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.

Wrong answer!

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.

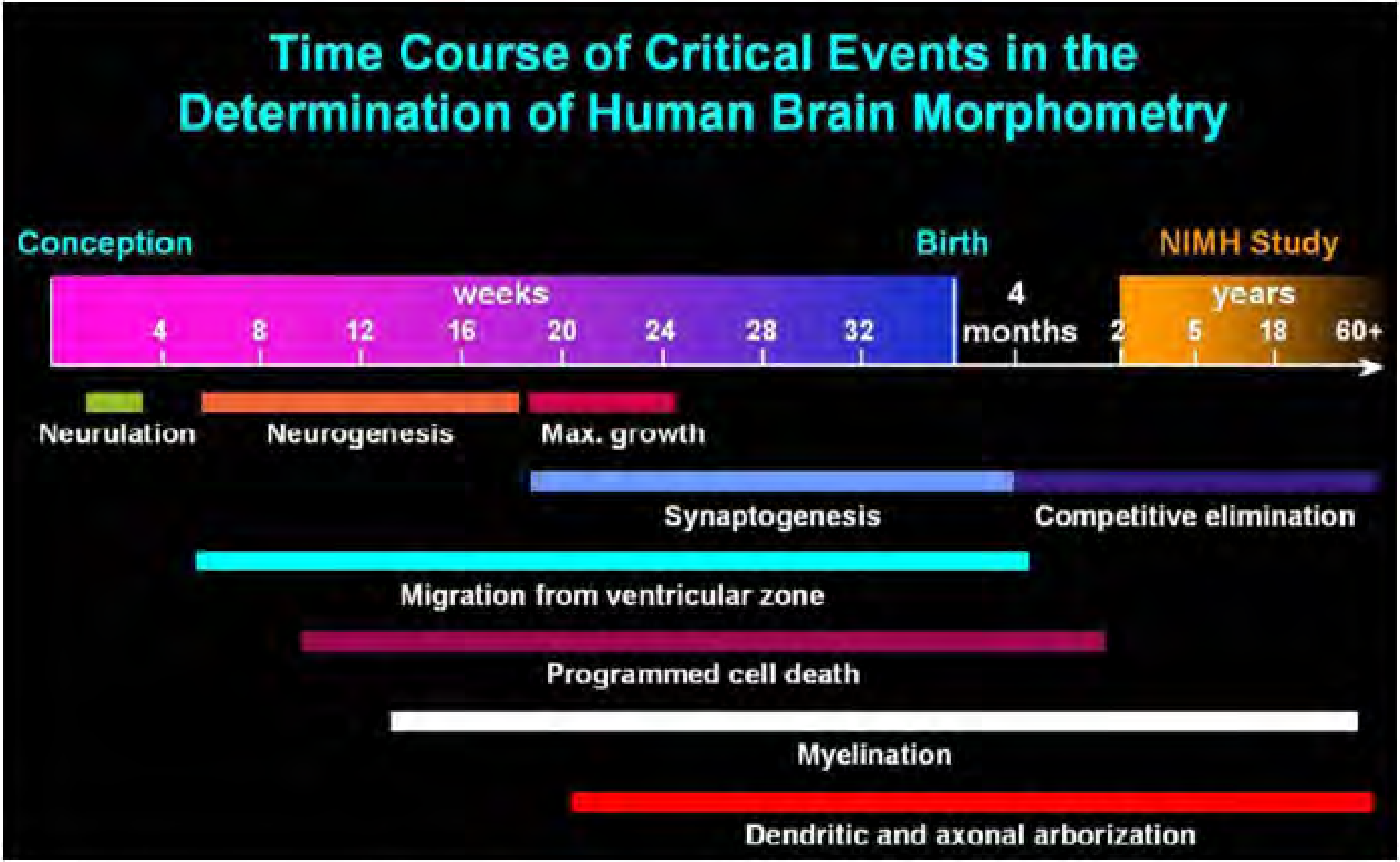


Fig. 1. Sequence of events in brain maturation.

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

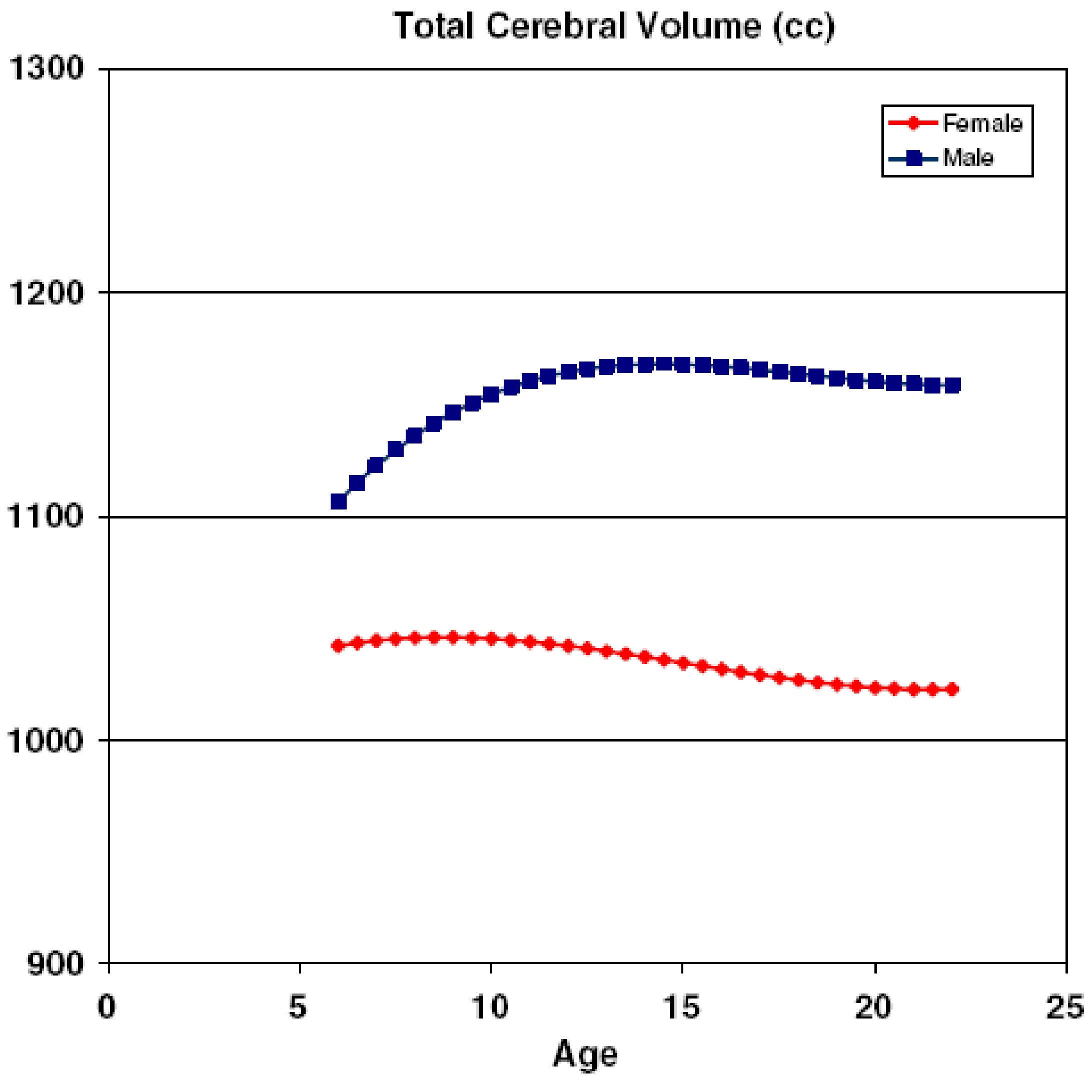


Fig. 3. Total cerebral volume (TCV) by age for 224 females (375 scans) in red and 287 males (532 scans) in blue.

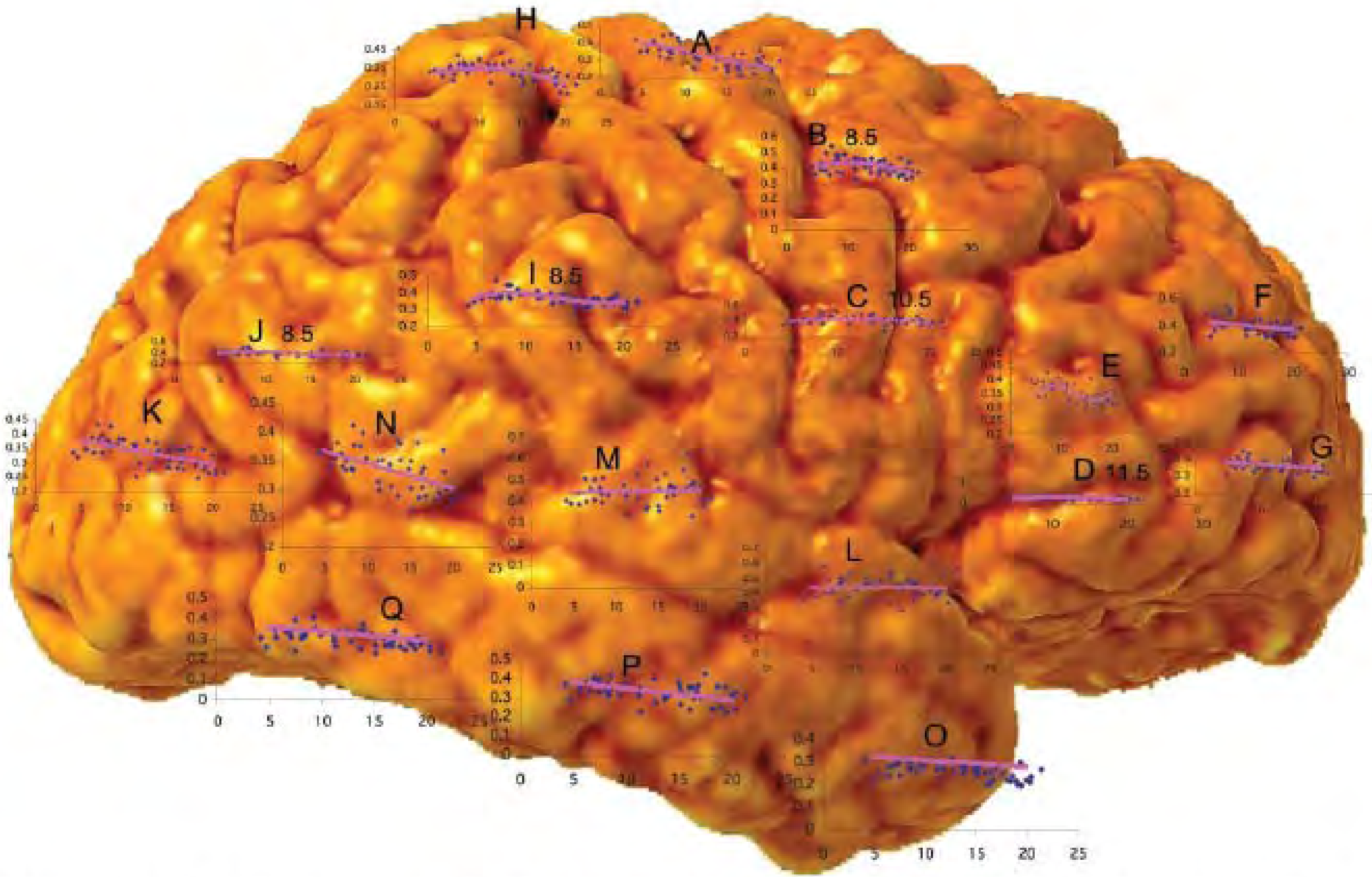


Fig. 1. Mixed-model regression plots at regions of interest over the cortical surface. The following regions were selected for analyses in each hemisphere: A, precentral gyrus and primary motor cortex; B, superior frontal gyrus, posterior end near central sulcus; C, inferior frontal gyrus, posterior 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.

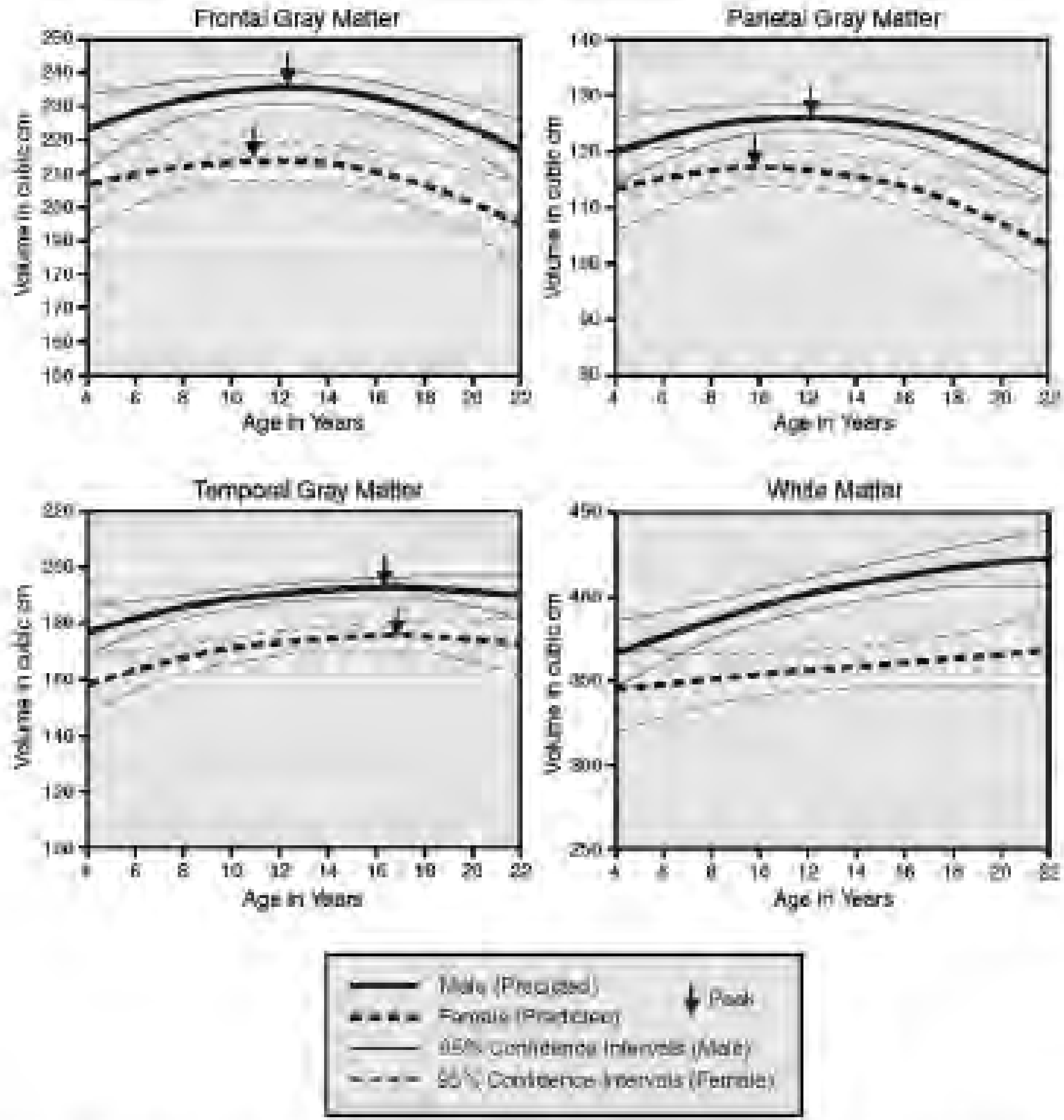
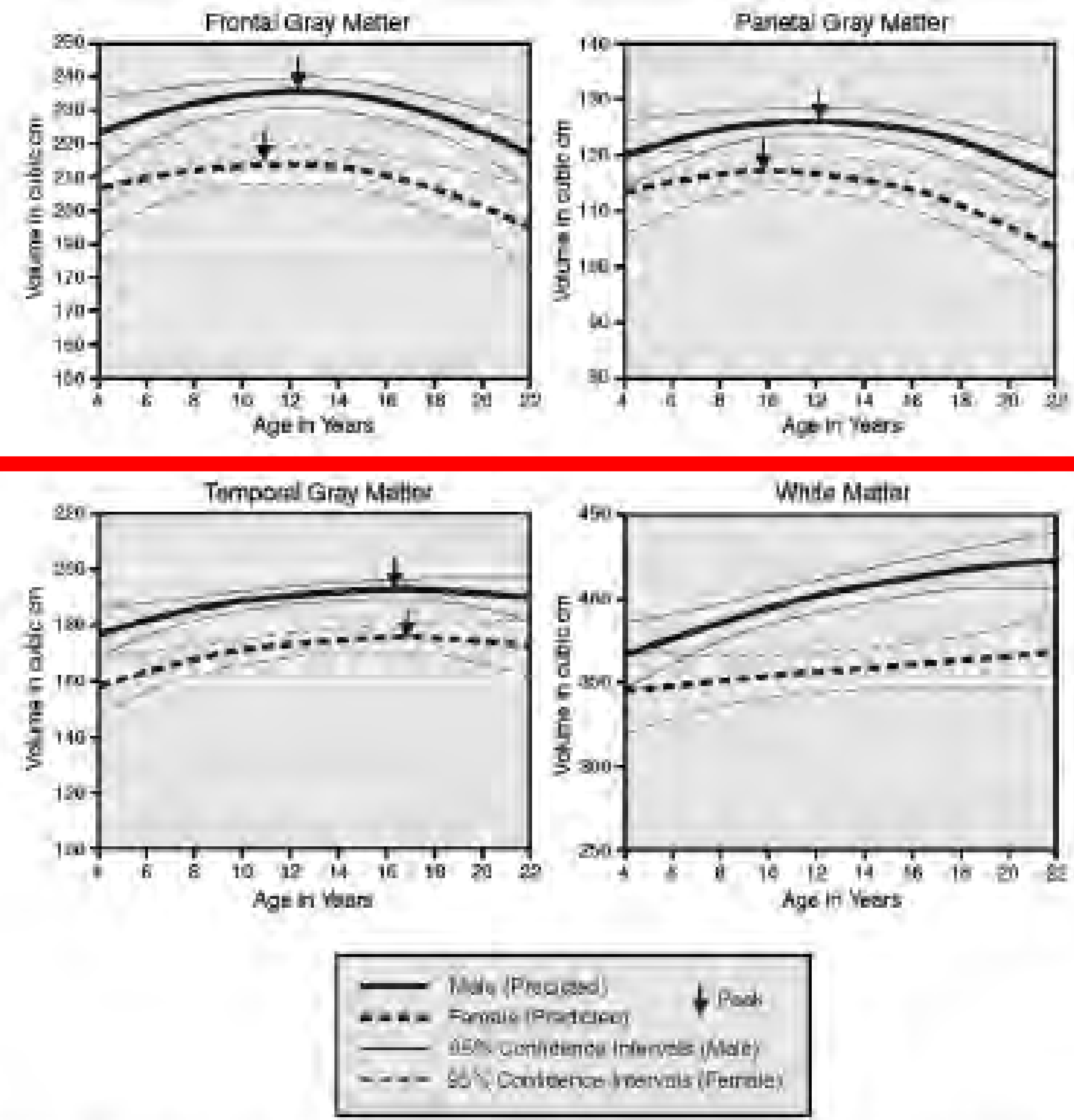


Fig. 5. Frontal GM, parietal GM, and temporal GM volumes: 243 scans from 145 subjects (scans acquired at approximately 2-year intervals). The arrows indicate peak volume. (I need to remove the WM figure from this panel as I show it in Fig. 8. I am rerunning these measures on the updated sample so that all will be consistent.)



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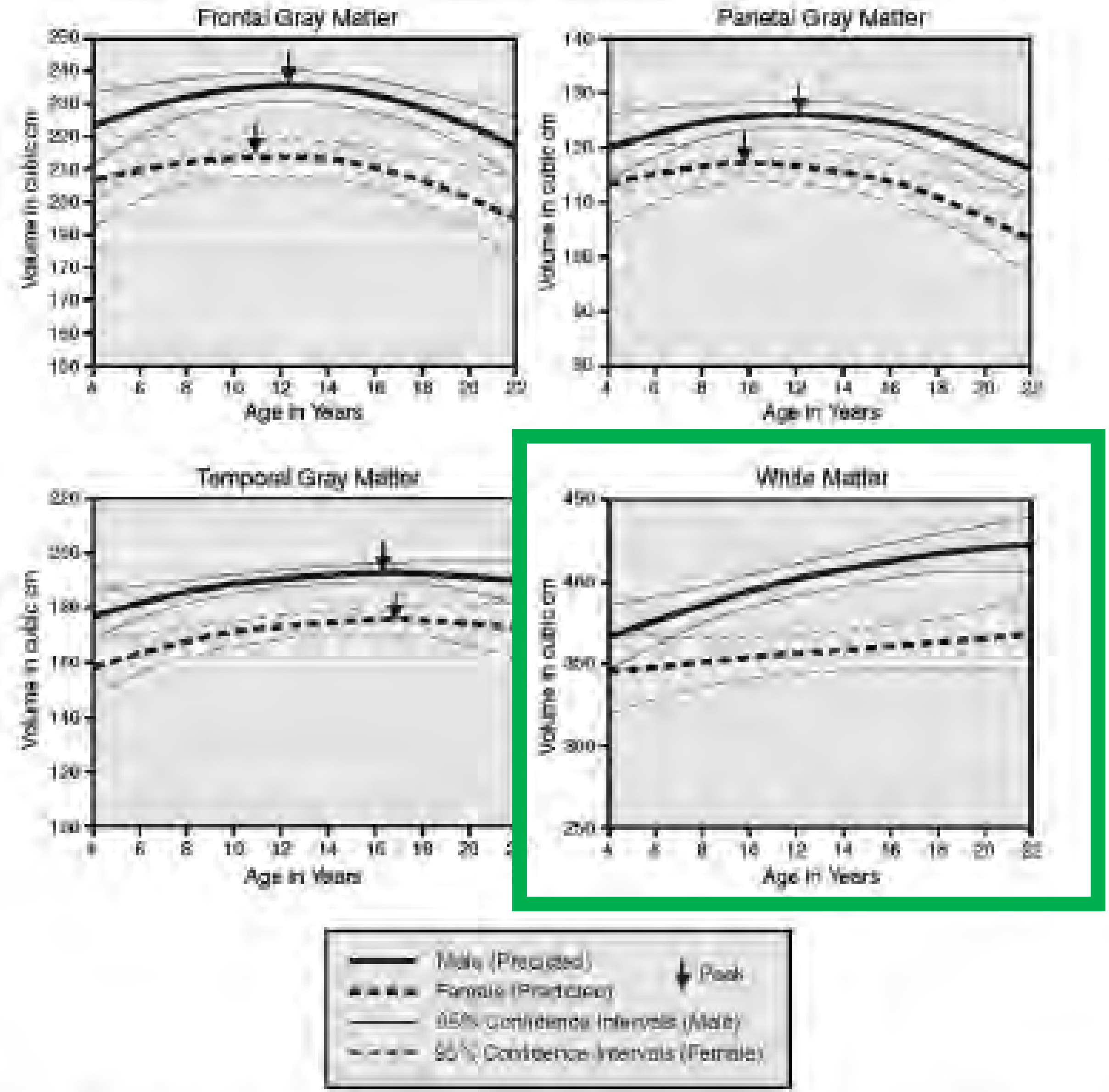

