
<td>1.33</td>
<td>1.11-1.59</td>
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<tr>
<td>SNAP-25 (T1065G)</td>
<td>Family</td>
<td>1.19</td>
<td>1.03-1.38</td>
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<tr>
<td>Serotonin Transporter (5-HTLPRlong)</td>
<td>Case-control</td>
<td>1.31</td>
<td>1.09-1.59</td>
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<tr>
<td>Serotonin HTR1B Receptor (G861C)</td>
<td>Family</td>
<td>1.44</td>
<td>1.14-1.83</td>
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</tbody>
</table>

OR, odds ratio; CI confidence interval; VNTR, variable number of tandem repeats

Redrawn from (Faraone, Perlis, Doyle, Smoller, Goralnick, Holmgren, & Sklar 2005)
Environmental Factors

Genes -> Brain Structure and Function -> Cognition -> Symptoms
Potential Environmental Factors

- Low Birth Weight
- Prenatal Exposure to Alcohol
- Prenatal Exposure to Nicotine
- Pre and Postnatal Exposure to Heavy Metals
  - Lead
  - Mercury
  - Manganese
- Persistent Organic Pollutants
- Dietary Factors
  - Food Additives
  - Omega-3 fatty acid deficiency
- Organophosphate pesticides
- Serious psychological trauma or severe early deprivation
An example - Lead

• Although lead poisoning due to exposure has decreased considerably in many developed countries in recent years, high level exposure remains very common in children in developing countries.

• Also it has become clear over time that serious negative consequences can result from much lower levels of exposure to lead than had originally been thought.

• In fact it has not been possible to identify a safe lower limit for exposure to lead.
An example - Lead

There is evidence to suggest ADHD symptoms and cognitive deficits can be associated with exposures at low levels.

• Thomson and colleagues (1989) reported a dose relationship between blood lead levels and teacher rated hyperactivity in a general population sample of Edinburgh schoolchildren.

• Tuthill (1996) showed a dose response relationship between hair lead levels (from 1 – 11.3 parts per million) and both an AD-HKD diagnosis and teacher rated attention problems.

• More recently associations have been reported between low level lead exposure and a range of cognitive measures including
  – Impulse control
  – Reinforcement learning
  – The CANTAB measures of
    • spatial working memory
    • attention set shifting
    • planning
An example - Lead

- Nigg has calculated that if a two-fold risk of AD-HKD was associated with lead levels above 5mcg/dl
- Low level lead exposure would account for 25% of the cases of ADHD in the United States
- Even a more conservative increase in risk of between 25-50% would still account for between 6 and 12% of cases

These cases would of course be potentially preventable!
Gene – environment interactions and correlations

Genes → Brain Structure and Function → Cognition → Symptoms → Environmental Factors
Gene-environment interactions (GxE)

Occur when there is a genetic sensitivity to a particular environmental effect or when an environmental factor activates a genetic effect that would otherwise remain dormant.

Dopamine transporter gene and psychosocial adversity on ADHD among 15-year-olds from a community sample

Laucht M et al. Arch Gen Psychiatry 2007; 64: 585–590
Gene-environment correlations

This takes into account the fact that parents pass on both genes and environment to their children and that these two factors are often correlated with each other making their impact on the child difficult to separate.

• “Passive”
  • Parents pass on both genes and environment to their children
  • e.g. the children of intelligent parents are likely to receive both the genes associated with higher intellectual abilities and an environment conducive to learning

• “Evocative”
  • Child’s genetic makeup leads to them eliciting a particular type of response from others thus creating a particular type of environment around themselves
  • e.g. a loud demanding child is likely to elicit more negative responses from others than a more passive quiet child

• “Active”
  • Individuals select their environments according to their temperaments
  • e.g. the impulsive, risk-taking child may be drawn to a more risk-taking peer group and therefore be exposed to more dangerous situations than would the more fearful child
Brain – Structural Differences

Valera et al. (2007) meta-analysis of structural imaging studies in ADHD.

Global reductions for the ADHD subjects compared to normal controls (SMD 0.408, p < 0.001).