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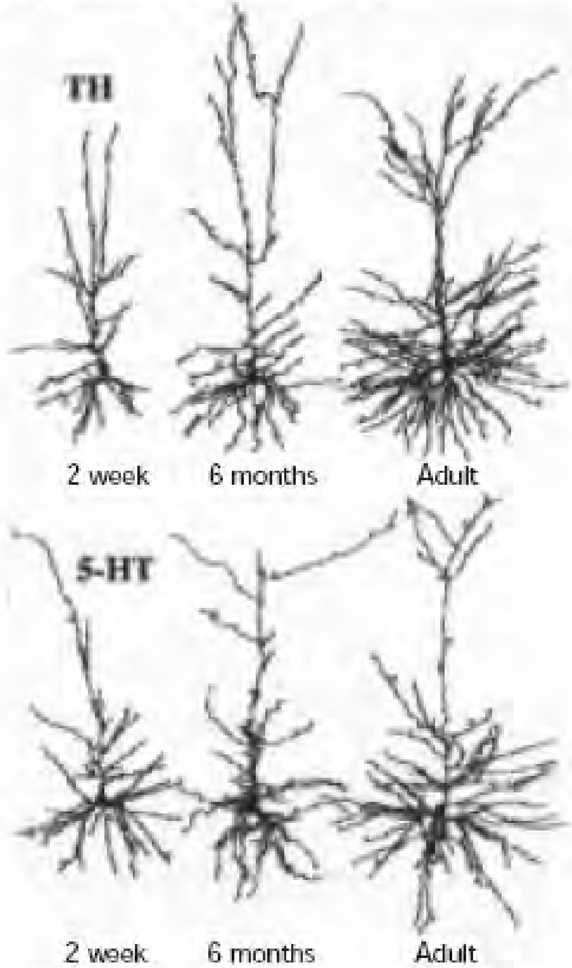
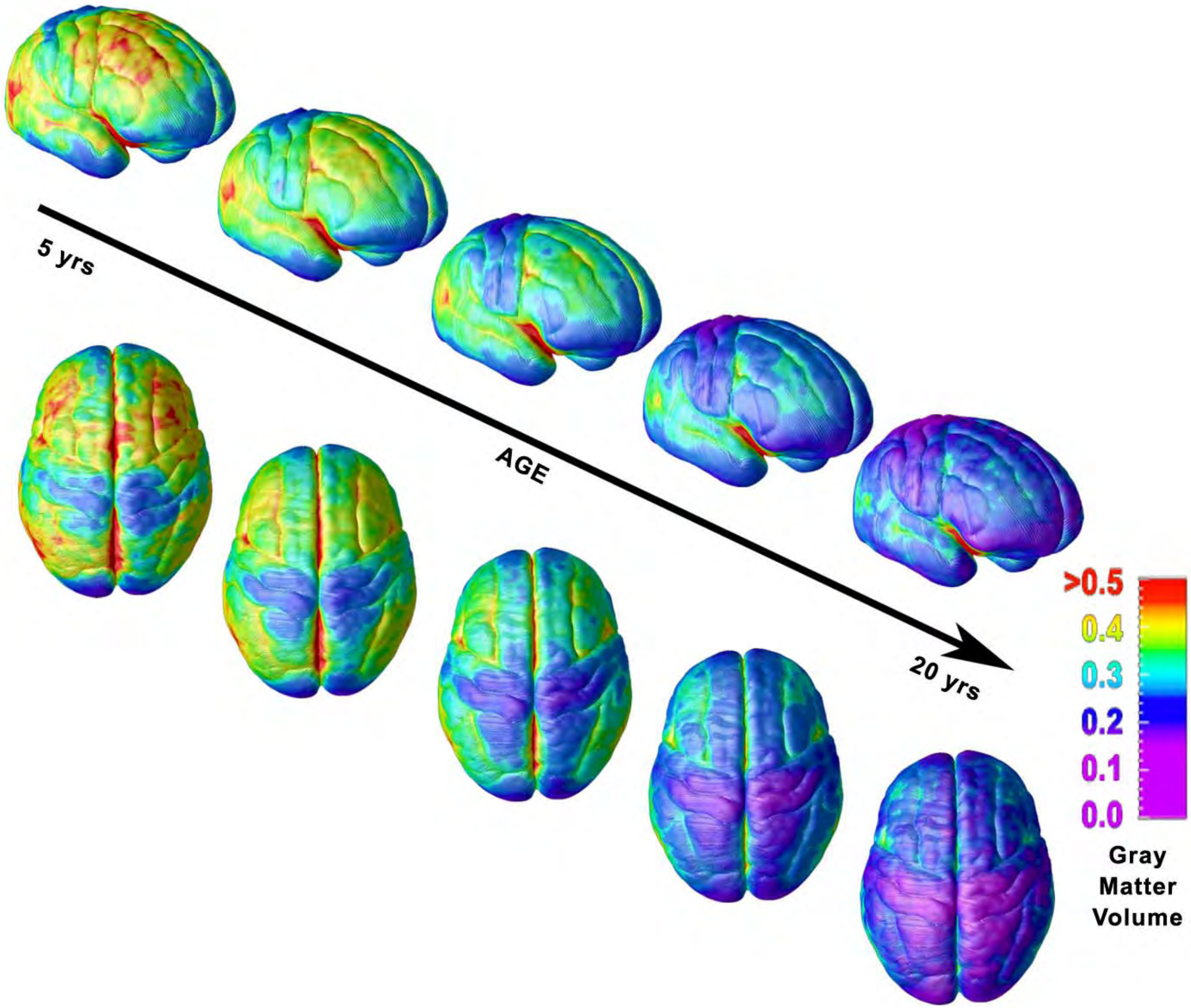
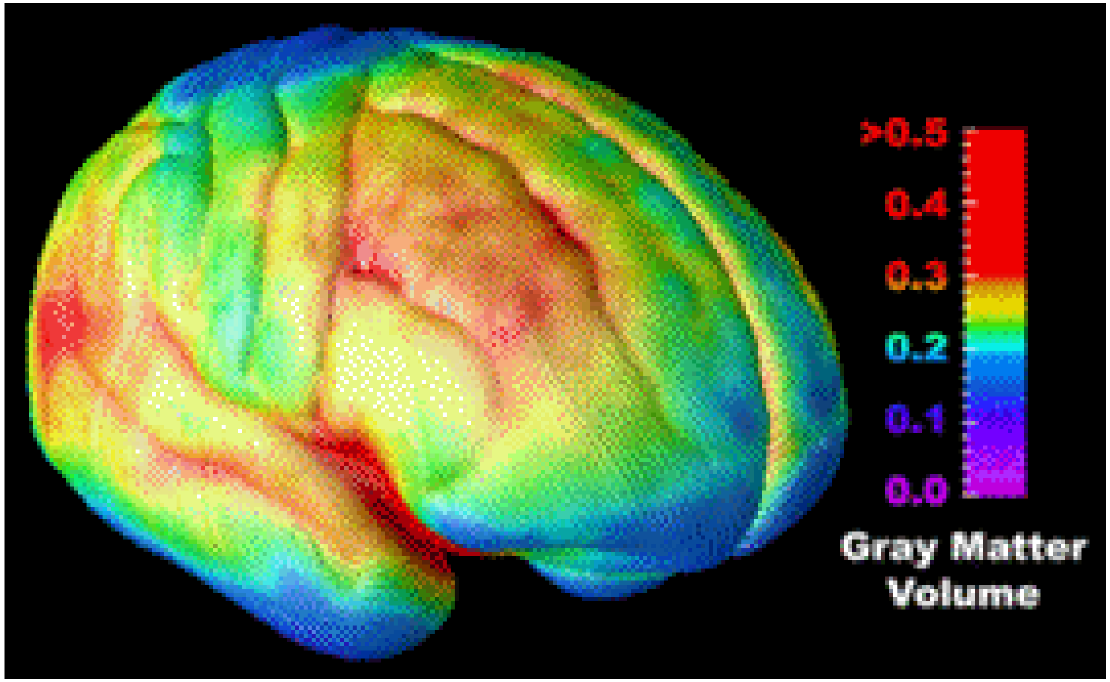
Figure 2

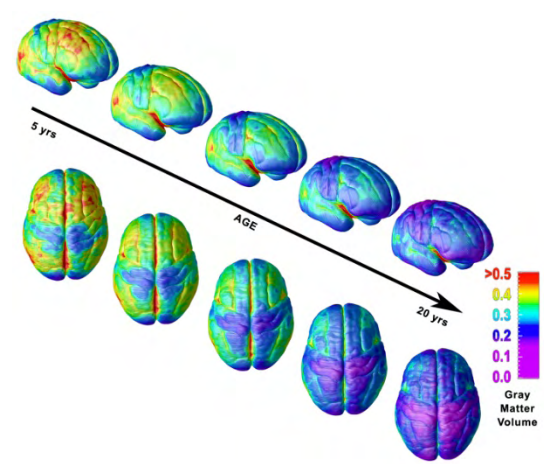
Elaboration of pyramidal cell dendritic arbor and dopamine inputs in postnatal development of the primate prefrontal cortex.

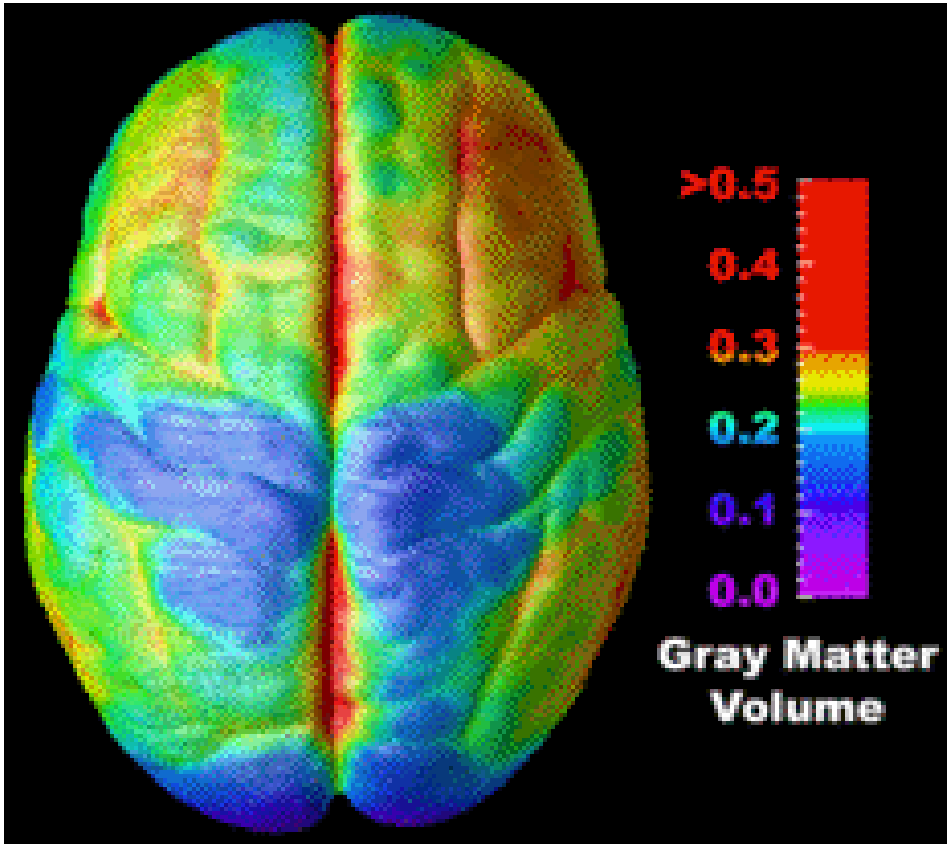



5 yrs
AGE
20 yrs
>0.5
0.4
0.3
0.2
0.1
0.0
Gray
Matter
Volume



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 perrforming 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.





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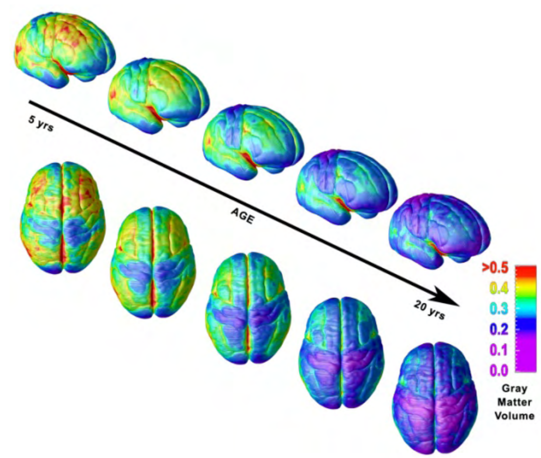
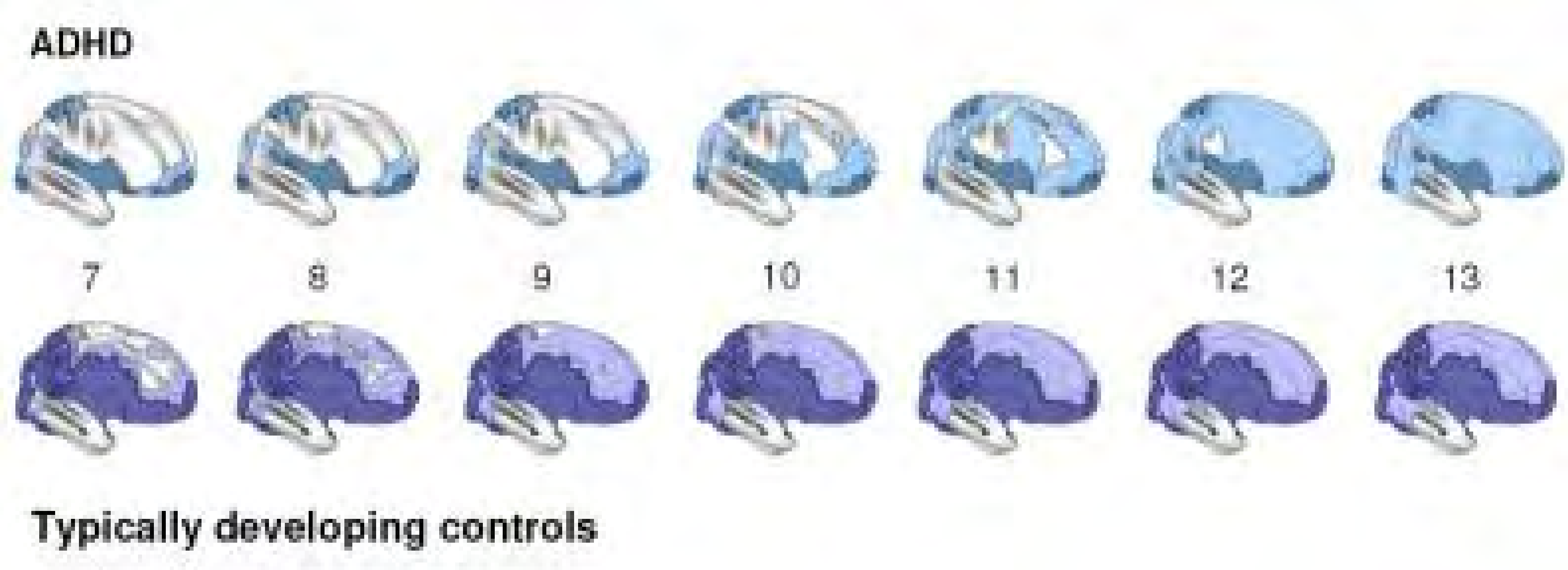


ADHD is associated with delay in brain maturation



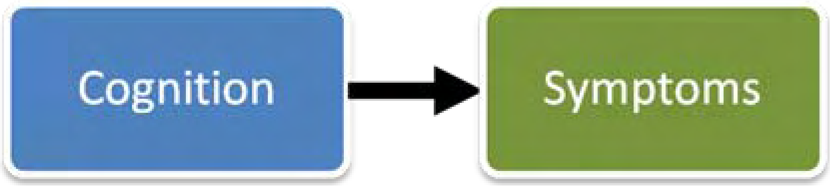
Maturation of the brain, as reflected in the age at which a cortex area attains peak thickness, in ADHD (above) and normal development (below). Lighter areas are thinner, darker areas...

Shaw et al PNAS (2007)

Environmental Factors

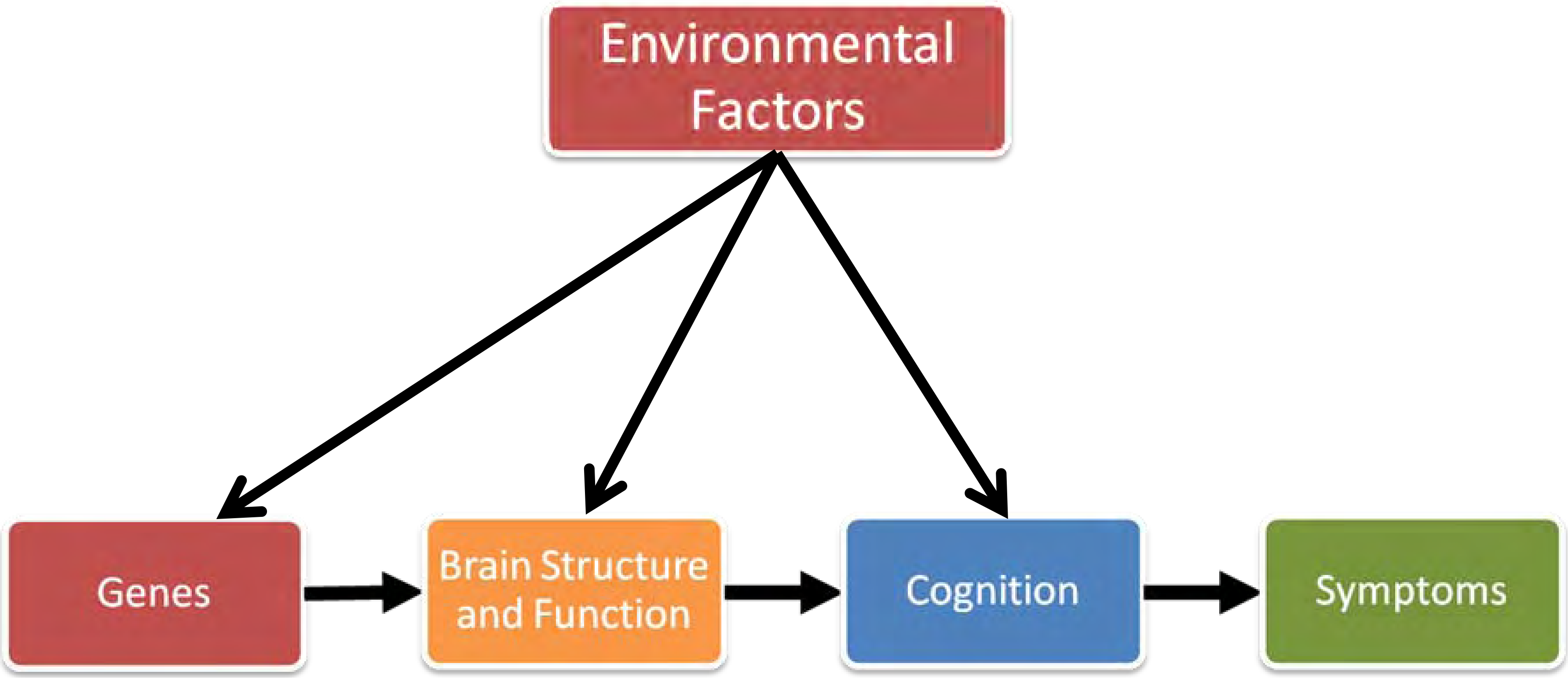
Symptoms

What causes ADHD?



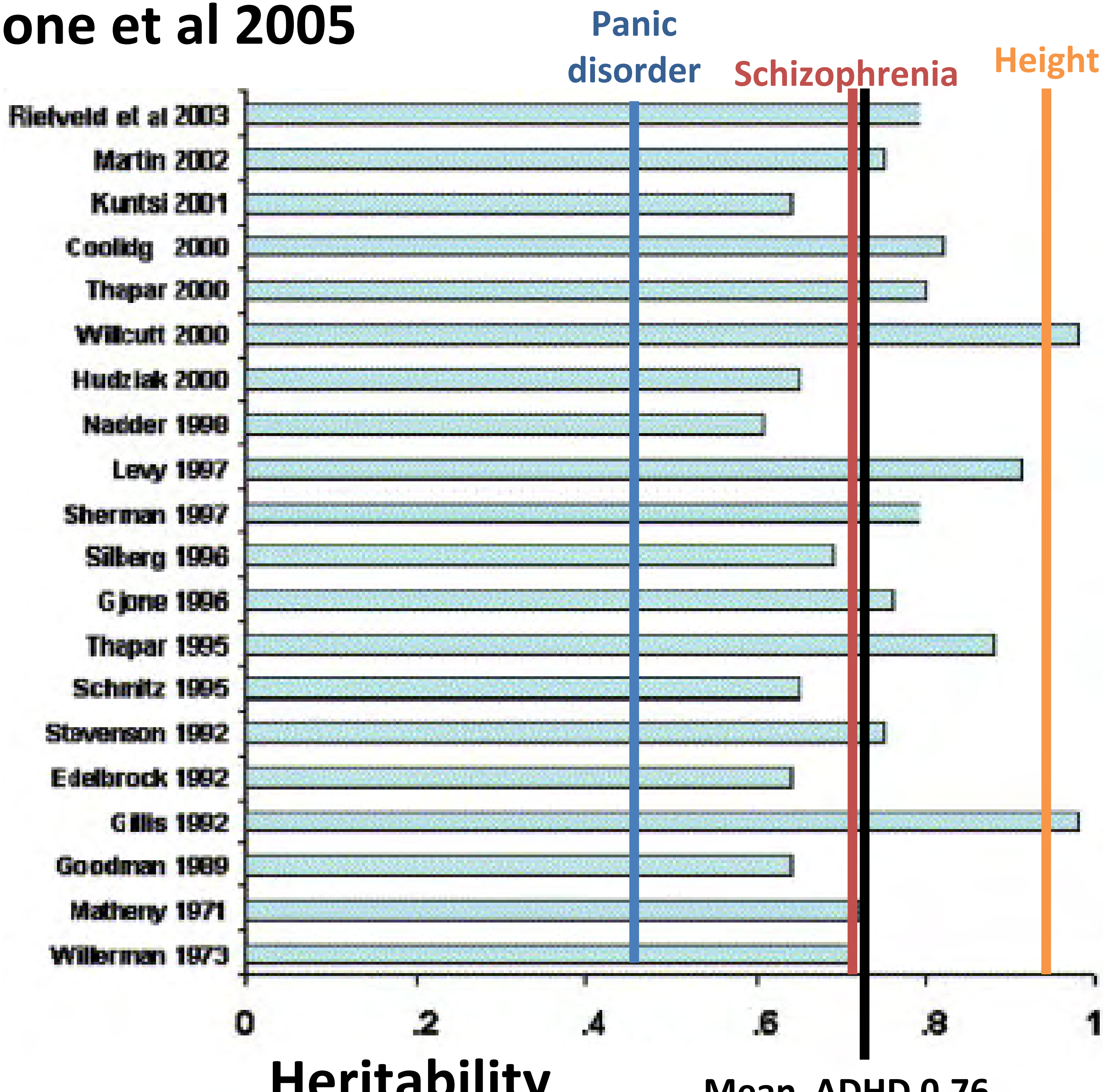
What causes ADHD?

What causes ADHD?



What causes ADHD?

Faraone et al 2005

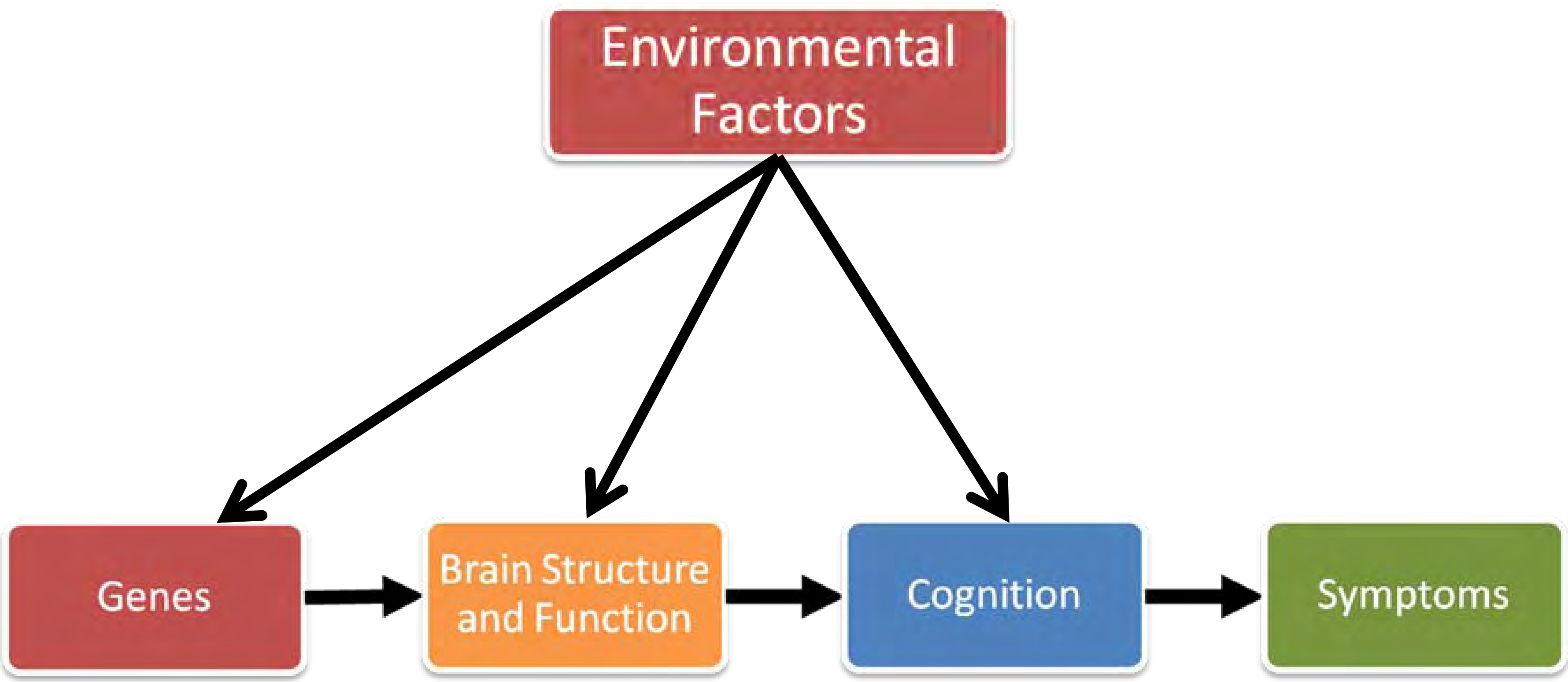


Significant pooled odds ratios for gene variants examined in three or more case-control or family-based studies

Gene	Study Design	Pooled OR	95% CI
Dopamine D4 Receptor (exon III VNTR, 7 repeat)	Family	1.16	1.03-1.31
Dopamine D4 Receptor (exon III VNTR, 7 repeat)	Case-control	1.45	1.27-1.65
Dopamine D5 Receptor (CA repeat, 148bp)	Family	1.24	1.12-1.38
Dopamine Transporter (VNTR, 10-repeat)	Family	1.13	1.03-1.24
Dopamine β-Hydroxylase (Taql A)	Case-control	1.33	1.11-1.59
SNAP-25 (T1065G)	Family	1.19	1.03-1.38
Serotonin Transporter (5-HTTLPRlong)	Case-control	1.31	1.09-1.59
Serotonin HTR1B Receptor (G861C)	Family	1.44	1.14-1.83

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.

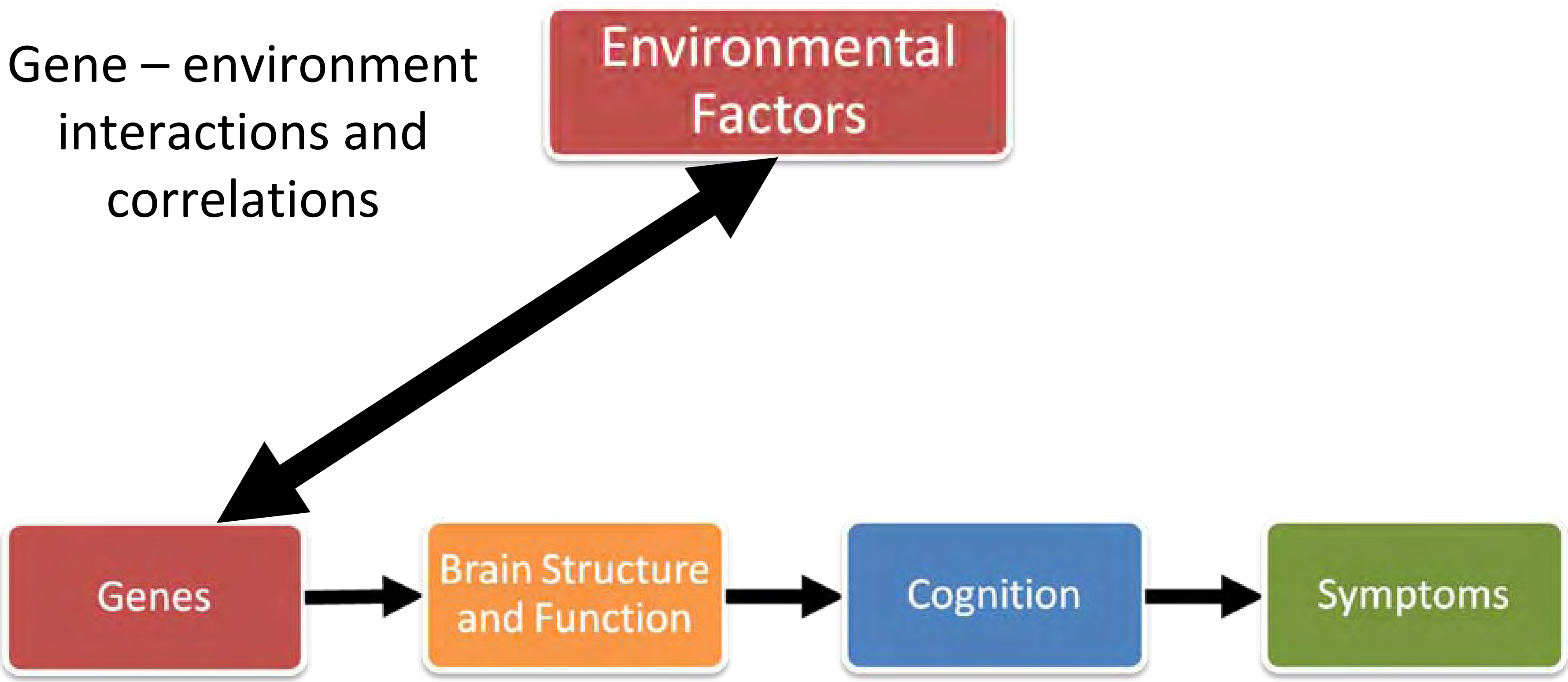
- Tuthill (1996) showed a dose response relationship between hair lead levels (from 1 – 11.3 parts per million) and both an AD-HKD diagnosis and teacher rated attention problems.

- 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!

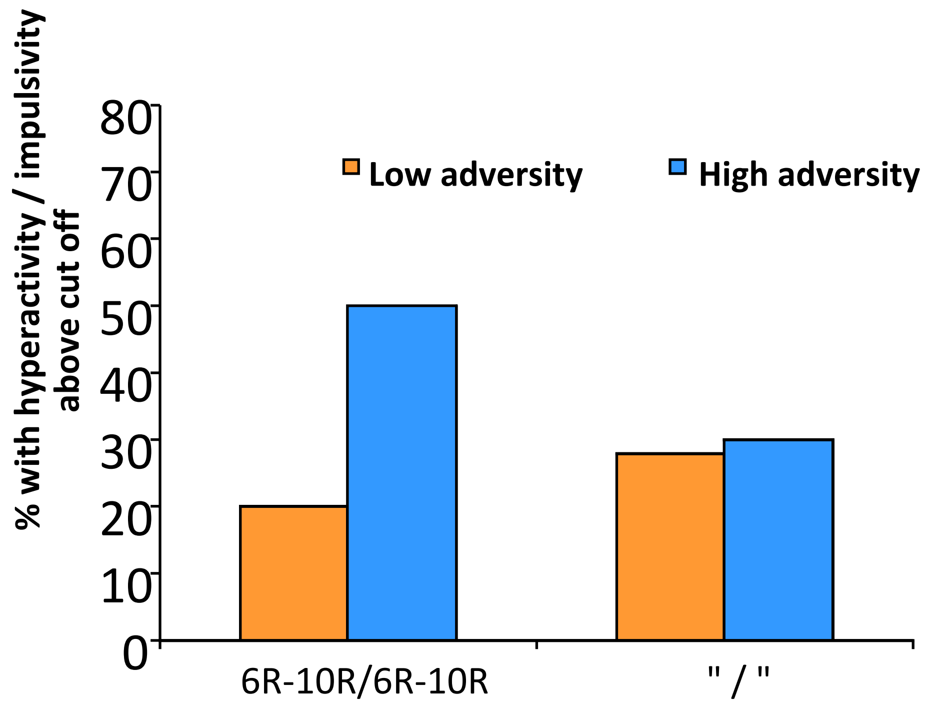


Gene – environment interactions and correlations
Environmental Factors
Genes
Brain Structure and Function
Cognition
Symptoms

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

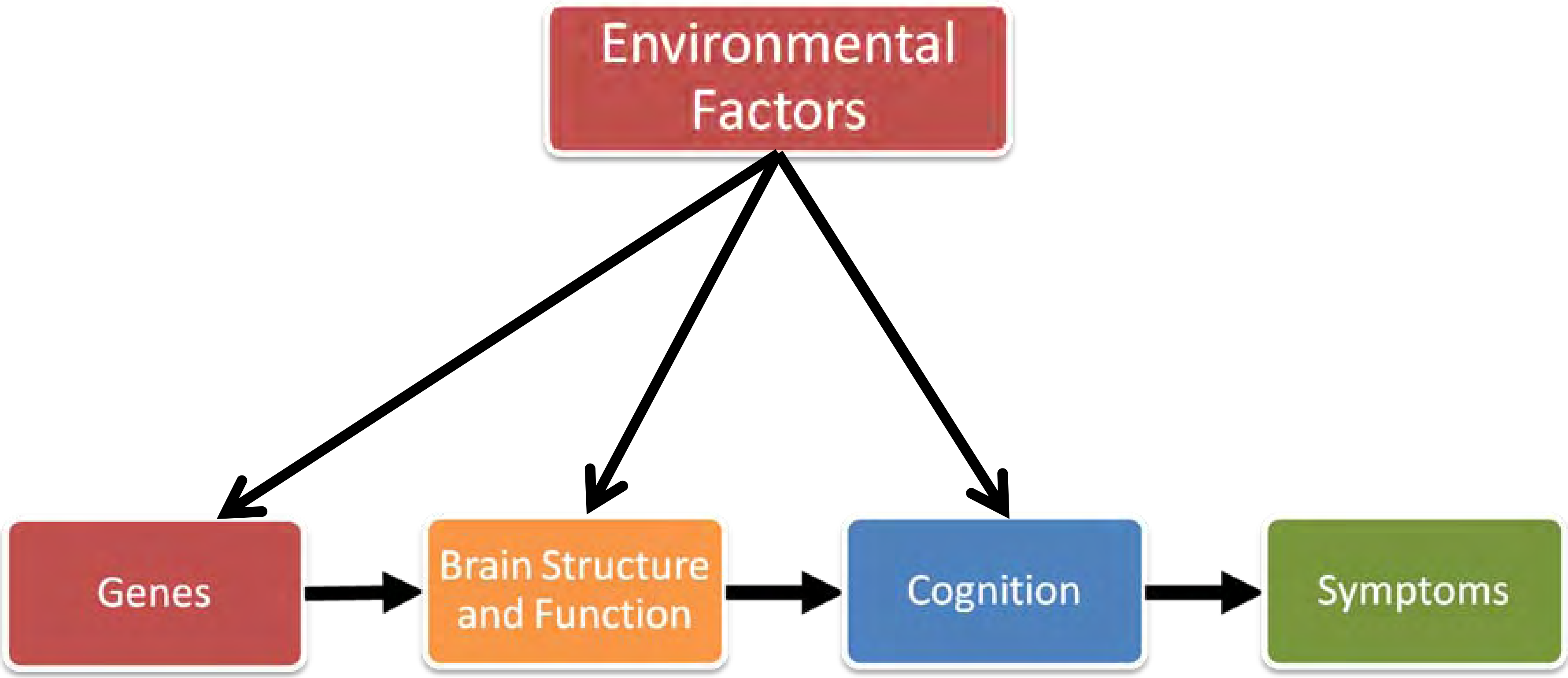


Laucht M et al. *Arch Gen Psychiatry* 2007; 64: 585–590

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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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

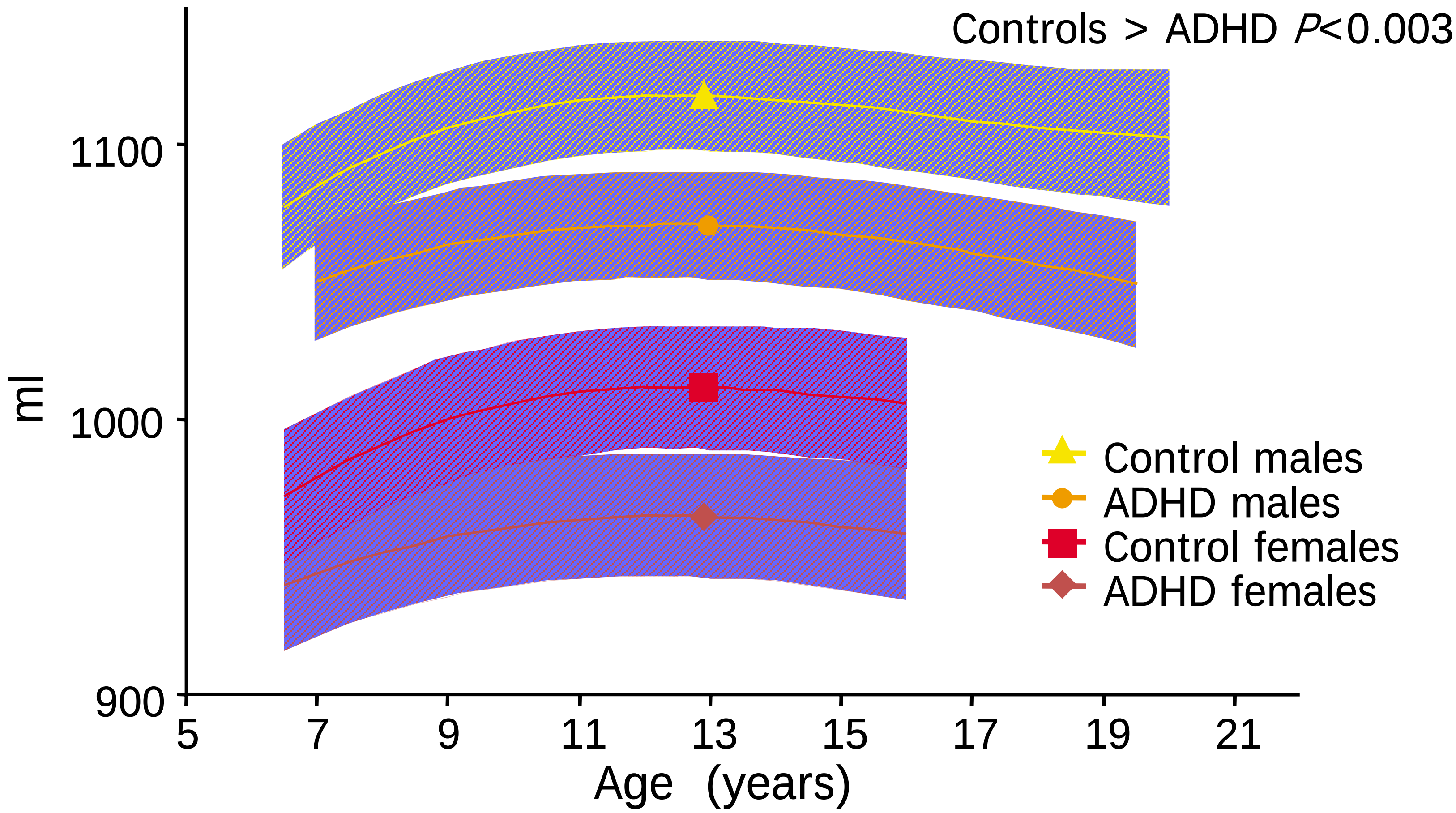
- Total and right cerebral volume
- Cerebellum including vermis,
- Corpus callosum
- Right caudate

Large differences but reported in < 3 studies

- Frontal lobes,
- Prefrontal cortex
- Deep frontal white matter (total and right and left).
- Temporal lobe