Differences Supported in 3+ studies
- Total and right cerebral volume
- Cerebellum including vermis,
- Corpus callosum
- Right caudate

Large differences but reported in < 3 studies
- Frontal lobes,
- Prefrontal cortex
- Deep frontal white matter (total and right and left).
- Temporal lobe
AETIOLOGY

Neuroanatomy – total brain volume

Controls > ADHD \( P < 0.003 \)

Castellanos et al 2002
AETIOLOGY

Neuroanatomy – caudate volume

Controls > ADHD, p<0.05
Interaction with age, p<0.05

Castellanos et al. 2002
AETIOLOGY

Neuroanatomy – cerebellar volume

Controls > ADHD, p<0.001;
Adjusted, p=0.003

Castellanos et al 2002
Volume of caudate and DAT1 10-repeat

Volume of frontal grey and DRD4 4-repeat

Diffusion Tensor Imaging

An imaging technique that looks at connectivity between brain regions

Left Hemisphere

Right Hemisphere
Recent studies demonstrate a consistent pattern of frontal hypofunction, altered activity patterns in the anterior cingulate, prefrontal cortices, and the associated parietal, striatal, and cerebellar regions.

Task: Go/NoGo

Epstein et al. 2007
Brain – Functional Differences

Visuospatial Processing
 Allocation of Conscious
 Attentional Resources

Executive Functions:
 Regulation of Attention and Behaviour
 by representational Knowledge

Processing and Recognition of
 Visual and Auditory Features

"Gyroscope"
 for Movement and Thought?

a The basal ganglia circuits are not shown in this view. They are however thought to contribute to the automatic planning, selection, initiation and execution of complex movements and thoughts.
Electrophysiology

Taken together the EEG and ERP research in ADHD suggests that there are multiple activation deficits in the posterior and anterior attention networks which occur within a sub-second range and which causally precede either inhibitory or executive control.
ADHD and Attention

- A meta-analysis of studies investigating attentional processes in ADHD concluded that there is no evidence for a deficit of either reflexive or sustained attention in ADHD (Huang-Pollock & Nigg 2003).
Weighted mean effect size of the difference between groups with and without ADHD (Willcutt et al 2008)
Neuropsychological Functions

- Executive functioning ("Cognitive control")
  - Control of motor response and behaviour ("Inhibition")
  - Working memory
  - Planning / organization
  - State regulation / activation
  - Set shifting
- Non executive memory processes
- Motivation (Including delay aversion)
- Response speed / variability
Weighted mean effect size of the difference between groups with and without ADHD (Willcutt et al 2008)
Executive functioning ("Cognitive control")

- Control of motor response and behaviour ("Inhibition")
- Working memory
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- Set shifting
A “single cause” model of ADHD

Genetic factors

Dopaminergic and Noradrenergic abnormalities in Fronto / striatal pathways

Behavioural Inhibition deficits

Broader Executive Dysfunction

ADHD Symptoms

Biological

Cognitive

Behaviour
Go Signal X
Stop Signal 0
Stop Signal Reaction Time
Weighted mean effect size of the difference between groups with and without ADHD
Weighted mean effect size of the difference between groups with and without ADHD

- IQ/academic achievement
  - Full scale IQ (137)
  - Reading achievement (85)
  - Math achievement (57)
  - Spelling achievement (23)

- Executive functions
  - Response inhibition (58)
  - Working memory (28)
  - Set shifting (31)
  - Planning (31)
  - Fluency (12)
  - Interference control (16)
  - Vigilance (35)
  - Time reproduction (5)

- Delay aversion
  - Maudsley delay aversion (4)
  - Choice delay task (6)

- Response speed/variability
  - Reaction time (26)
  - Motor speed (18)
  - Naming speed (20)
  - Response variability (18)
Why is working memory important?

• Verbal and spatial abilities – national curriculum assessments

• Verbal – literacy

• Spatial – mathematics and science
Spatial Working Memory

![Graph showing the relationship between search errors and difficulty level for ADHD and Control groups. The graph indicates a higher number of search errors as the difficulty level increases.](image)
• working memory were not dependent on inhibitory deficits
• Therefore these may represent different pathways
CORRECT
DMTS: ADHD vs Control (Drug Naive)

DMtS: Controls Vs. DAT

Redrawn from - Sahakian et al. (1988) Brain, 111, 695-718
Possibly?