AETIOLOGY

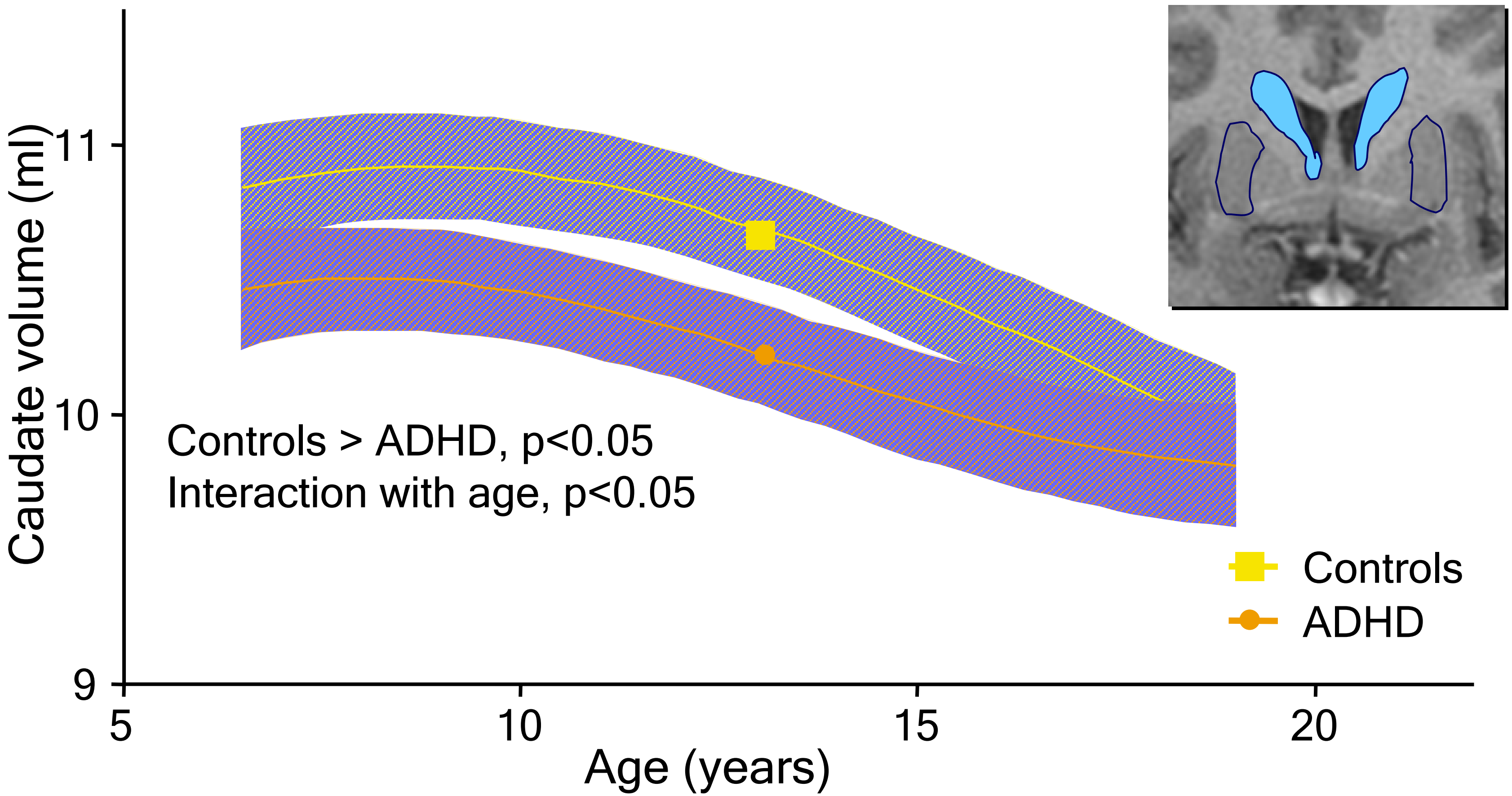
Neuroanatomy – total brain volume



Castellanos *et al* 2002

AETIOLOGY

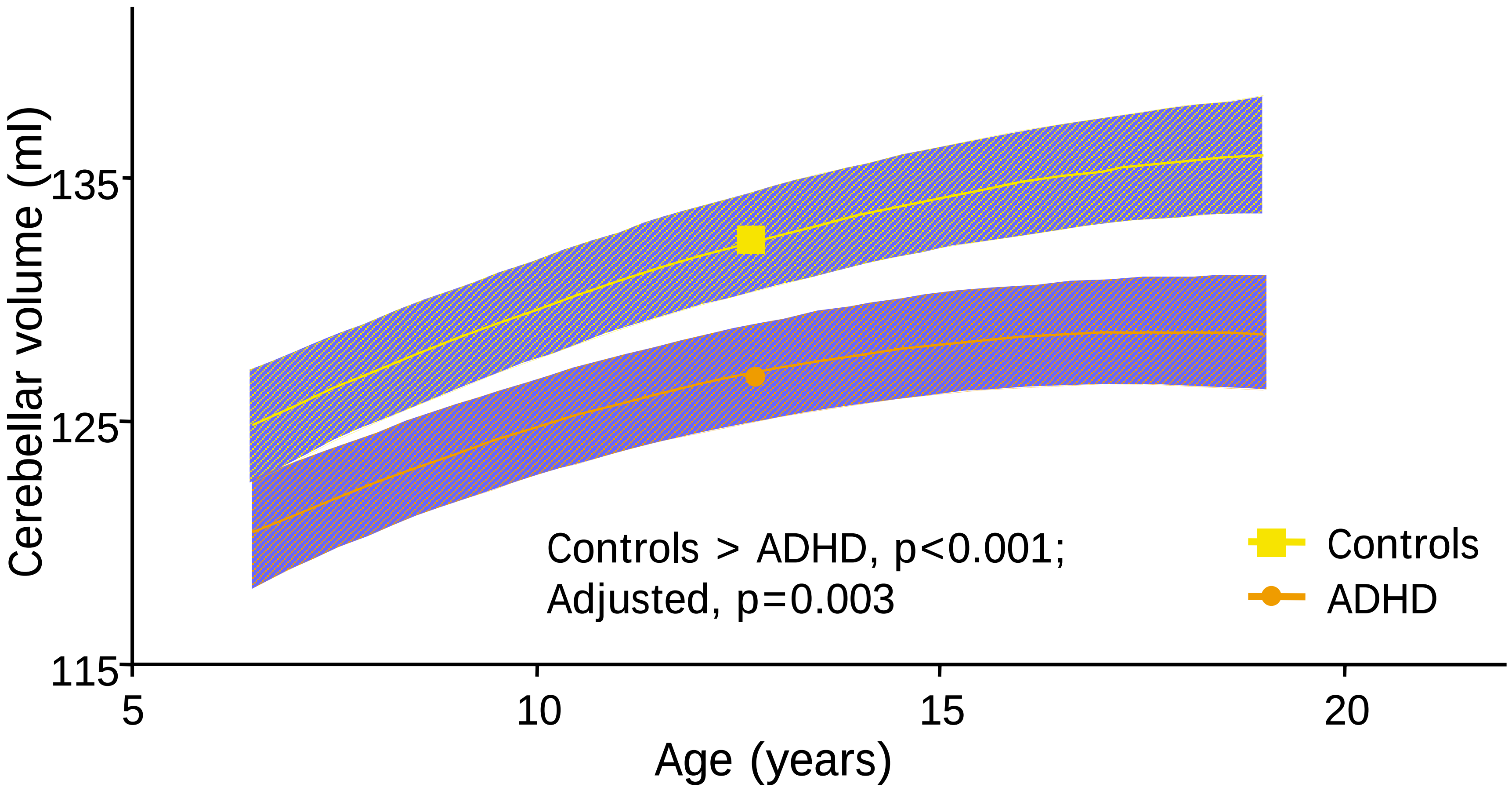
Neuroanatomy – caudate volume



Castellanos *et al* 2002

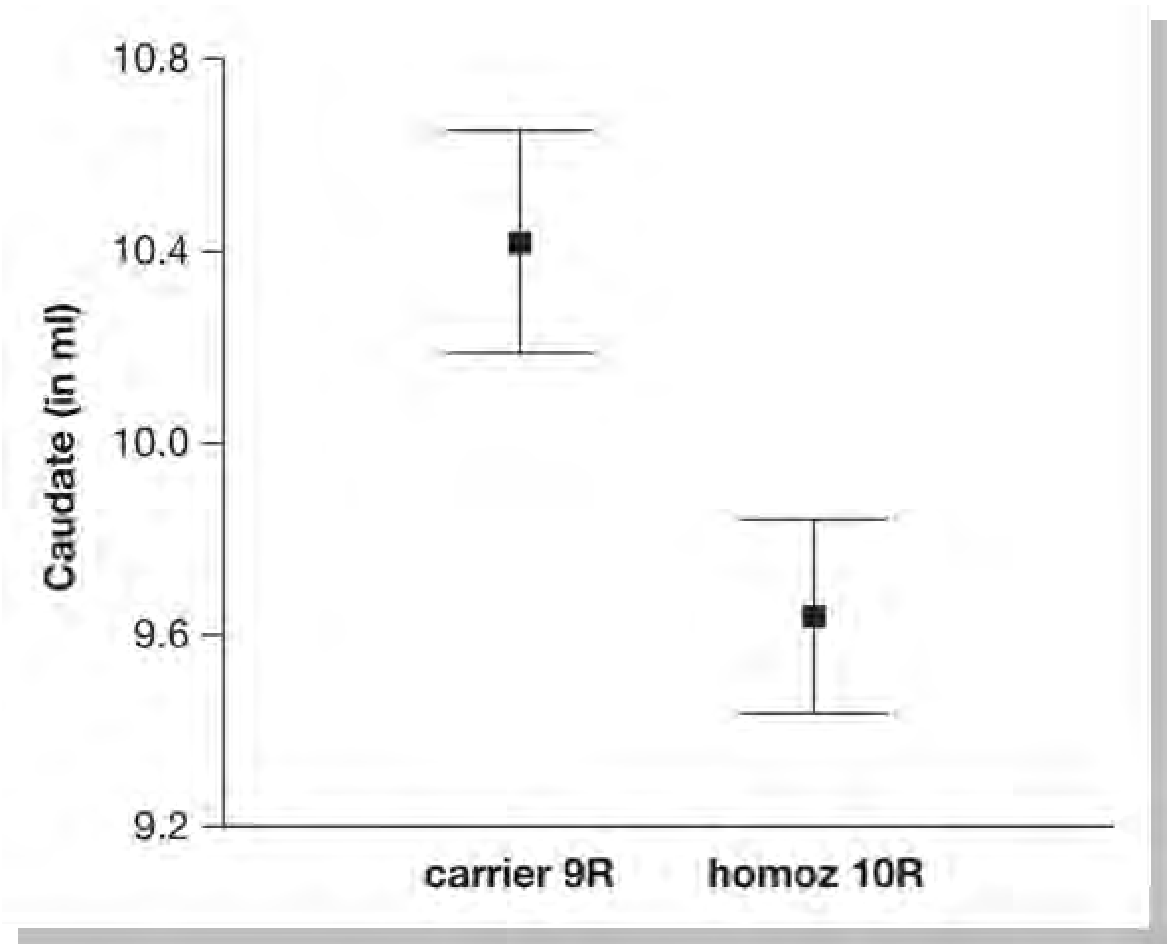
AETIOLOGY

Neuroanatomy – cerebellar volume



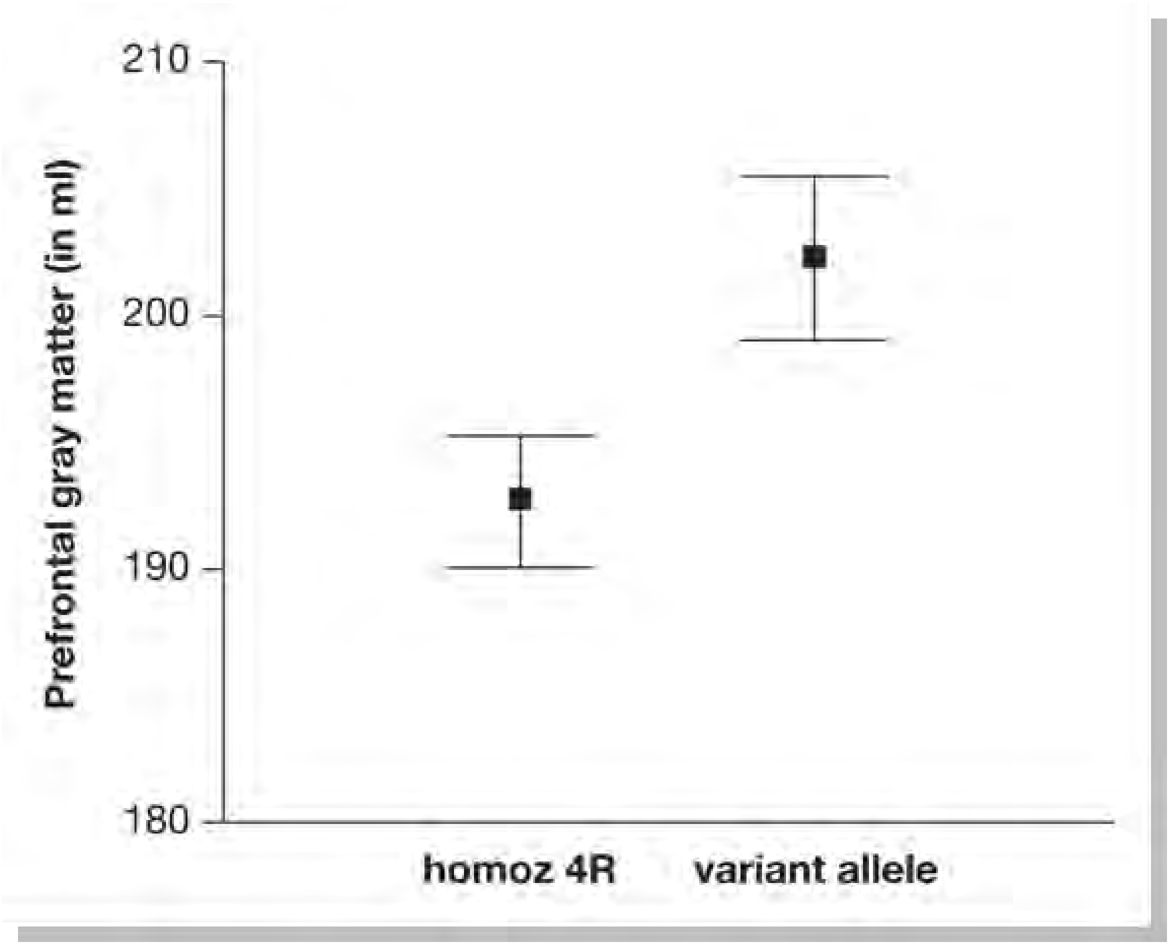
Castellanos *et al* 2002

Volume of caudate and DAT1 10-repeat



Durston S et al. *Mol Psychiatry* 2005; 10: 678–685

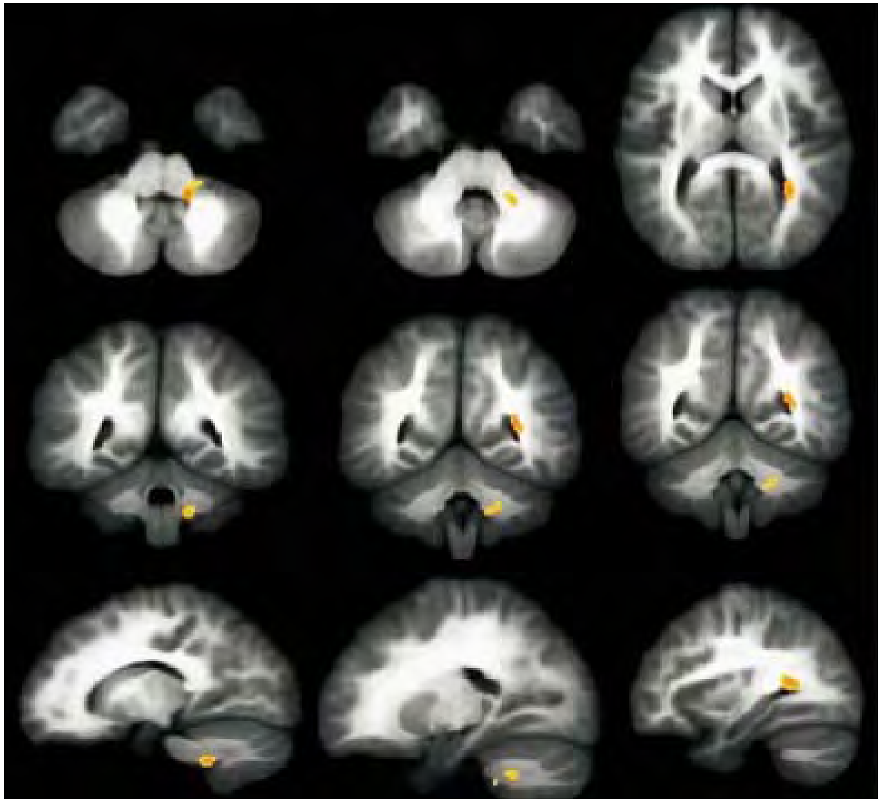
Volume of frontal grey and DRD4 4-repeat



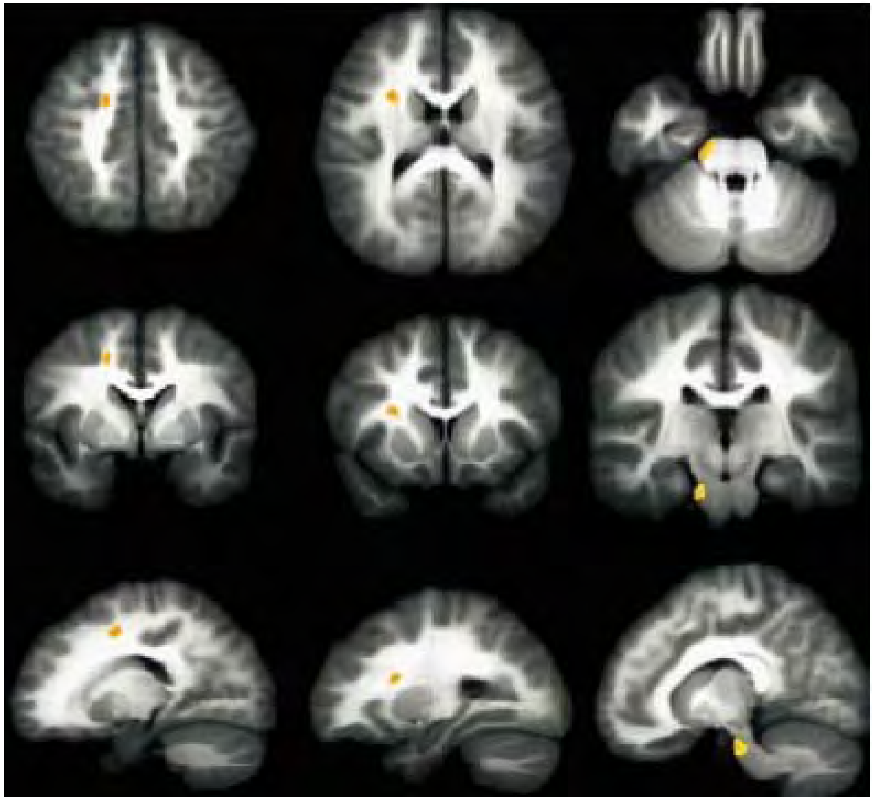
Durston S et al. *Mol Psychiatry* 2005; 10: 678–685

Diffusion Tensor Imaging

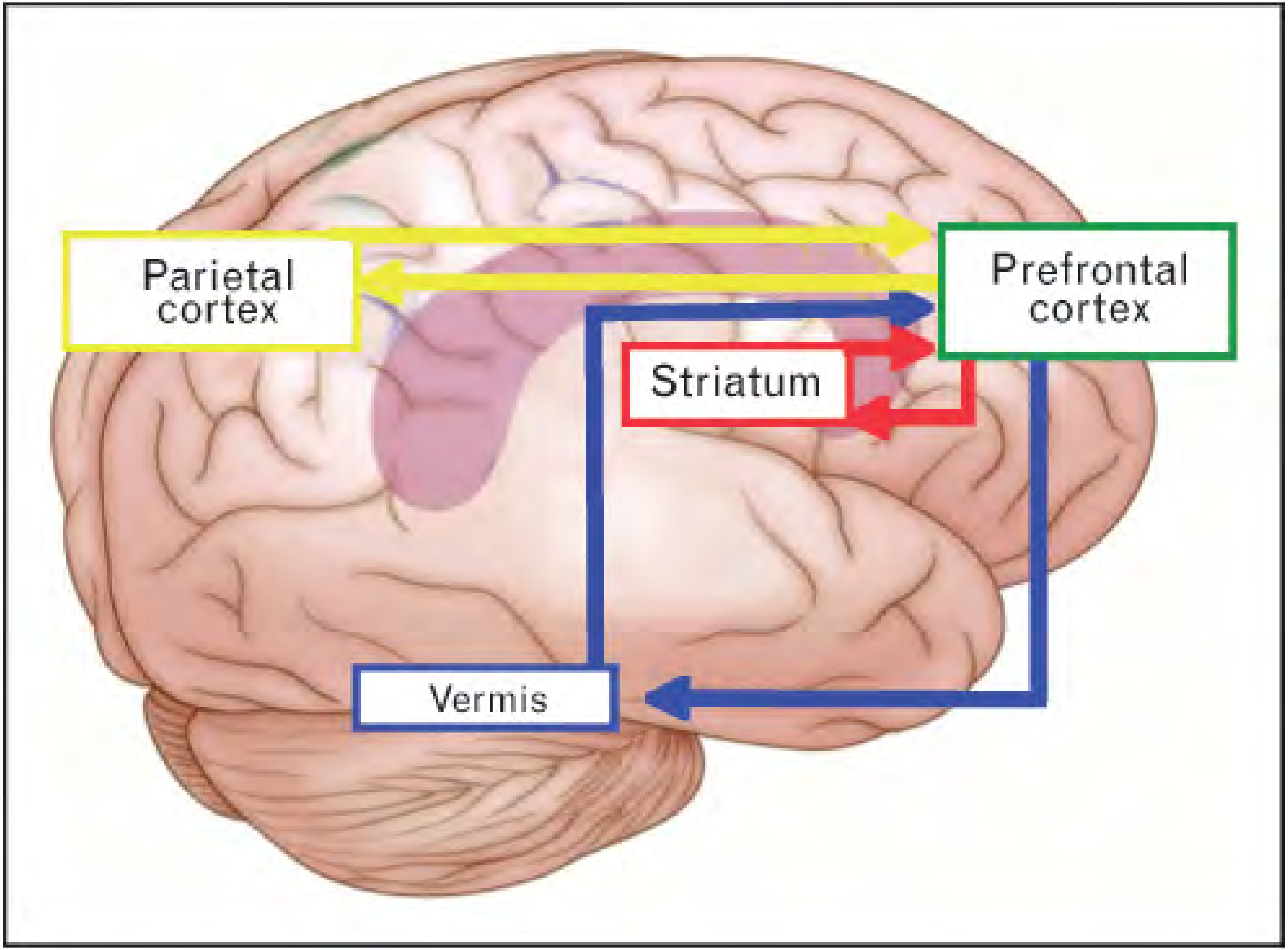
An imaging technique that looks at connectivity between brain regions



Left Hemisphere

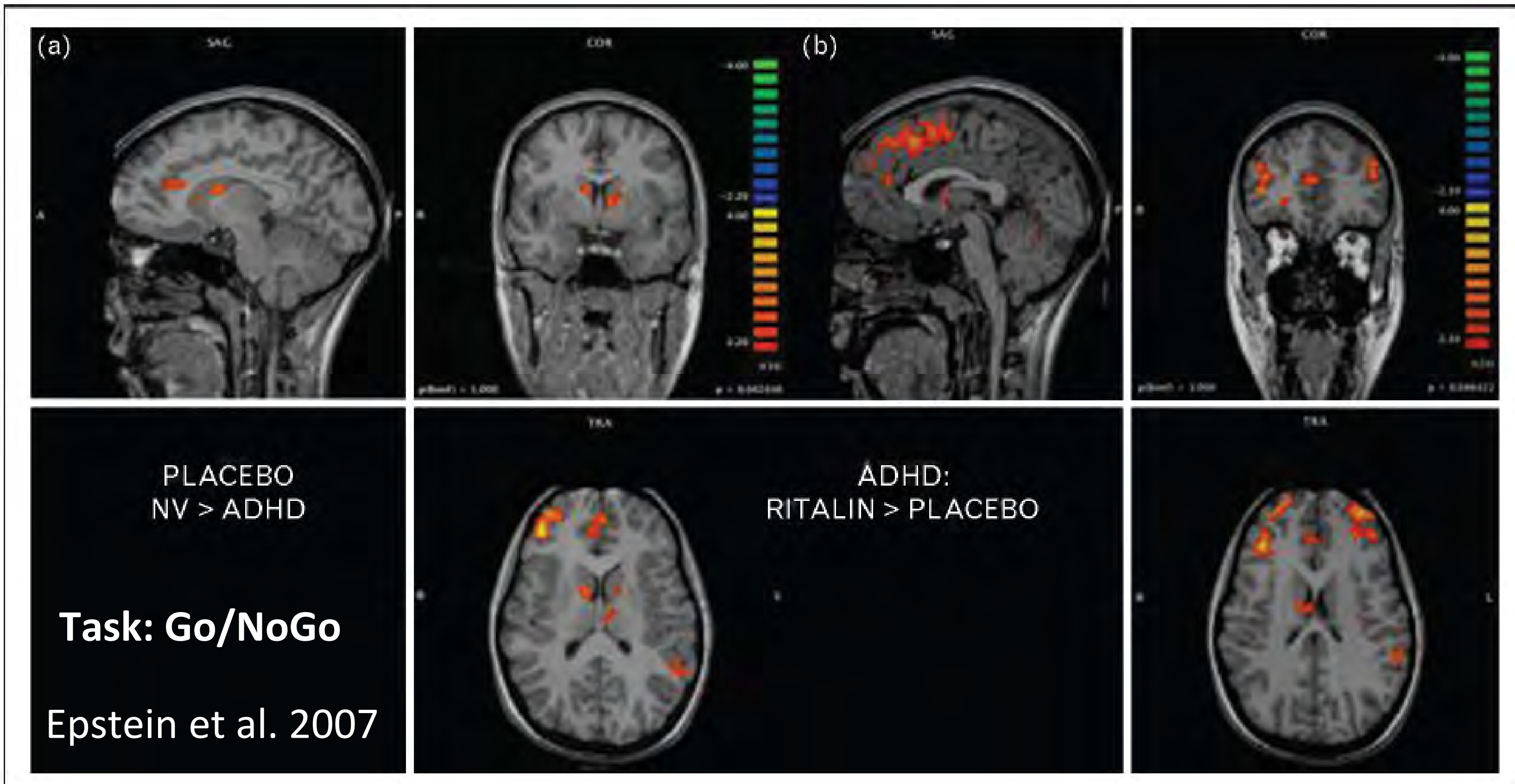


Right Hemisphere

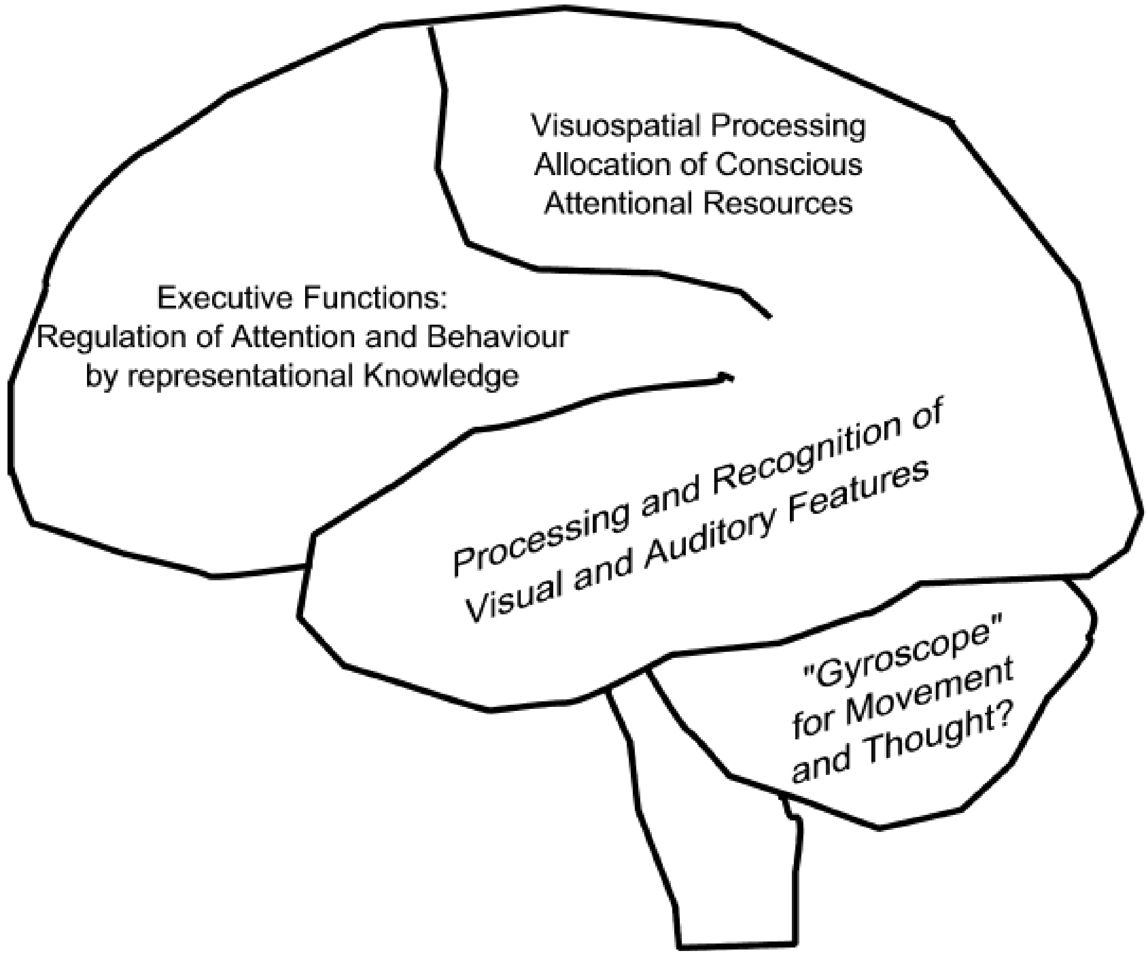

Parietal cortex
Prefrontal cortex
Striatum
Vermis

Brain – Functional Differences

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

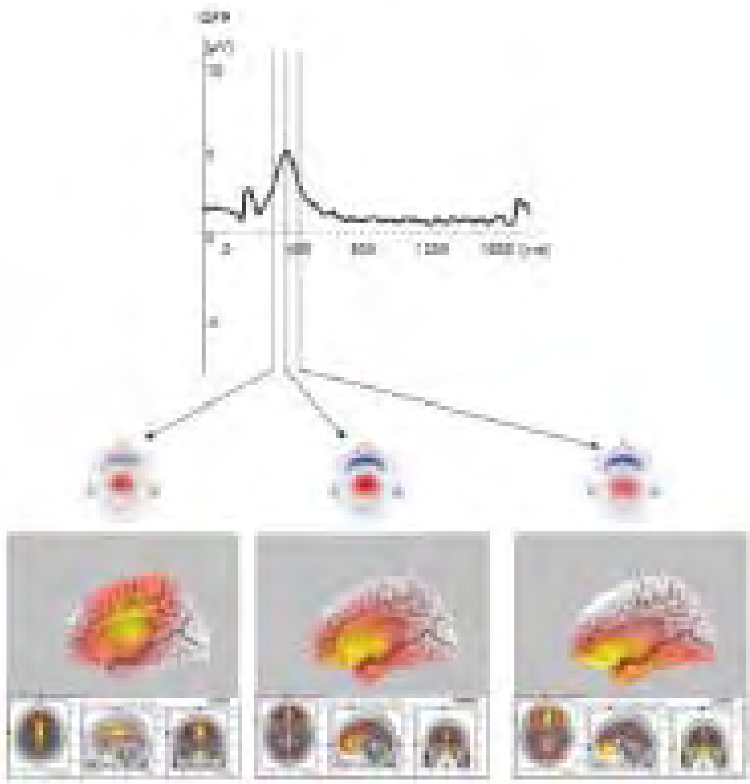


Brain – Functional Differences

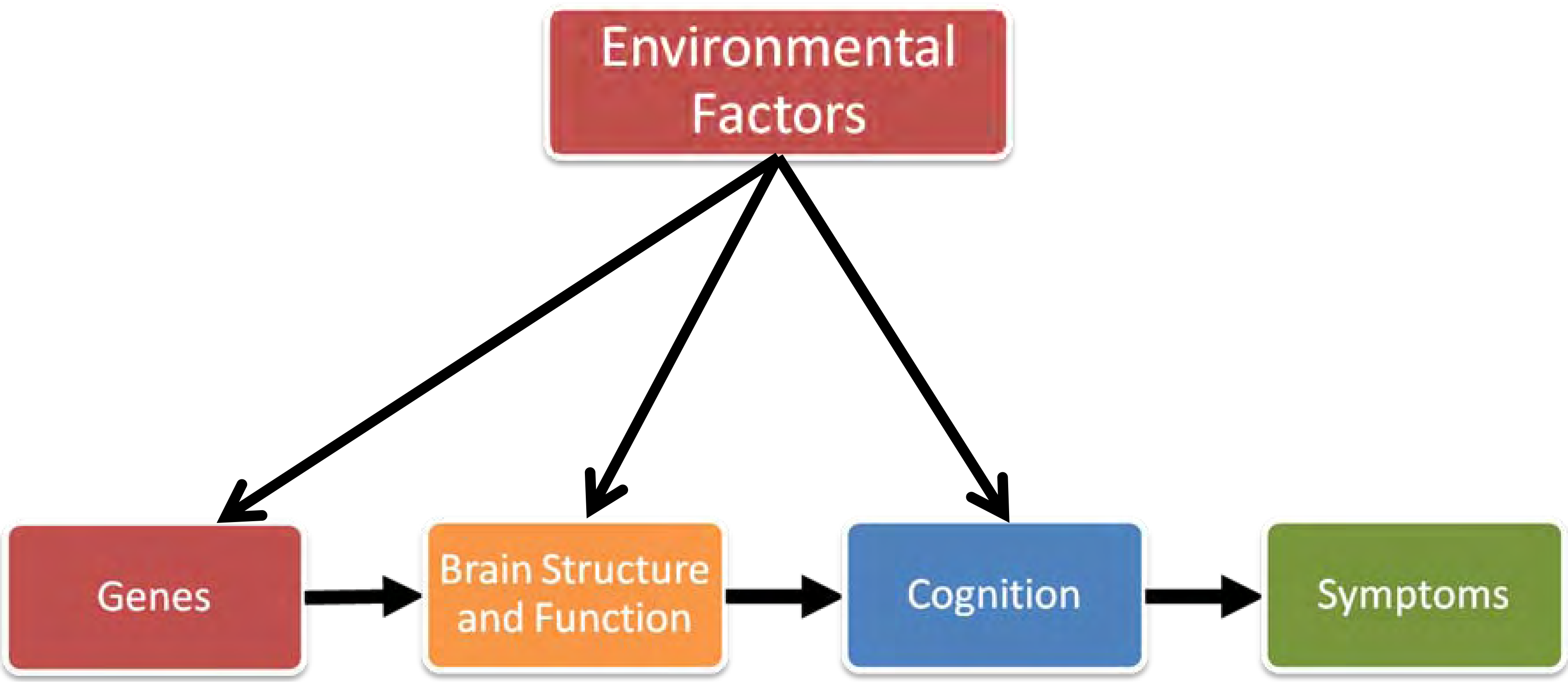


[a] The basal ganglia circuits are not shown in this view. They are however thought to contribute to the automatic planning, selection, initiation and execution of complex movements and thoughts.

Electrophysiology



Taken together the EEG and ERP research in ADHD suggests that there 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.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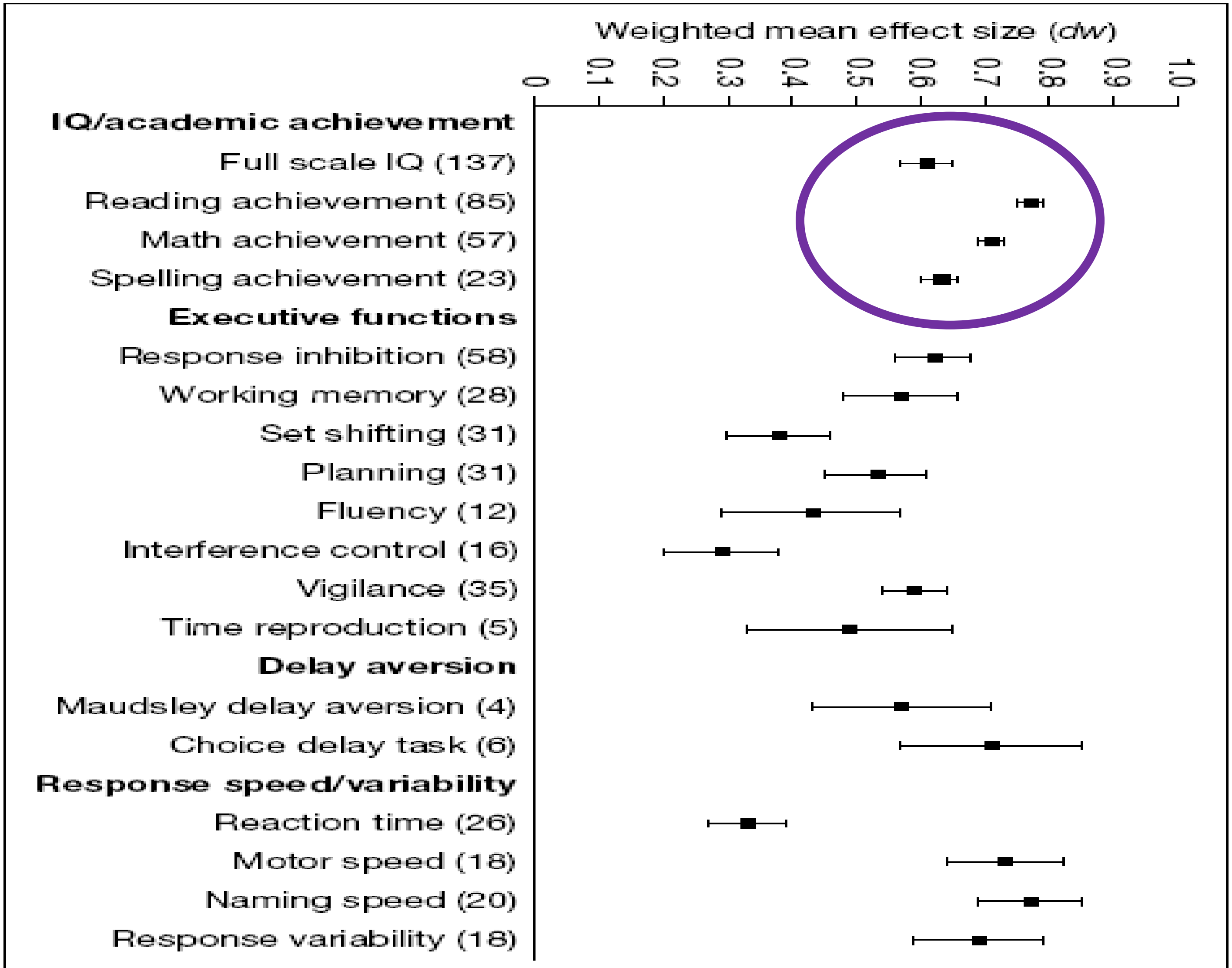
ADHD and Attention

- 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).

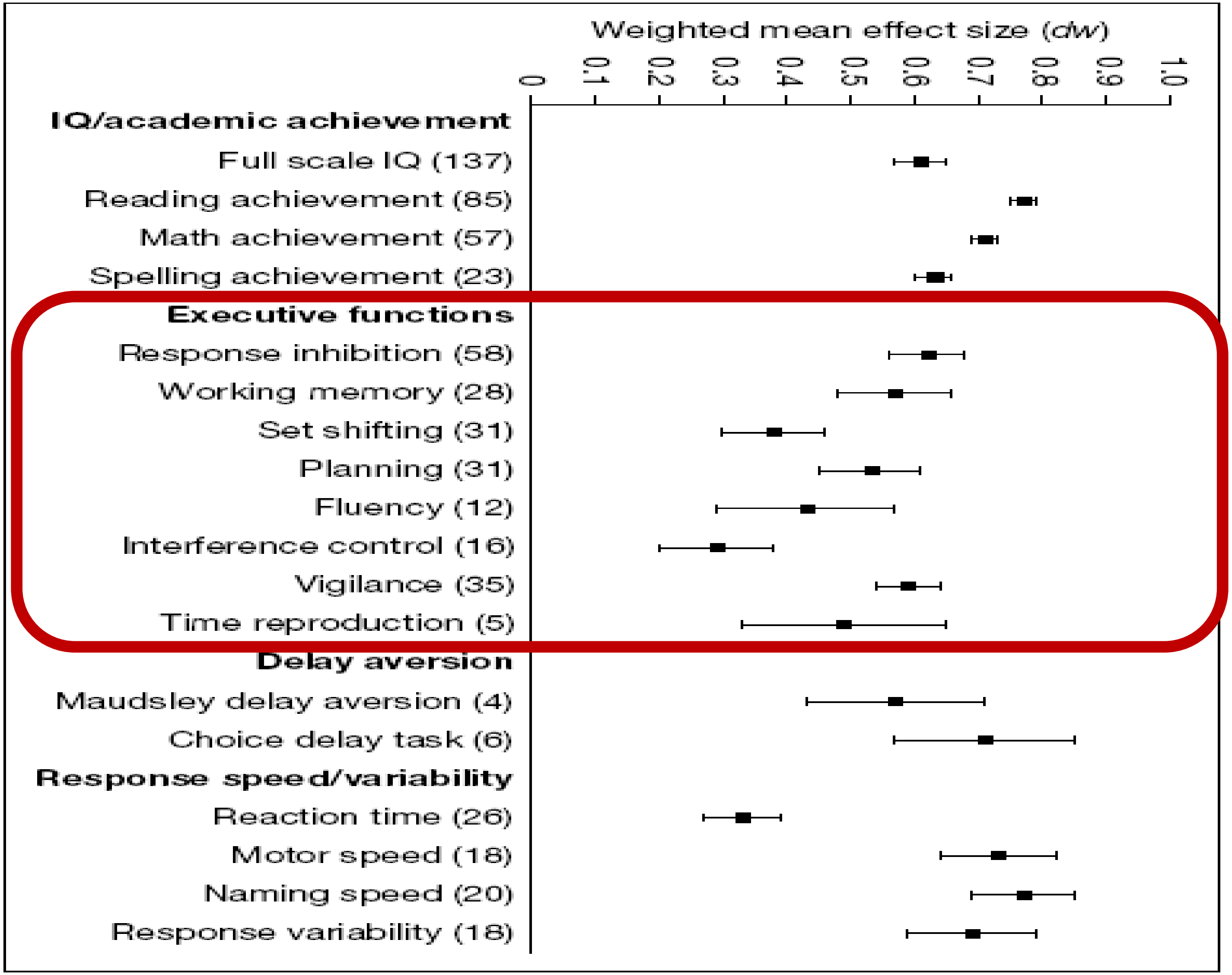
Weighted mean effect size of the difference between groups with and without ADHD (Willcutt et al 2008)



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

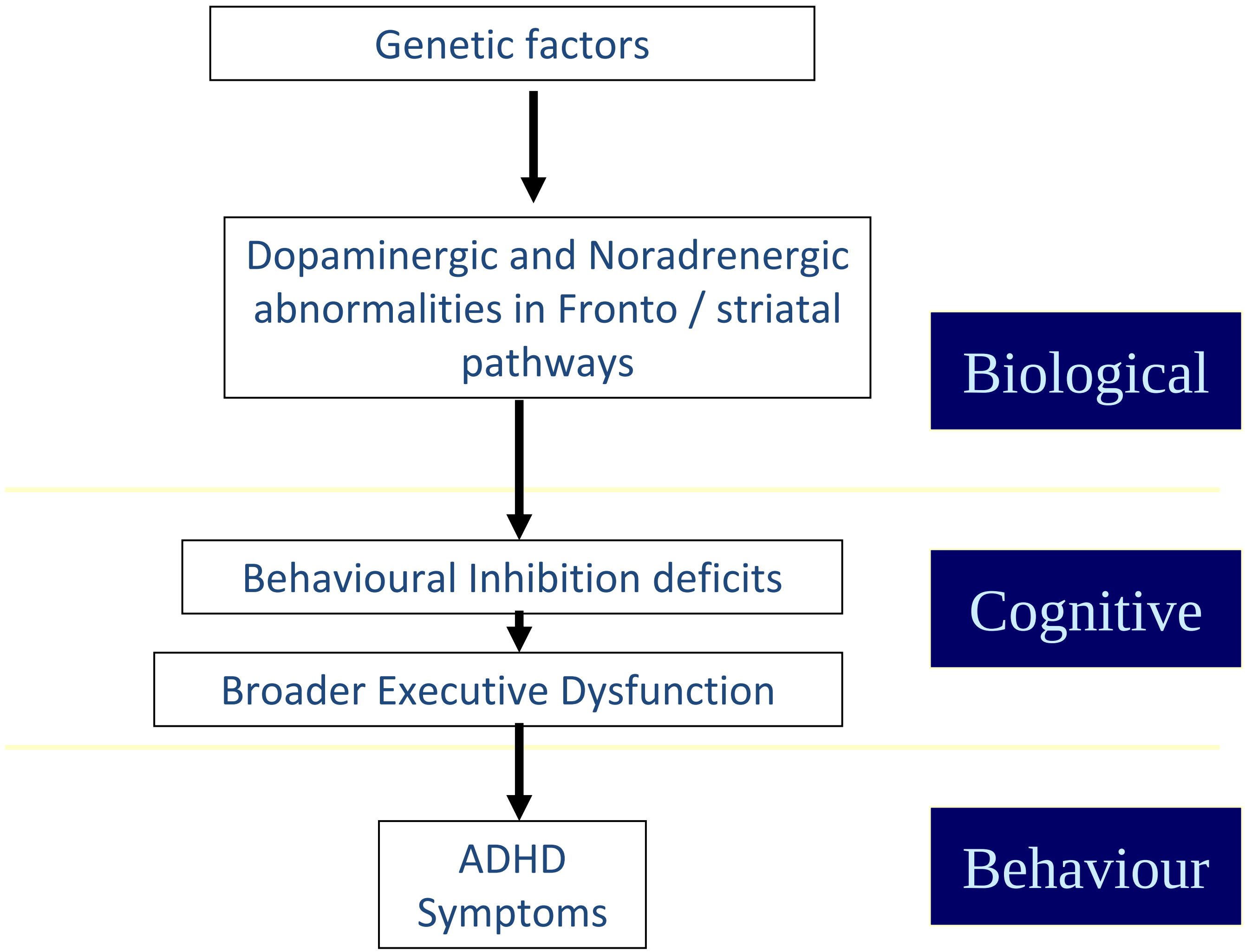
Weighted mean effect size of the difference between groups with and without ADHD (Willcutt et al 2008)



Executive functioning (“Cognitive control”)

- Control of motor response and behaviour (“Inhibition”)
- Working memory
- Planning / organization
- State regulation / activation
- Set shifting