Genetic factors

Dopaminergic and Noradrenergic abnormalities in Fronto / striatal pathways

Behavioural Inhibition deficits

Working Memory Deficits

Non-Working Memory Deficits

ADHD Symptoms
Genetic factors

Dopaminergic and Noradrenergic abnormalities in Fronto/striatal pathways

Behavioural Inhibition deficits

ADHD Symptoms

Non-Working Memory Deficits

Working Memory Deficits

Or ?
Spatial – maintaining information
Spatial – manipulating information
Spatial Tasks - Results

% correct

Spatial Maintenance  Spatial Manipulation

ADHD  Typically Developing
Spatial Loads - Results

The graph shows the percentage of correct responses as a function of memory load for two groups: ADHD and Typically Developing. As the memory load increases from 1 to 7 items, the percentage of correct responses decreases for both groups. However, the ADHD group consistently performs at a lower percentage of correct responses compared to the Typically Developing group, indicating a greater impact of memory load on their performance. The error bars indicate the variability in the data.
Executive functioning ("Cognitive control")

- Control of motor response and behaviour ("Inhibition")
- Working memory
- Planning / organization
- State regulation / activation
- Set shifting
Weighted mean effect size of the difference between groups with and without ADHD
Neuropsychological Functions

- Attention and arousal
- Executive functioning (“Cognitive control”)
  - Control of motor response and behaviour (“Inhibition”)
  - Working memory
  - Planning / organization
  - State regulation / activation
  - Set shifting
- Non executive memory processes
- Motivation (Including delay aversion)
- Response speed / variability
Weighted mean effect size of the difference between groups with and without ADHD

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Weighted mean effect size ($d_w$)
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
DUAL PATHWAY MODEL (REVISED)

SEVERE EARLY DEPRIVATION → MESO-LIMBIC REWARD CIRCUITS → SHORTENED DELAY GRADIENT → DELAY AVERSION → HYP/IMP

CULTURAL DELAY RELATED DEMANDS → MESO-LIMBIC REWARD CIRCUITS

MESO-CORTICAL CONTROL CIRCUITS → INHIBITORY DYSFUNCTION → EXECUTIVE DYSFUNCTION

IA

DISRUPTED TASK ENGAGEMENT

SEVERE EARLY DEPRIVATION

DAT1 D2 D1 ? ?
Weighted mean effect size of the difference between groups with and without ADHD
<table>
<thead>
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<th>Hyperkinetic disorder vs controls effect size (d)</th>
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<tr>
<td>Spatial Working Memory</td>
</tr>
<tr>
<td>• BSE</td>
</tr>
<tr>
<td>• Strategy</td>
</tr>
<tr>
<td>Tower of London (Planning, working memory)</td>
</tr>
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<tr>
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<tr>
<td>Delayed Matching to Sample</td>
</tr>
<tr>
<td>Pattern Recognition</td>
</tr>
<tr>
<td>Spatial Recognition</td>
</tr>
<tr>
<td>PAL</td>
</tr>
<tr>
<td>• Tot errors</td>
</tr>
<tr>
<td>• Tot trials</td>
</tr>
<tr>
<td>Reaction Time</td>
</tr>
</tbody>
</table>

Rhodes, Coghill & Matthews (2005) Psychological Medicine
<table>
<thead>
<tr>
<th>Hyperkinetic disorder vs controls effect size (d)</th>
<th>Proportion ADHD cases with deficit (%)</th>
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<tbody>
<tr>
<td><strong>Spatial Working Memory</strong></td>
<td></td>
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<tr>
<td>• BSE</td>
<td>0.75</td>
</tr>
<tr>
<td>• Strategy</td>
<td>0.70</td>
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<tr>
<td><strong>Tower of London (Planning, working memory)</strong></td>
<td>0.38</td>
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<tr>
<td><strong>ID/ED Attentional Set Shifting</strong></td>
<td>0.46</td>
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<td><strong>Spatial Span</strong></td>
<td>0.60</td>
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<td>0.92</td>
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<td><strong>Pattern Recognition</strong></td>
<td>0.89</td>
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<tr>
<td><strong>Spatial Recognition</strong></td>
<td>0.72</td>
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<tr>
<td><strong>PAL</strong></td>
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<tr>
<td>• Tot errors</td>
<td>0.47</td>
</tr>
<tr>
<td>• Tot trials</td>
<td>0.58</td>
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<tr>
<td><strong>Reaction Time</strong></td>
<td>0.71</td>
</tr>
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<td><strong>Proportion ADHD cases with deficit (%)</strong></td>
<td></td>
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</table>
Variability of neuropsychological deficits in hyperkinetic disorder