A “single cause” model of ADHD

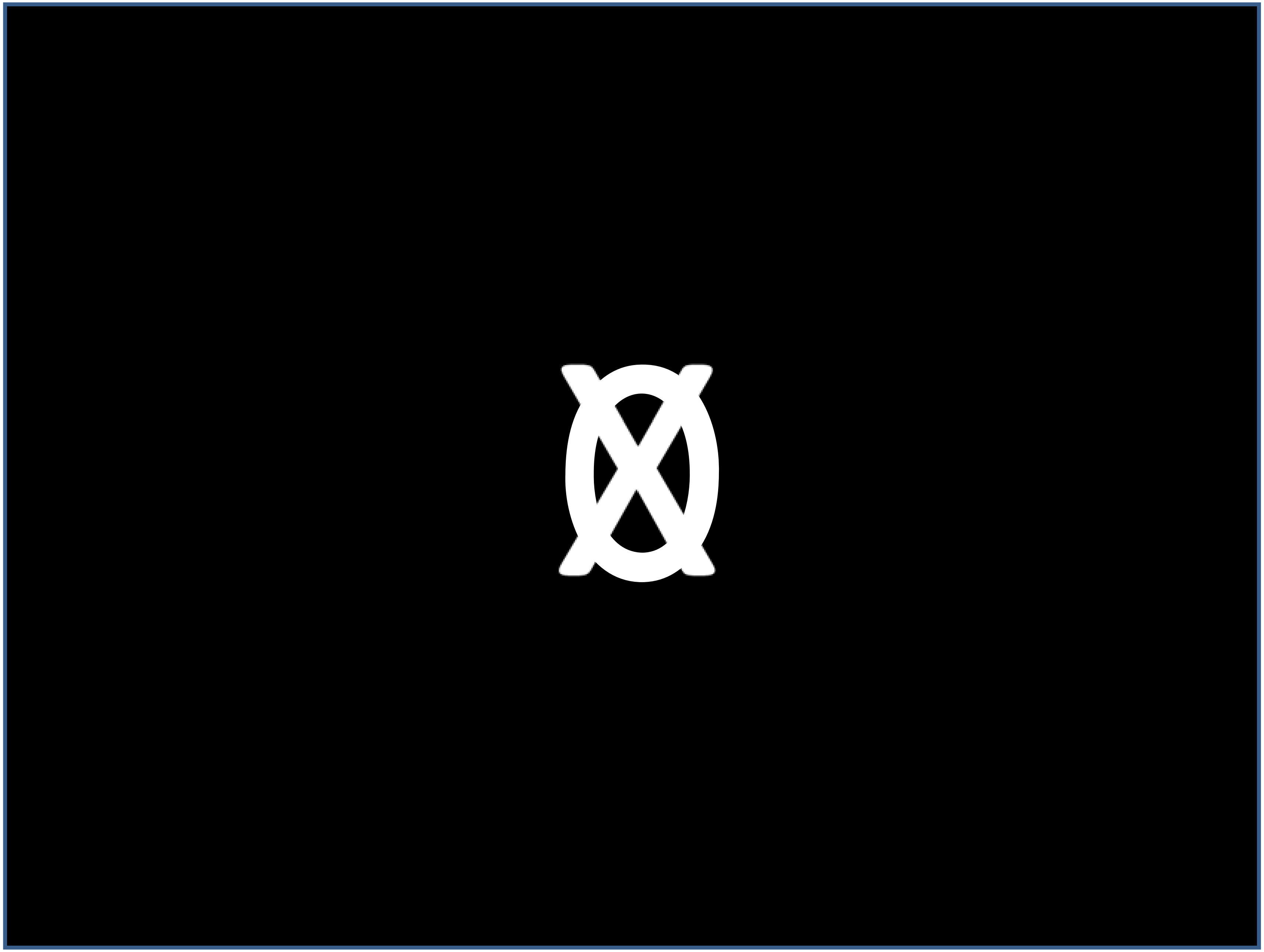


Go Signal

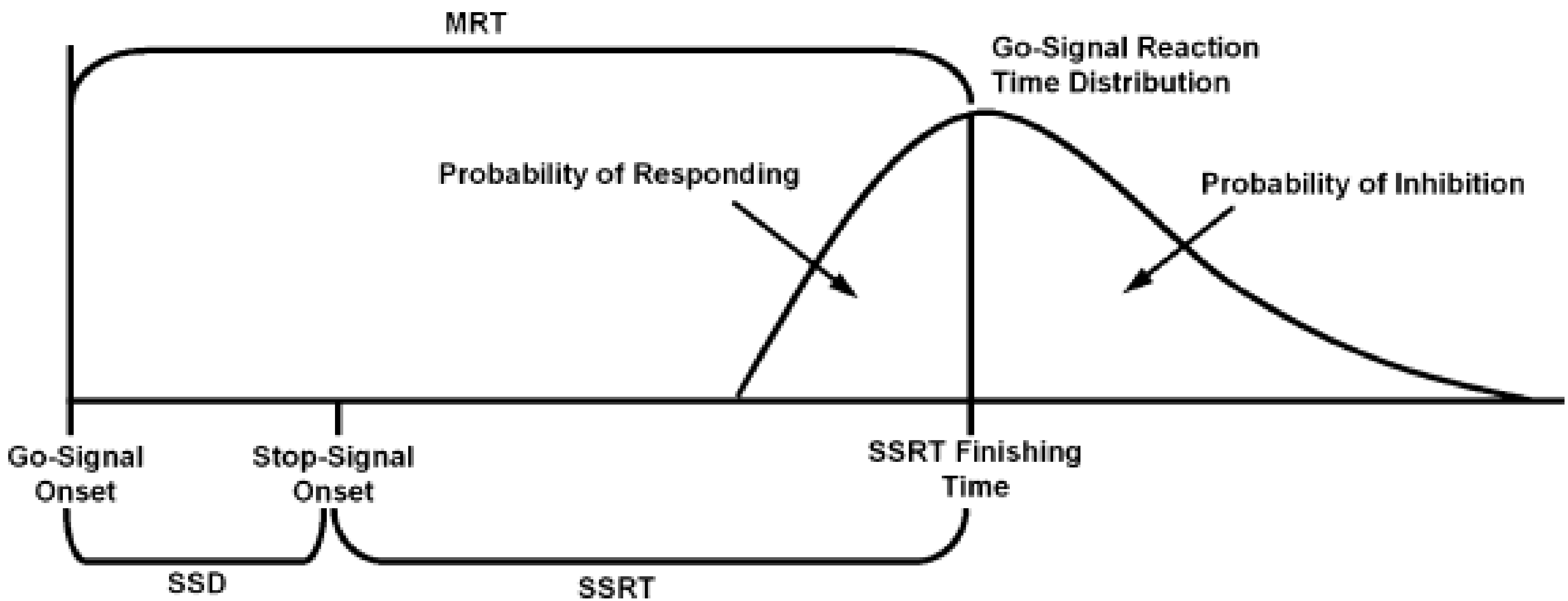
X

Stop Signal

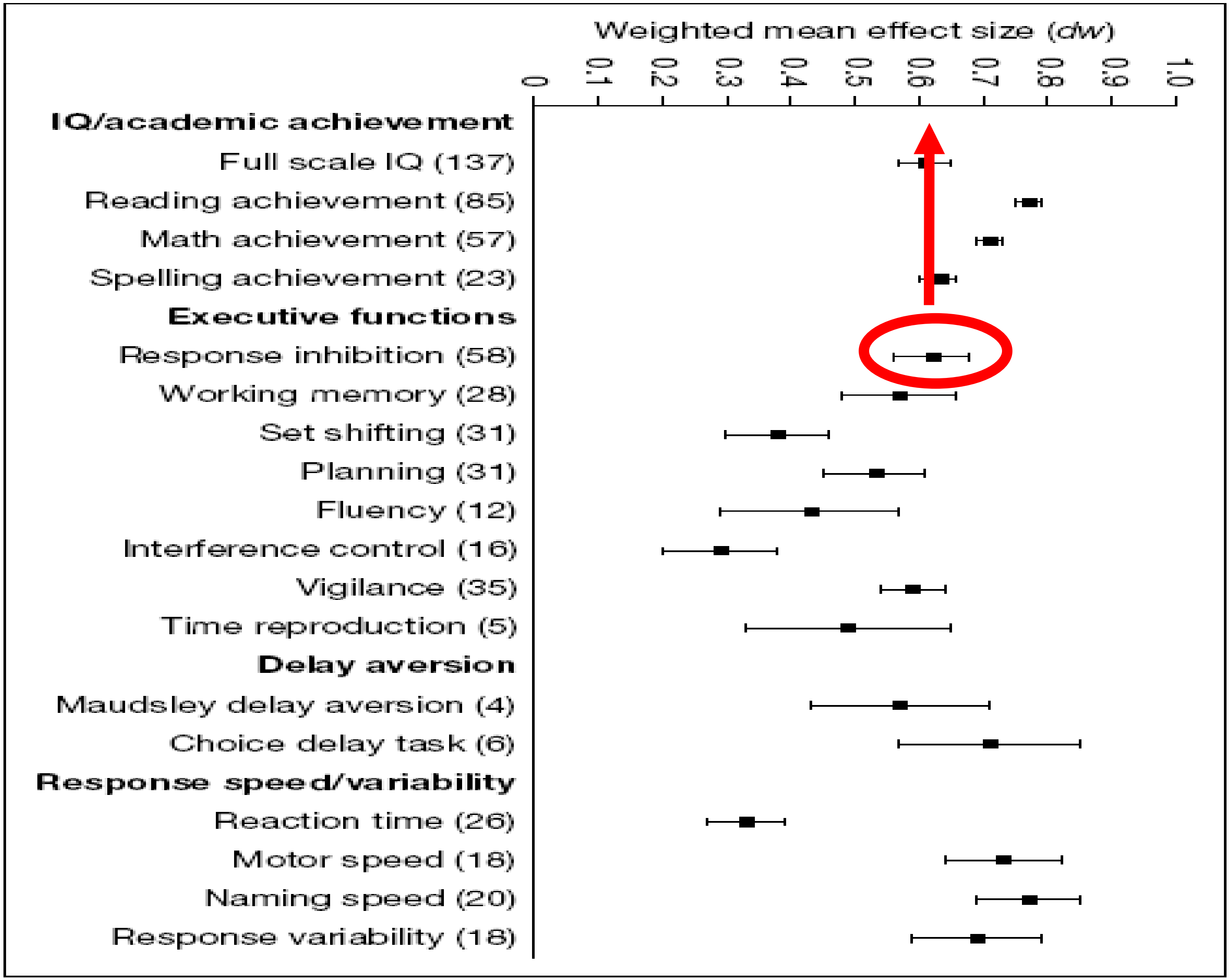
0



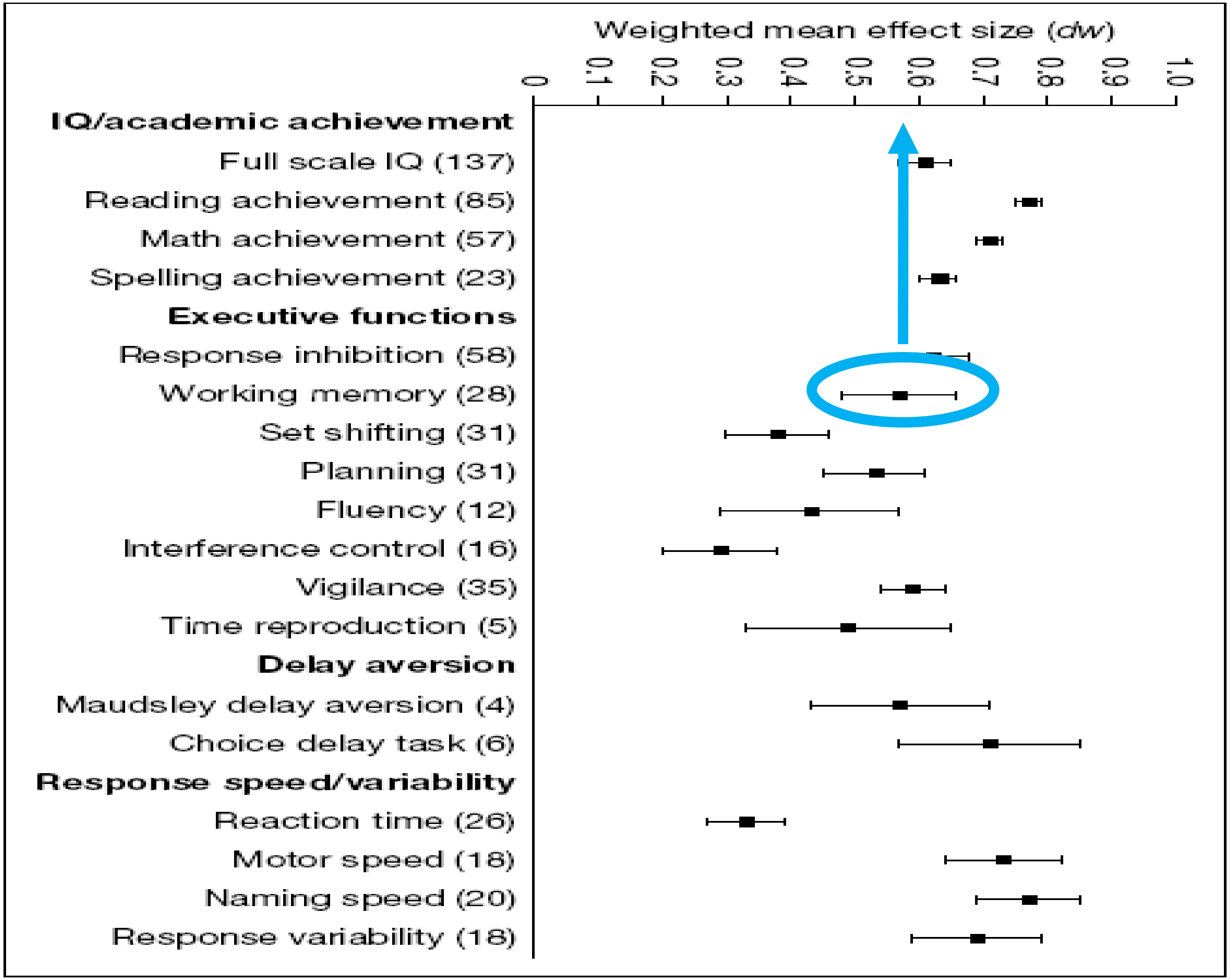
Stop Signal Reaction Time



Weighted mean effect size of the difference between groups with and without ADHD

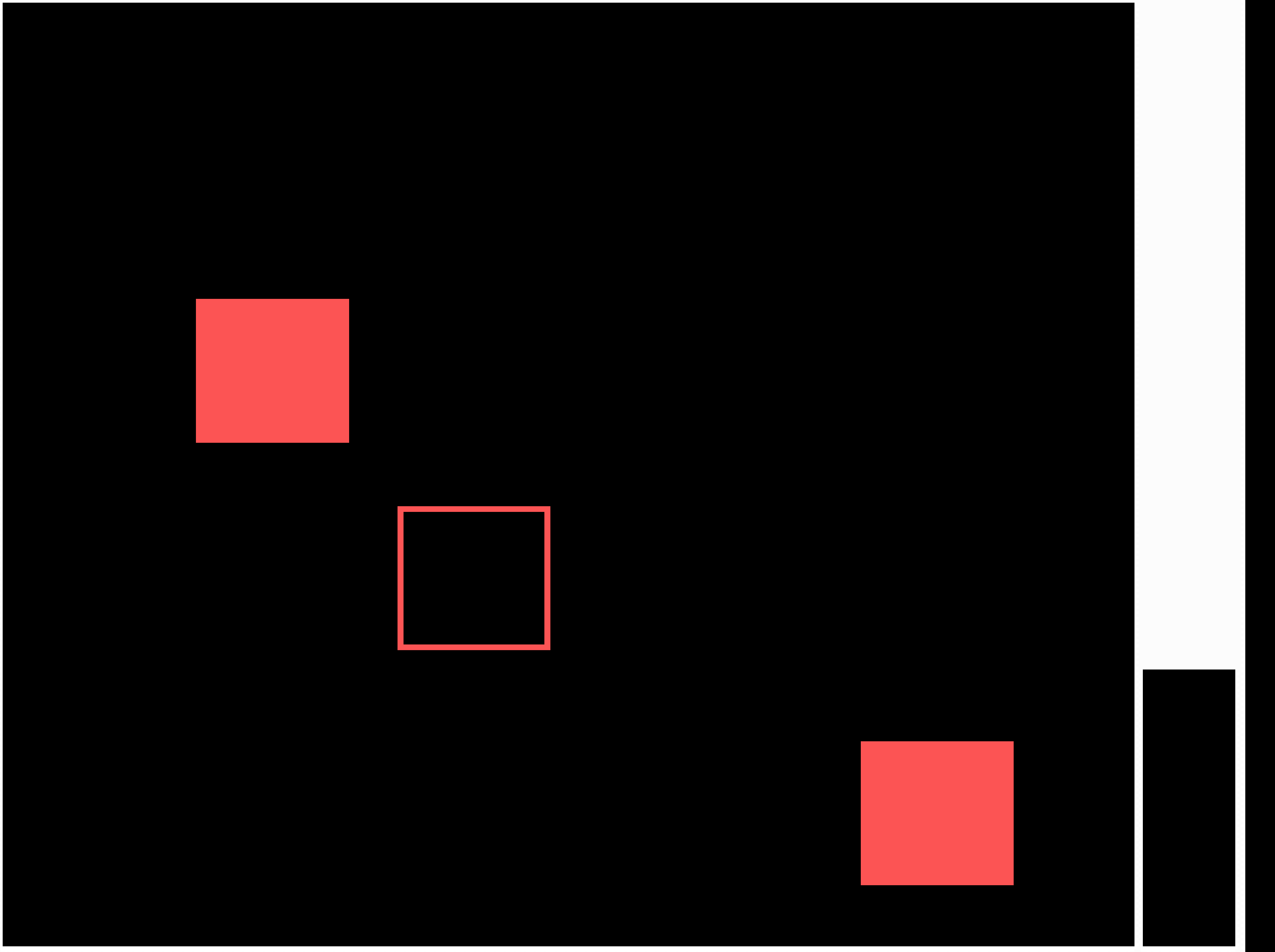


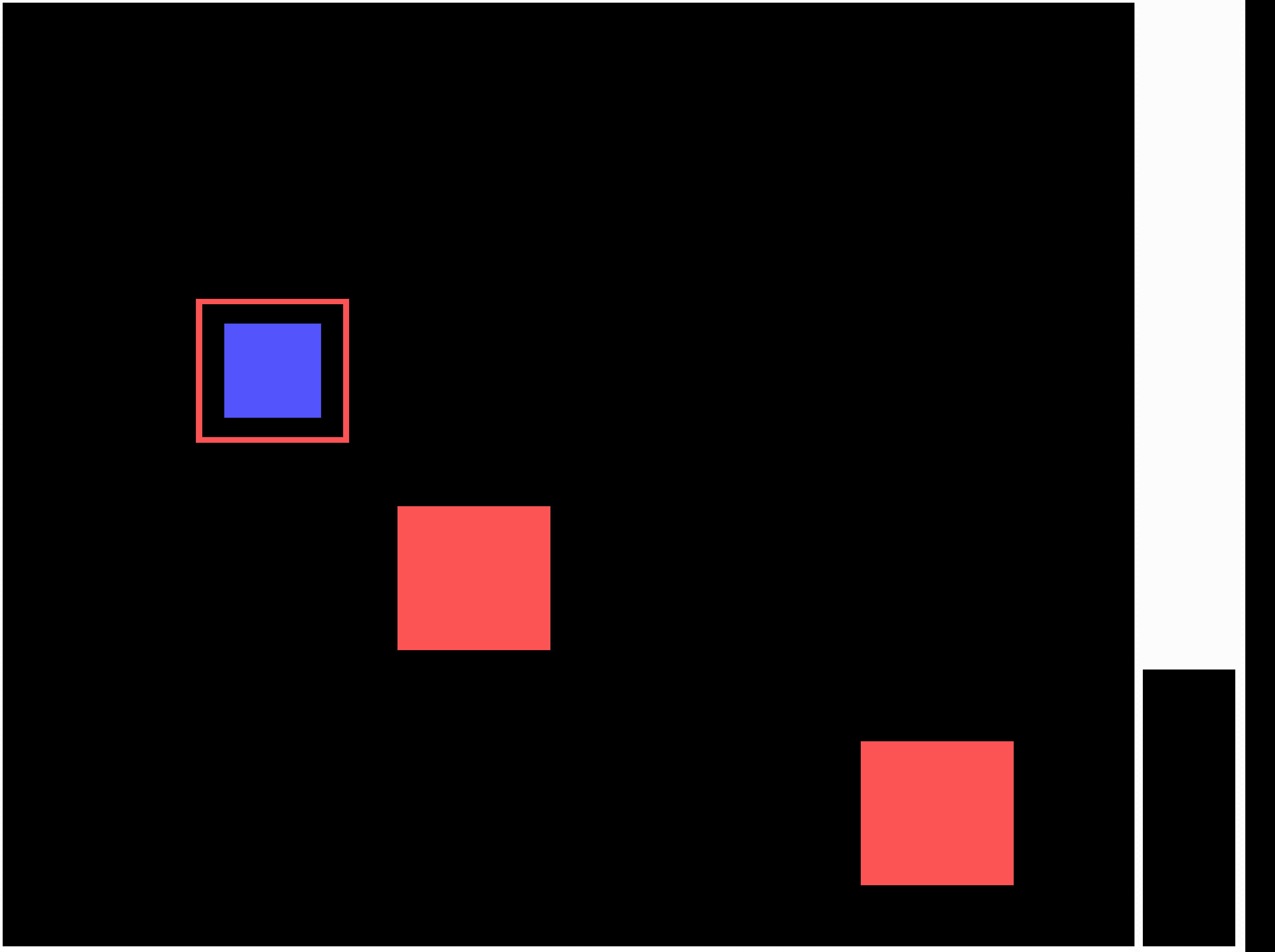
Weighted mean effect size of the difference between groups with and without ADHD



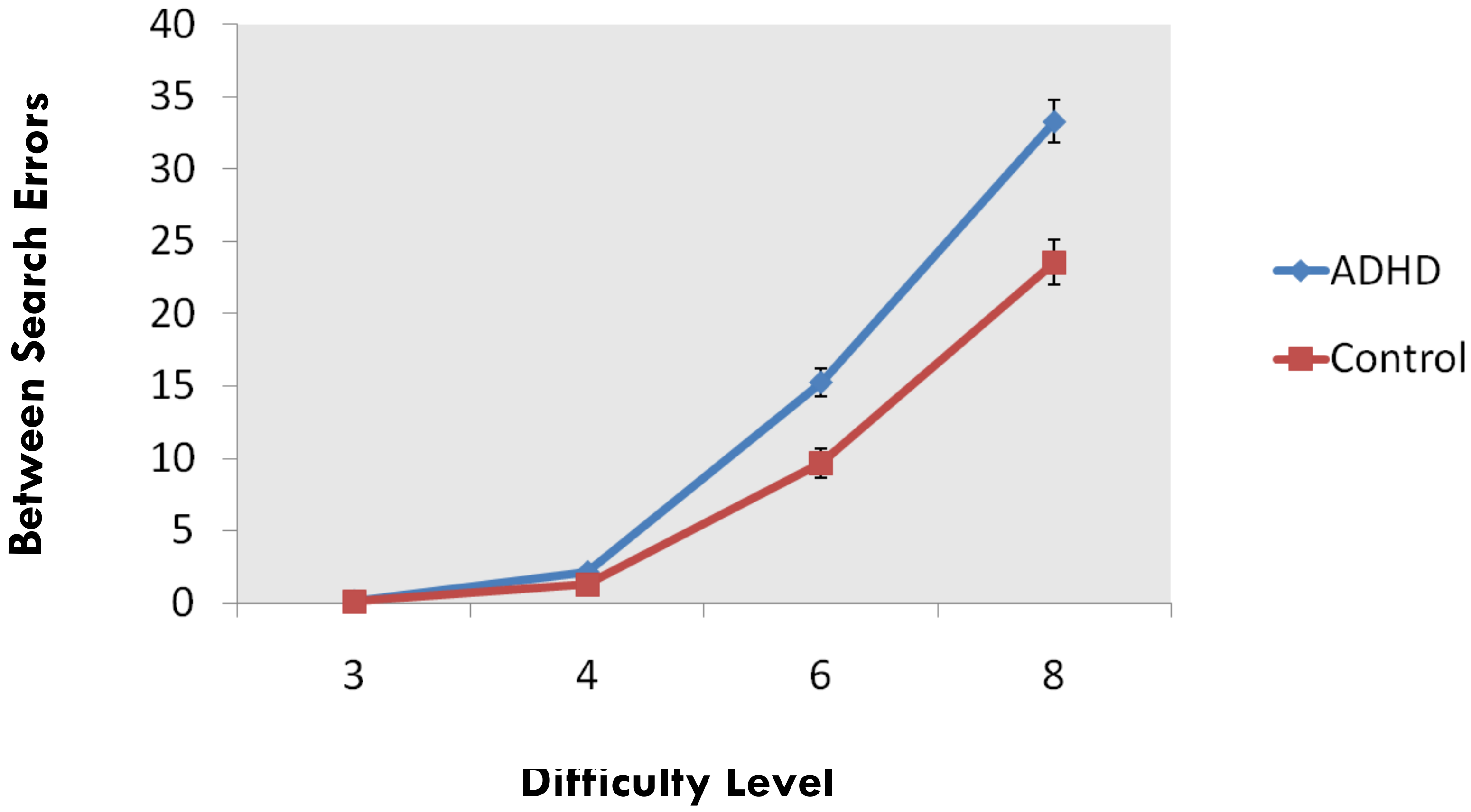
Why is working memory important?

- Verbal and spatial abilities – national curriculum assessments
- Verbal – literacy
- Spatial – mathematics and science

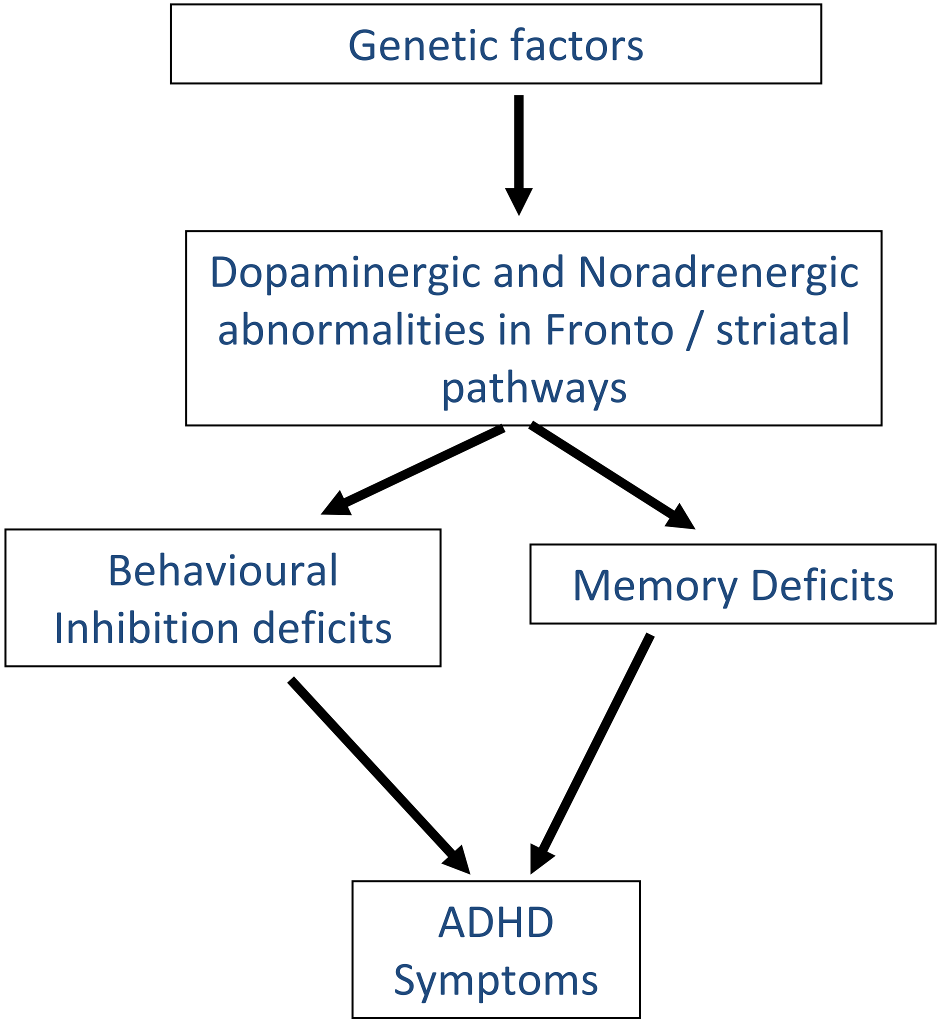


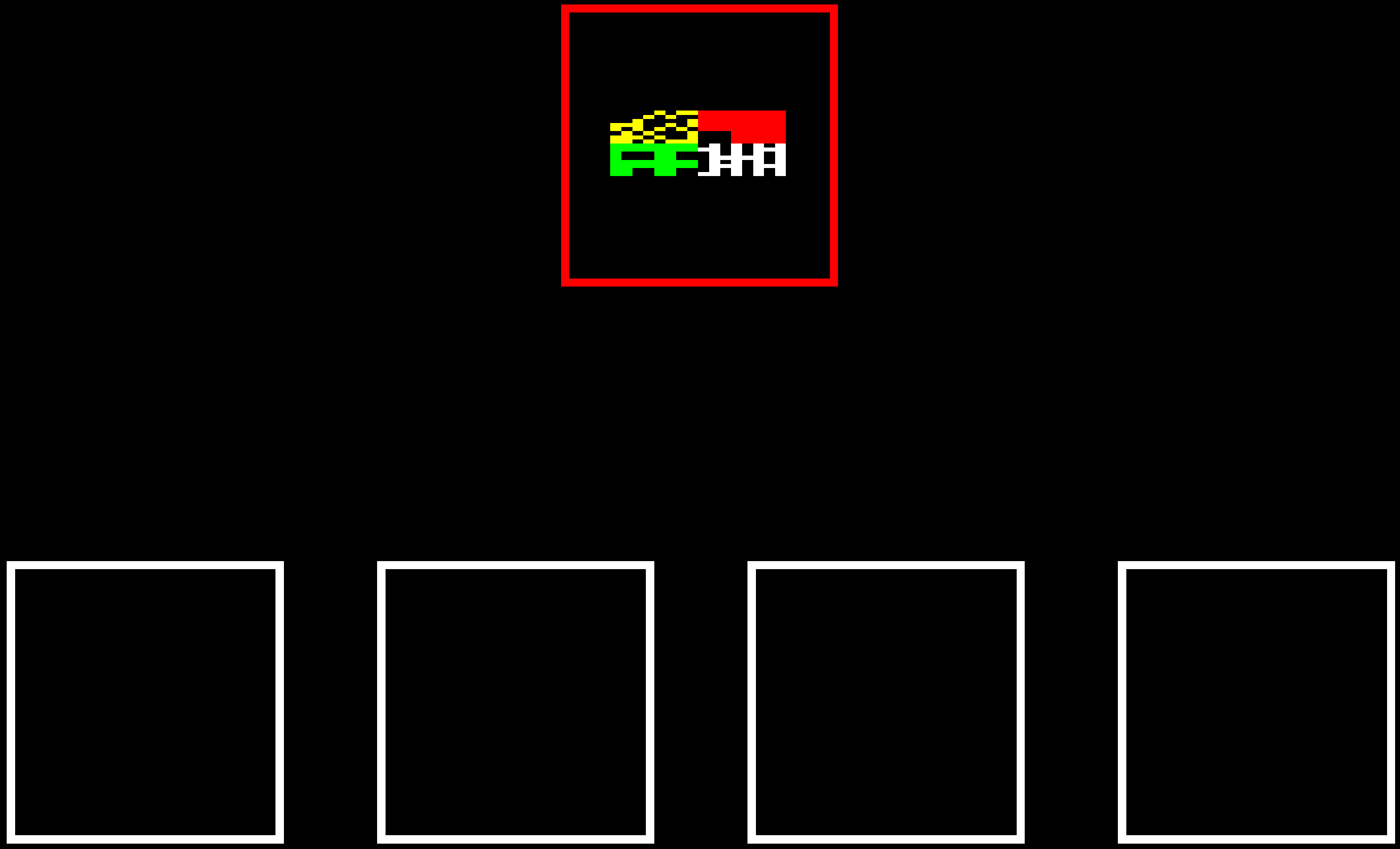


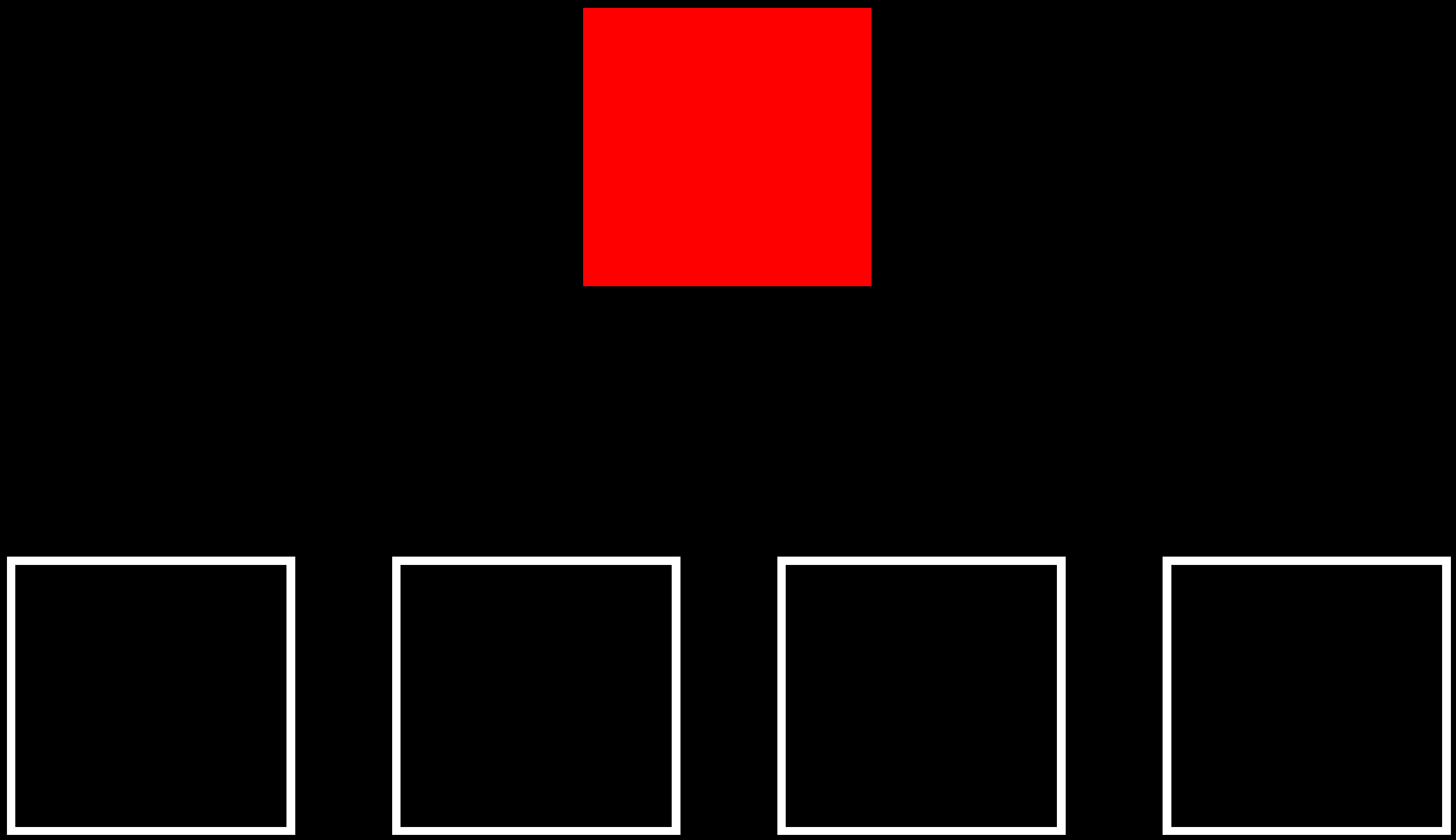
Spatial Working Memory

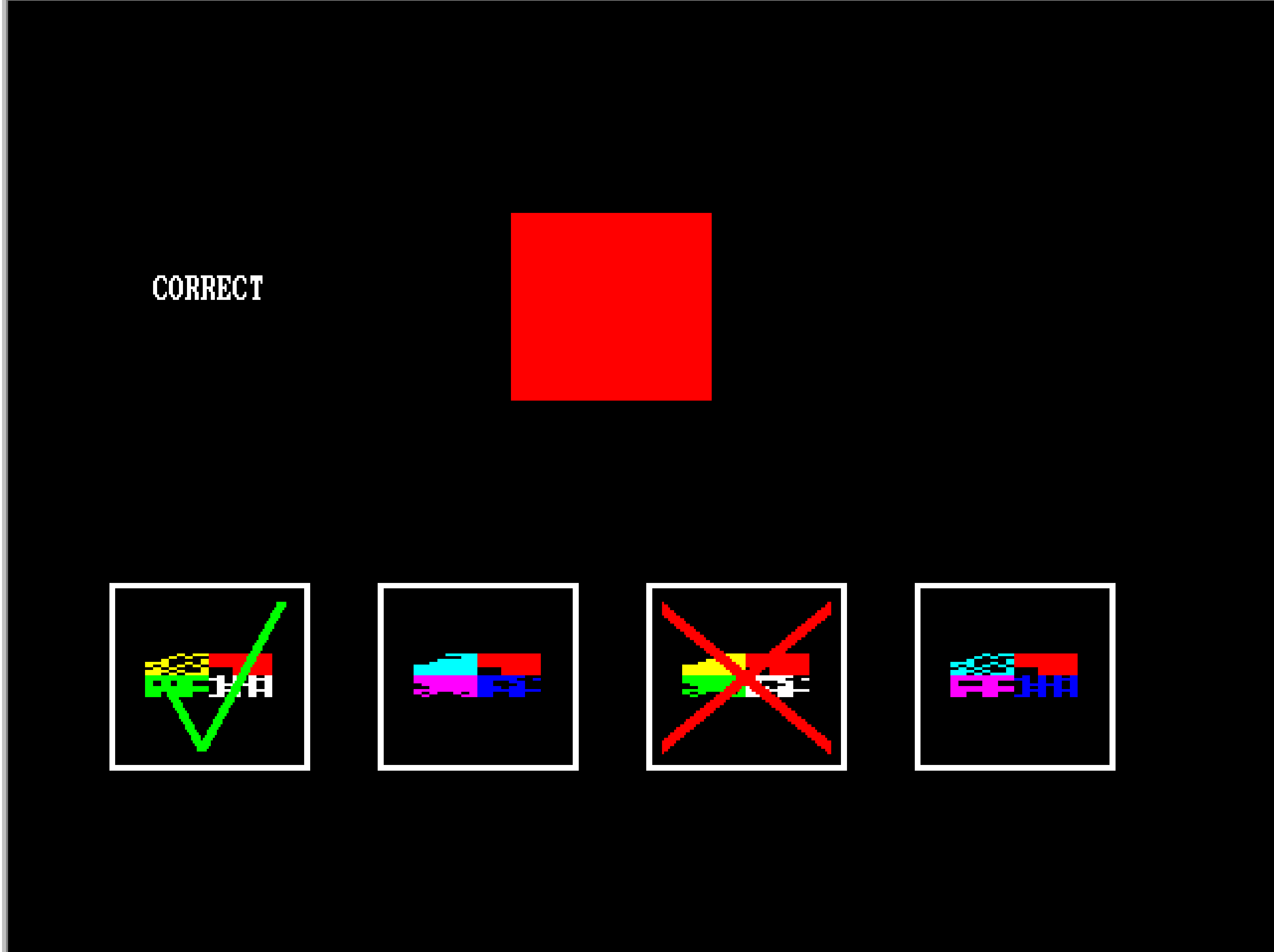


- working memory were not dependent on inhibitory deficits
- Therefore these may represent different pathways

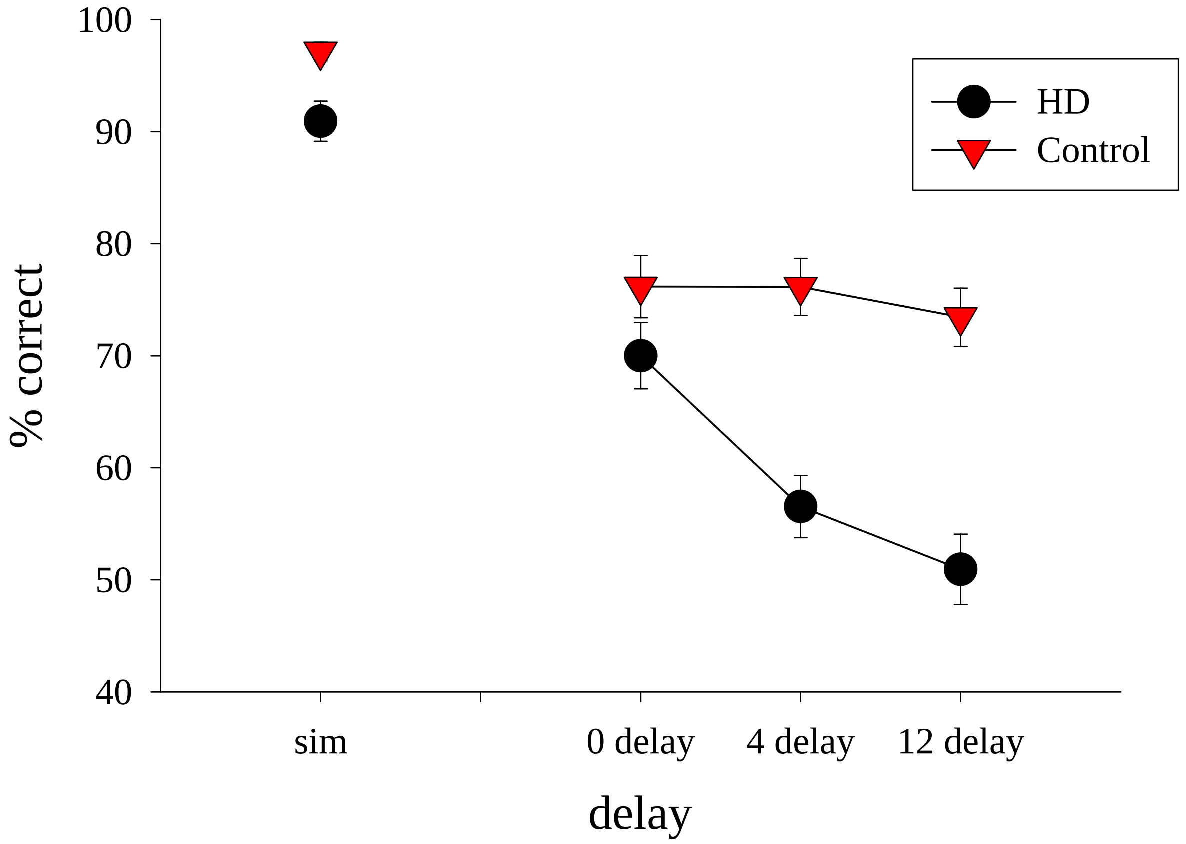




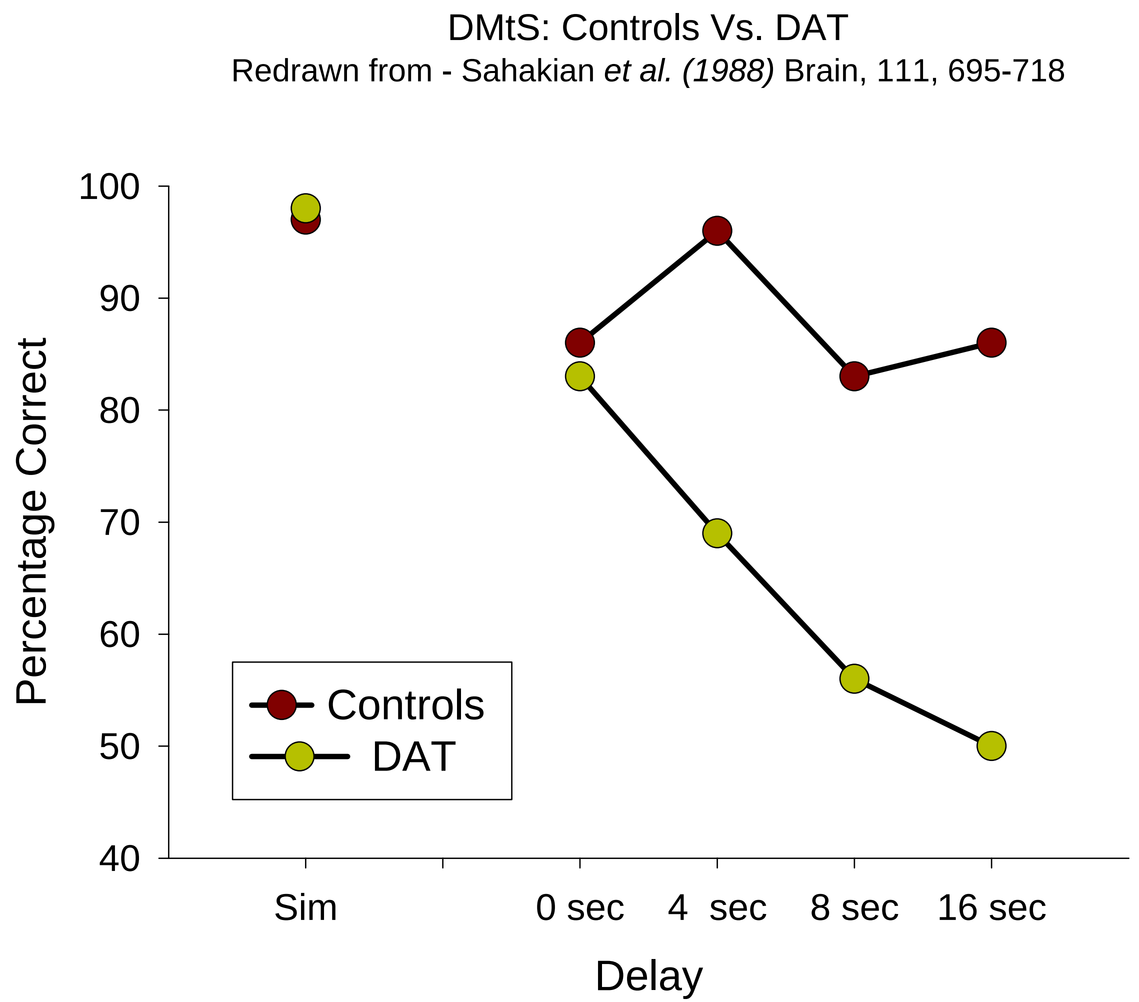



CORRECT

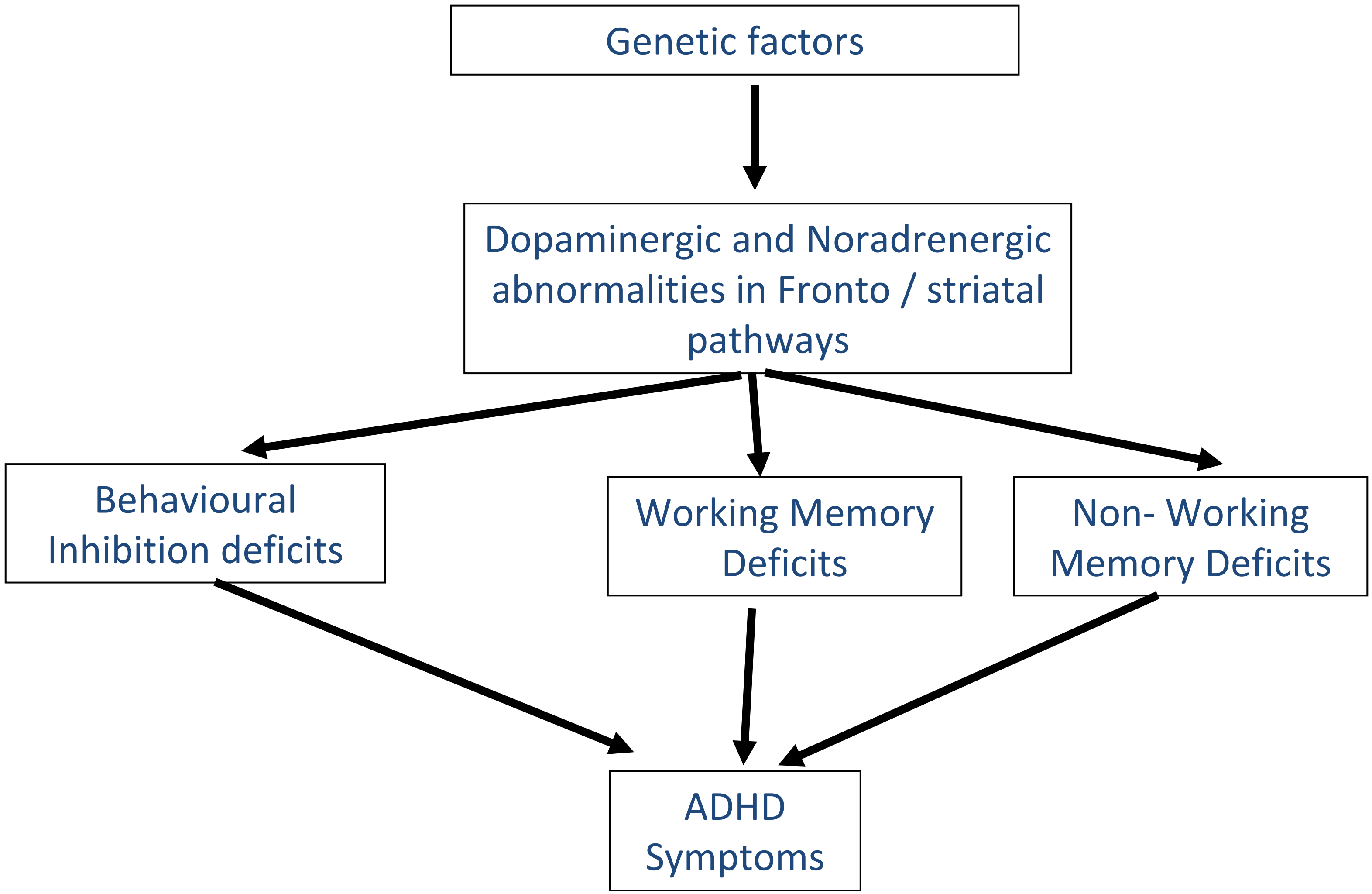
DMTS: ADHD vs Control (Drug Naive)



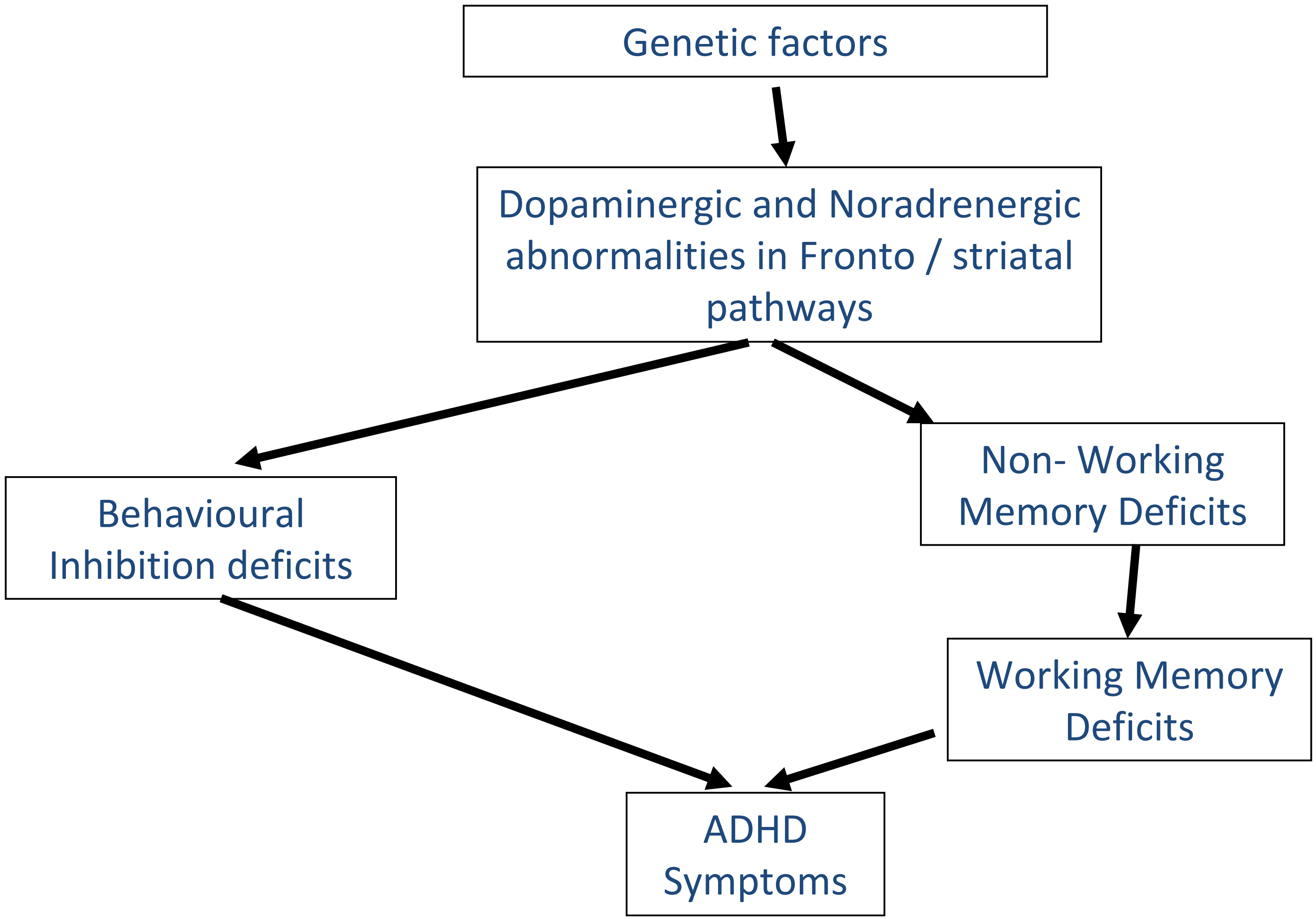
Rhodes, Coghill & Matthews (2004) Psychopharmacology


DMtS: Controls Vs. DAT
Redrawn from - Sahakian *et al. (1988)* Brain, 111, 695-718
100
90
80
70
60
50
40
Percentage Correct
Controls
DAT
Sim
0 sec
4 sec
8 sec
16 sec
Delay

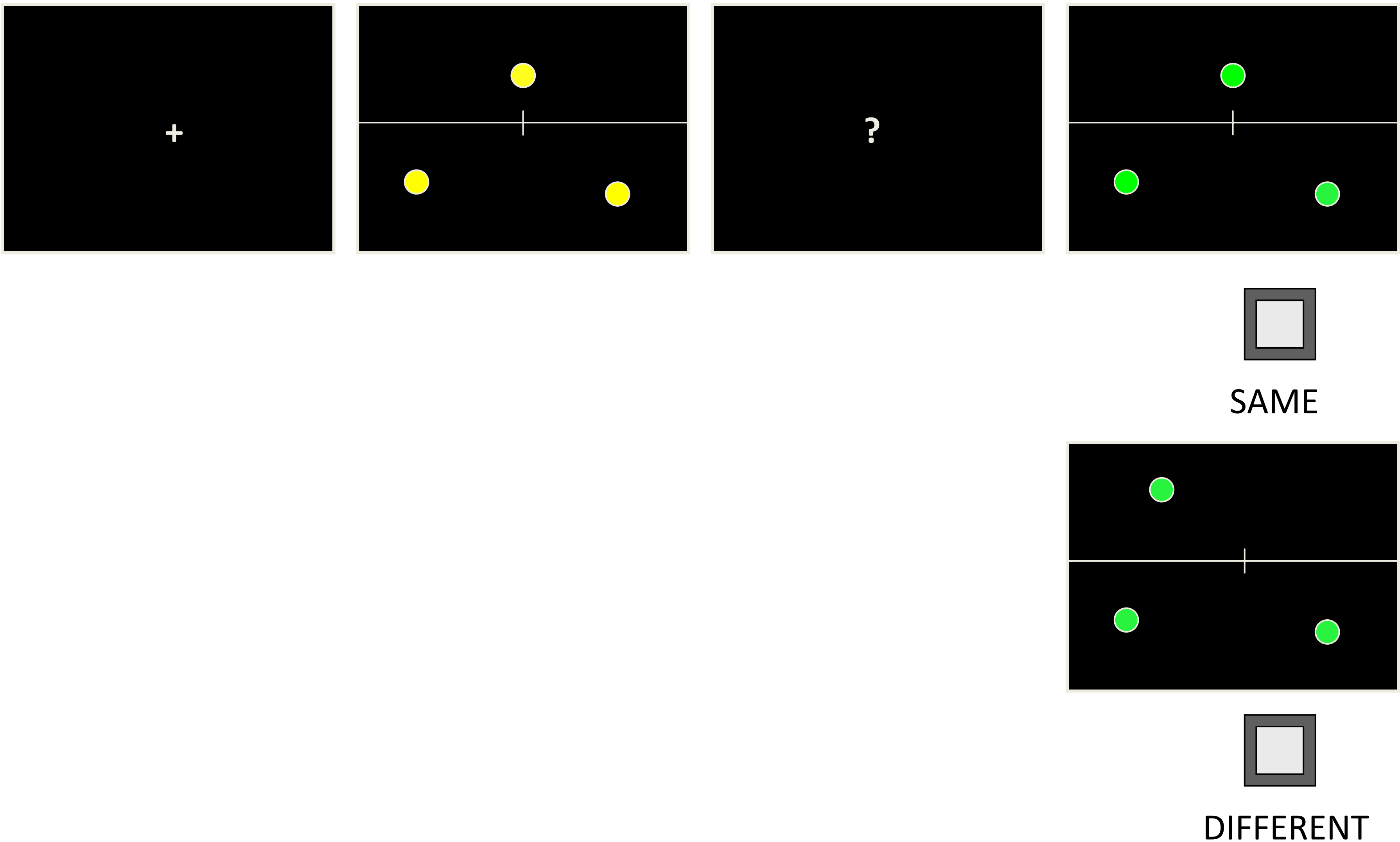
Possibly ?