![Bar chart showing the variability of neuropsychological deficits in hyperkinetic disorder. The x-axis represents the number of tasks, ranging from 0 to 8, and the y-axis represents the percent. The highest bar corresponds to 0 tasks, indicating the highest percentage.](chart.png)
There is considerable heterogeneity of neuropsychological deficits in ADHD

- The relationships between the different deficits is unclear
- None of the deficits identified so far seem to be sufficient to “cause” ADHD on their own
- The number of pathways to ADHD is unclear
- Some children with ADHD appear to have no discernable neuropsychological deficit
Do these neuropsychological deficits respond to treatment with stimulants?

If medication effective in the treatment of ADHD would expect it to improve performance on the task

And for any reduction in symptoms to be related to this improvement in task performance.
DMTS: ADHD vs Control (Drug Naive)

DMtS: Acute Challenge with methylphenidate
(including baseline for comparison)

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>Effect of chronic methylphenidate</th>
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</thead>
<tbody>
<tr>
<td>Spatial Working Memory</td>
<td>No significant effect of MPH on any measure</td>
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<tr>
<td>Stockings of Cambridge</td>
<td>No significant effect of MPH on any measure</td>
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<tr>
<td>ID/ED (attentional set-shifting)</td>
<td>No significant effect of MPH on any measure</td>
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<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>

Coghll, Rhodes & Matthews (2007) Biological Psychiatry
ADHD: Impact of Untreated & Undertreated ADHD continues through adolescence and into adulthood

**Healthcare System**
- 50% ↑ in bike accidents¹
- 33% ↑ in ER visits²
- 2–4 x more motor vehicle crashes³-⁵

**School & Occupation**
- 46% expelled⁶
- 35% drop out⁶
- Lower occupational status⁷

**Society**
- Substance use disorders:
  - 2 x risk⁸
  - Earlier onset⁹
  - Less likely to quit in adulthood¹⁰

**Family**
- 3–5 x ↑ parental divorce or separation¹¹,¹²
- 2–4 x ↑ sibling fights¹³

**Employer**
- ↑ parental absenteeism and productivity¹⁴

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³NHTSA, 1997.  
¹³Mash & Johnston, 1983.  
Patterns of ADHD across development

- Syndromatic
- Symptomatic
- Functional

% Remitted vs Age (year)
Patterns of ADHD across development

- Functional
- Remission

Age-Dependant Decline of ADHD: Another Look
The development of cognitive abilities in ADHD

Stockings of Cambridge - Problems Solved in Minimum Moves

Spatial Working Memory - Between Search Errors

Delayed Matching to Sample - Total Delays
The development of Spatial Working Memory in ADHD

**Between Search Errors**
- Effect of age
- No effect group
- No interaction

**Strategy Score**
- Effect of age
- Effect of group
- Interaction between age and group

Mean Age at T1 ≈ 10 years, Mean age at T2 ≈ 14 years
The development of other neuropsychological functions in ADHD

ID / ED Shift

Spatial Recognition

DMtS total delays

Pattern Recognition (no interaction)
Summary

- Children with ADHD exhibit a wide range of genetic, brain and neuropsychological differences.
- None of the simple single deficit models are likely to be sufficient to explain the causality of ADHD.
- Complex multiple models are much more likely.
- Whilst we are starting to see studies across different frames of reference further well controlled investigation into the relationship between symptoms, neuropsychological deficits. Pathophysiology and genetic and environmental causative agents are required.
- ADHD is a persistent disorder that often continues through into adulthood.
- Preliminary evidence suggests that the neuropsychological deficits are also persistent.