Genetic factors
Dopaminergic and Noradrenergic abnormalities in Fronto / striatal pathways
Behavioural Inhibition deficits
Working Memory Deficits
Non- Working Memory Deficits
ADHD Symptoms

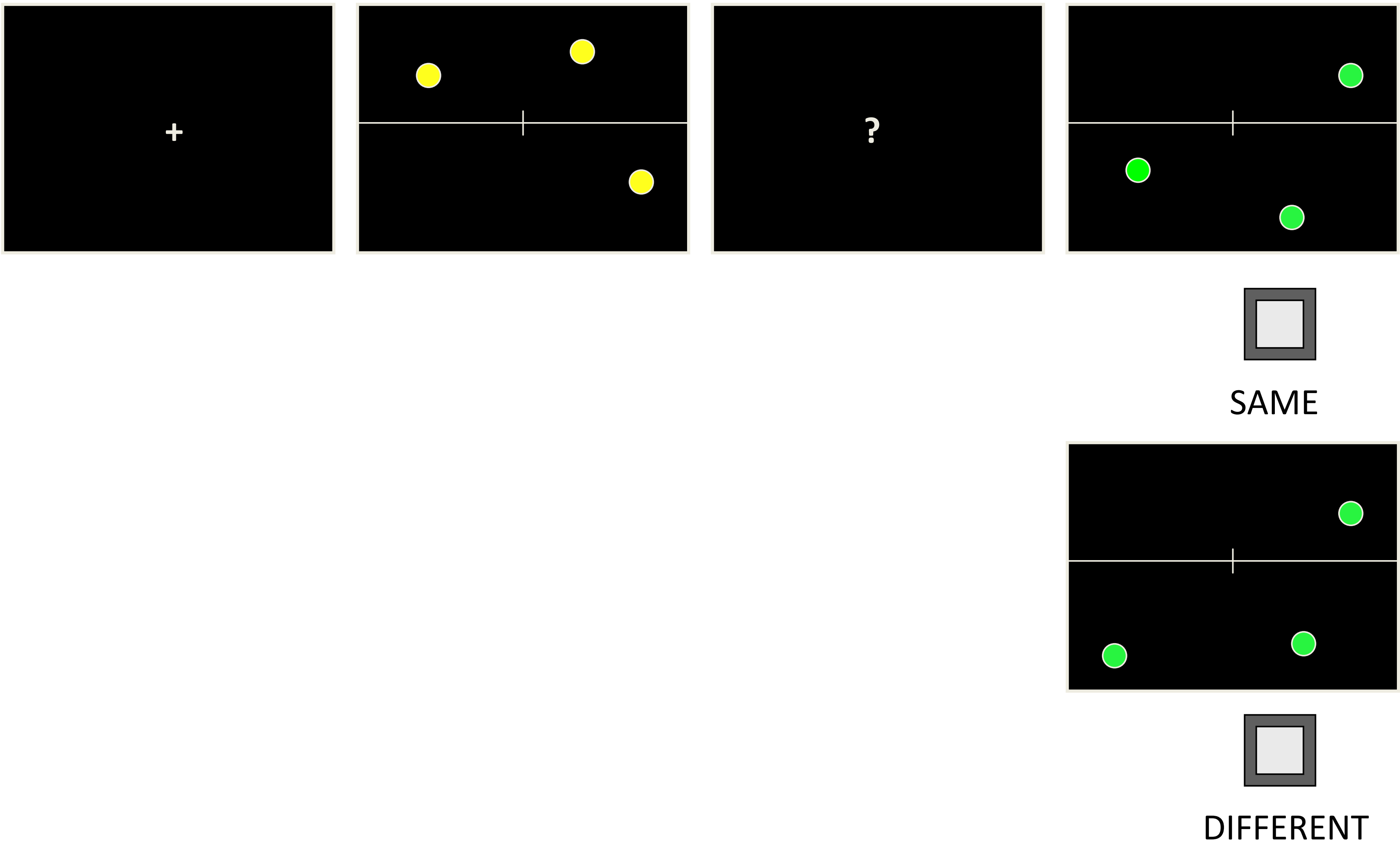
Or ?


Genetic factors
Dopaminergic and Noradrenergic abnormalities in Fronto / striatal pathways
Behavioural Inhibition deficits
Non- Working Memory Deficits
Working Memory Deficits
ADHD Symptoms

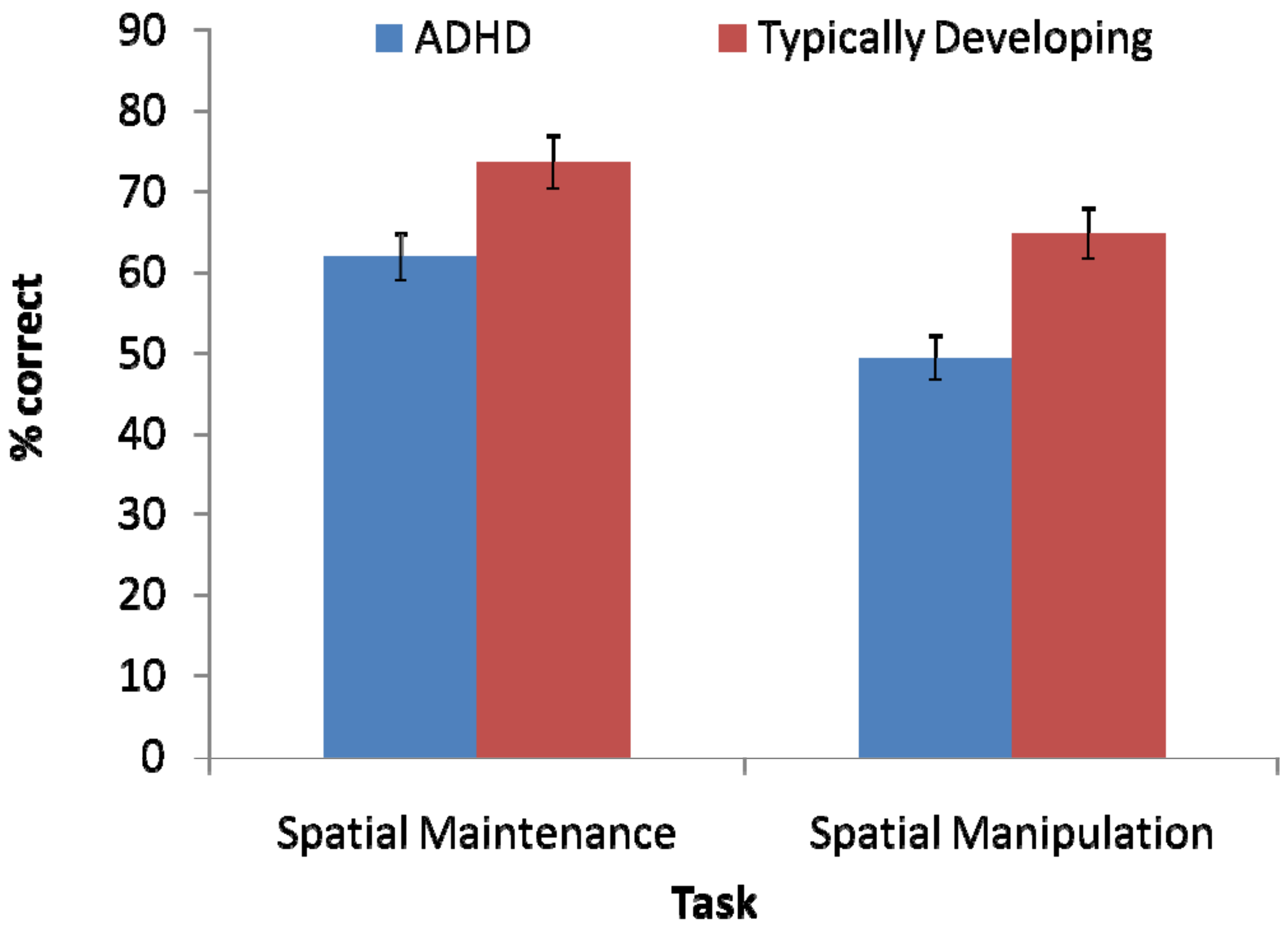
Spatial – maintaining information



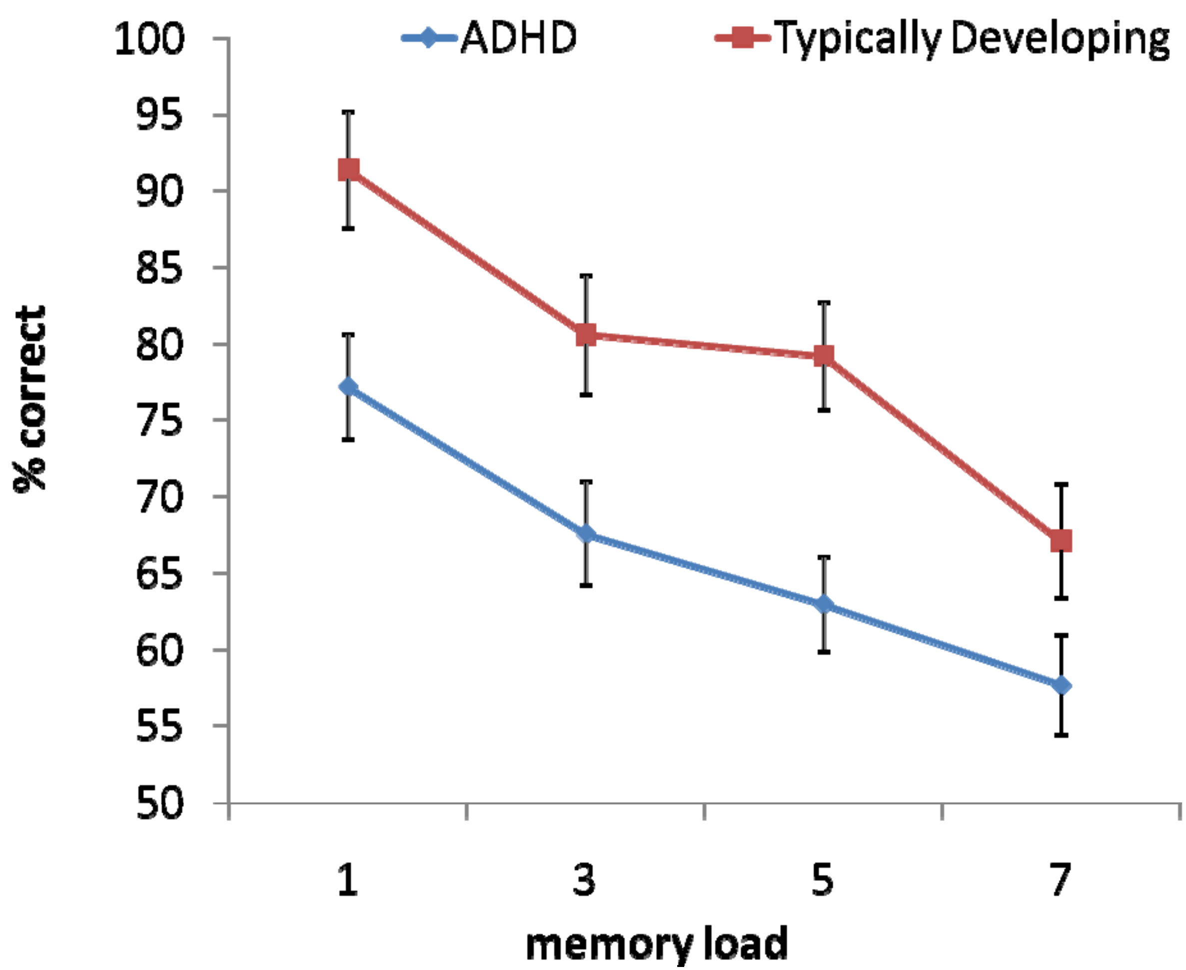
Spatial – manipulating information



Spatial Tasks - Results



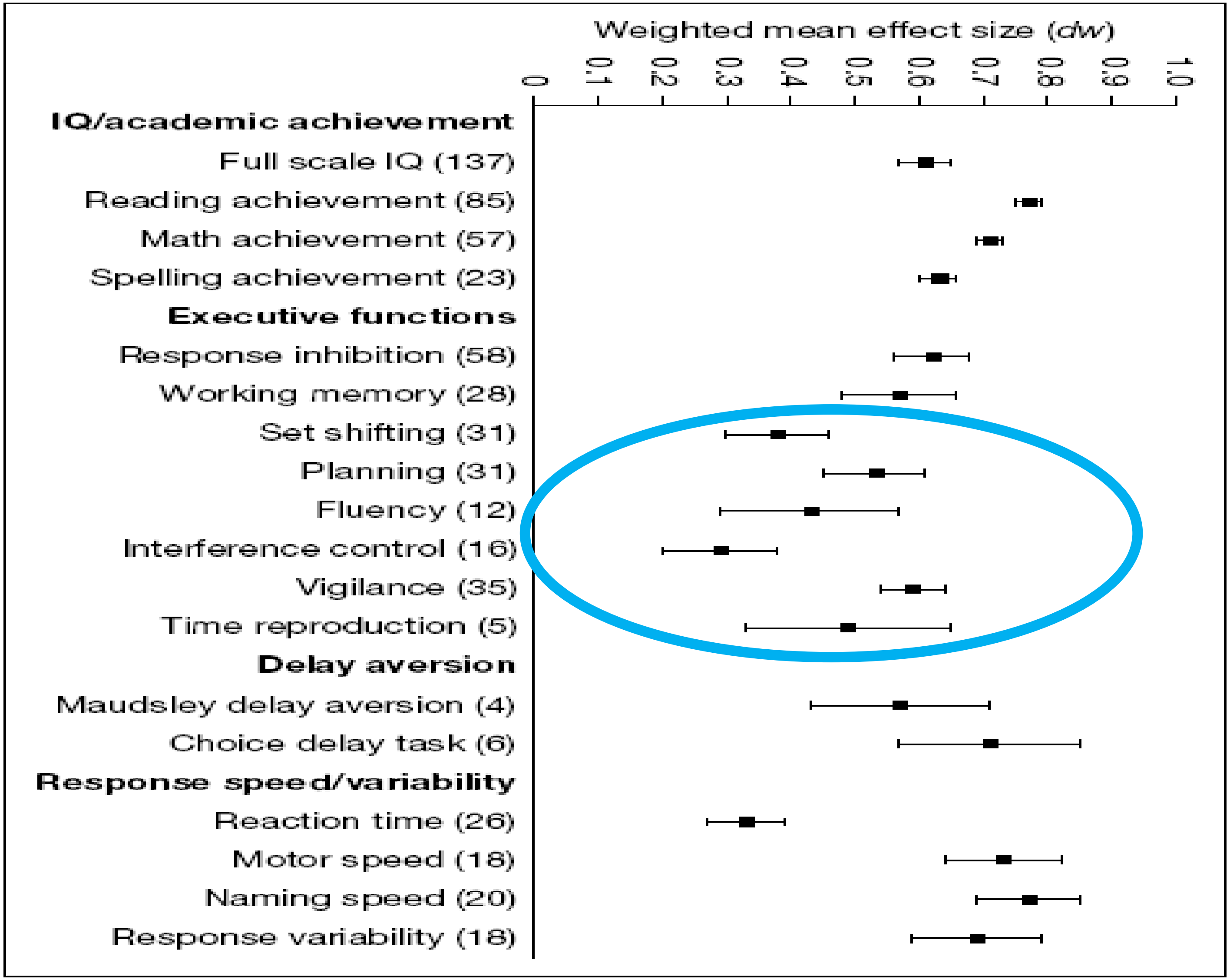
Spatial Loads - Results



Executive functioning ("Cognitive control")

- Control of motor response and behaviour ("Inhibition")
- Working memory
- Planning / organization
- State regulation / activation
- Set shifting

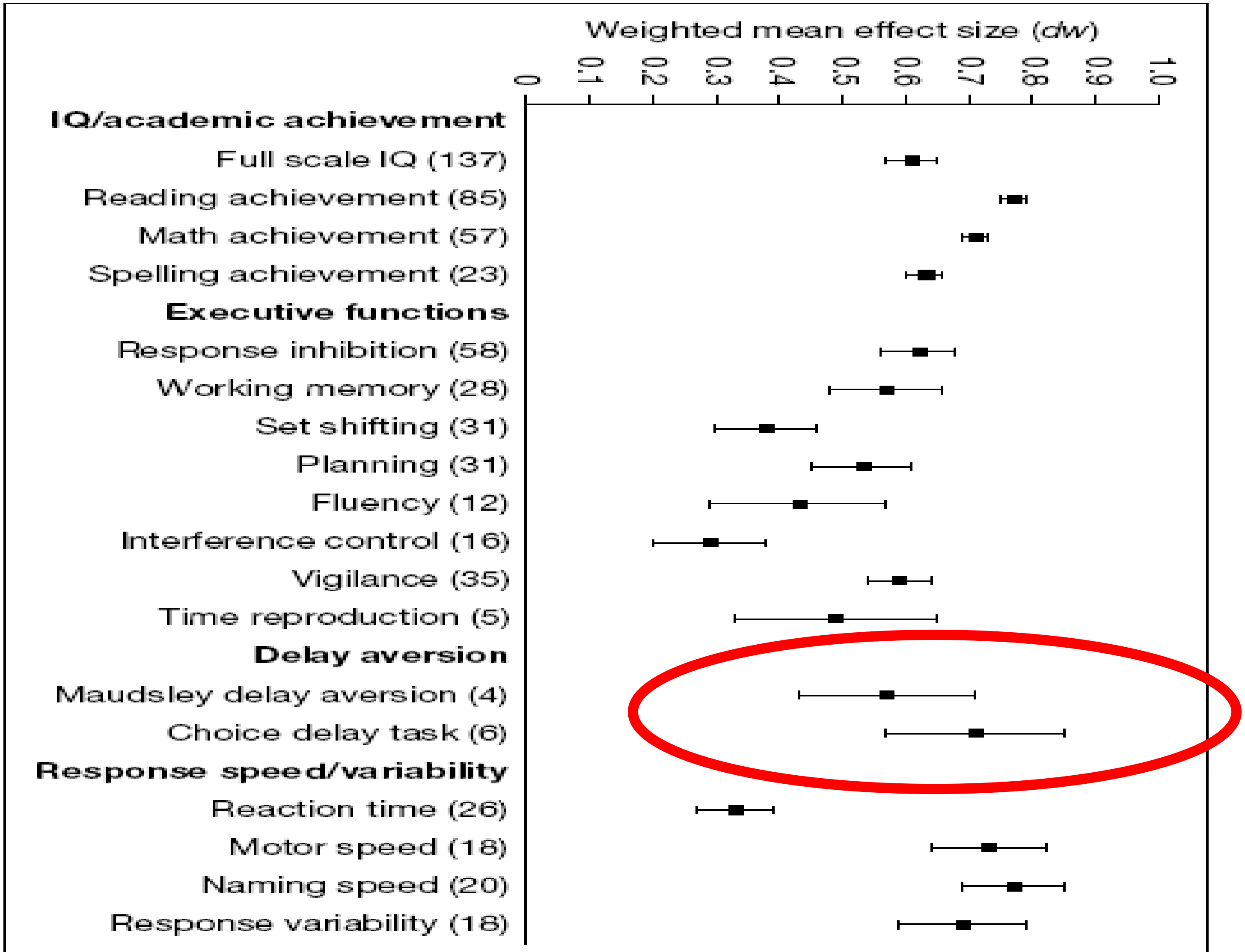
Weighted mean effect size of the difference between groups with and without ADHD



Neuropsychological Functions

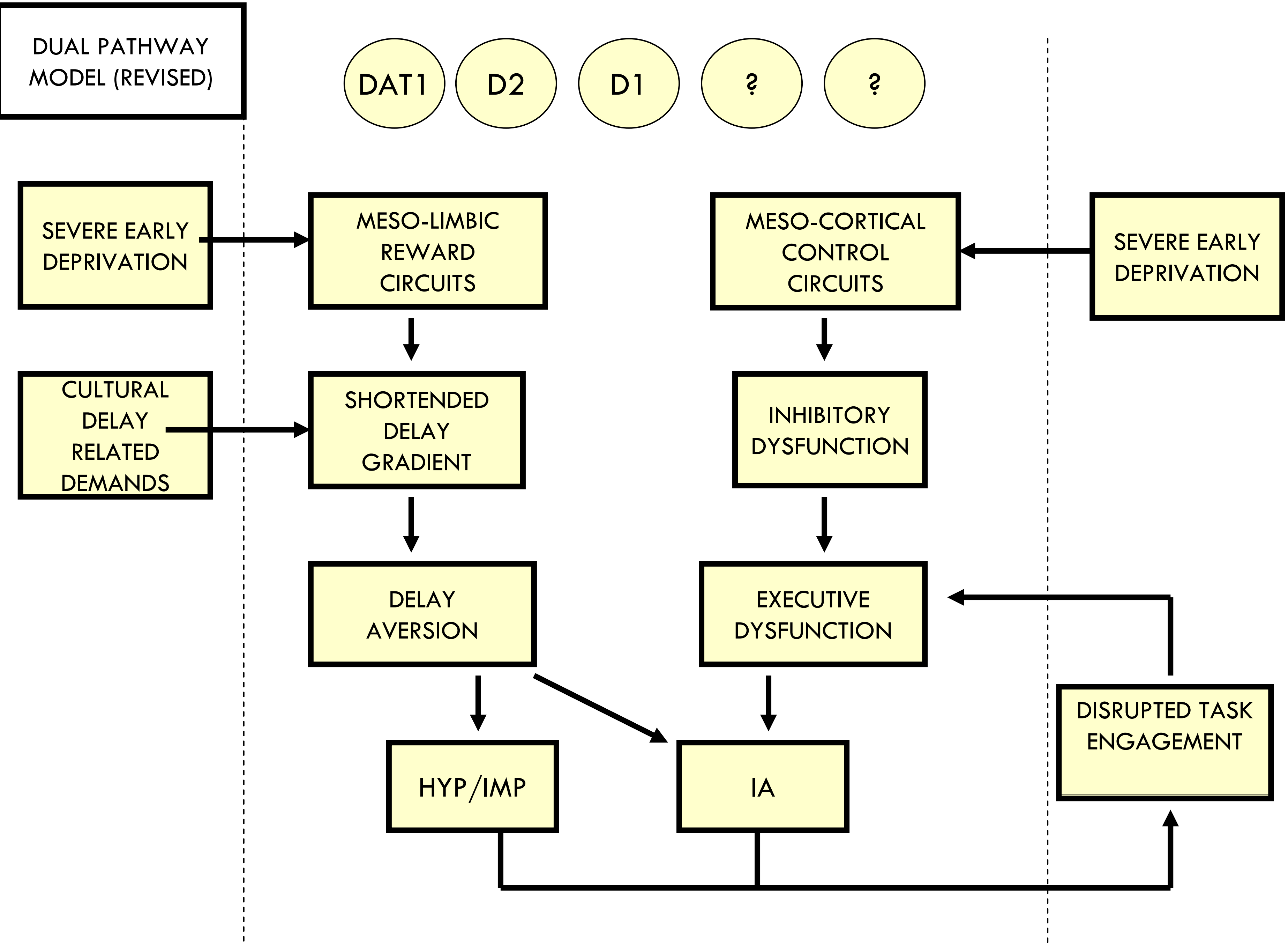
- Attention and arousal
- Executive functioning ("Cognitive control")
  - Control of motor response and behaviour ("Inhibition")
  - Working memory
  - Planning / organization
  - State regulation / activation
  - Set shifting
- Non executive memory processes
- Motivation (Including delay aversion)
- Response speed / variability

Weighted mean effect size of the difference between groups with and without ADHD

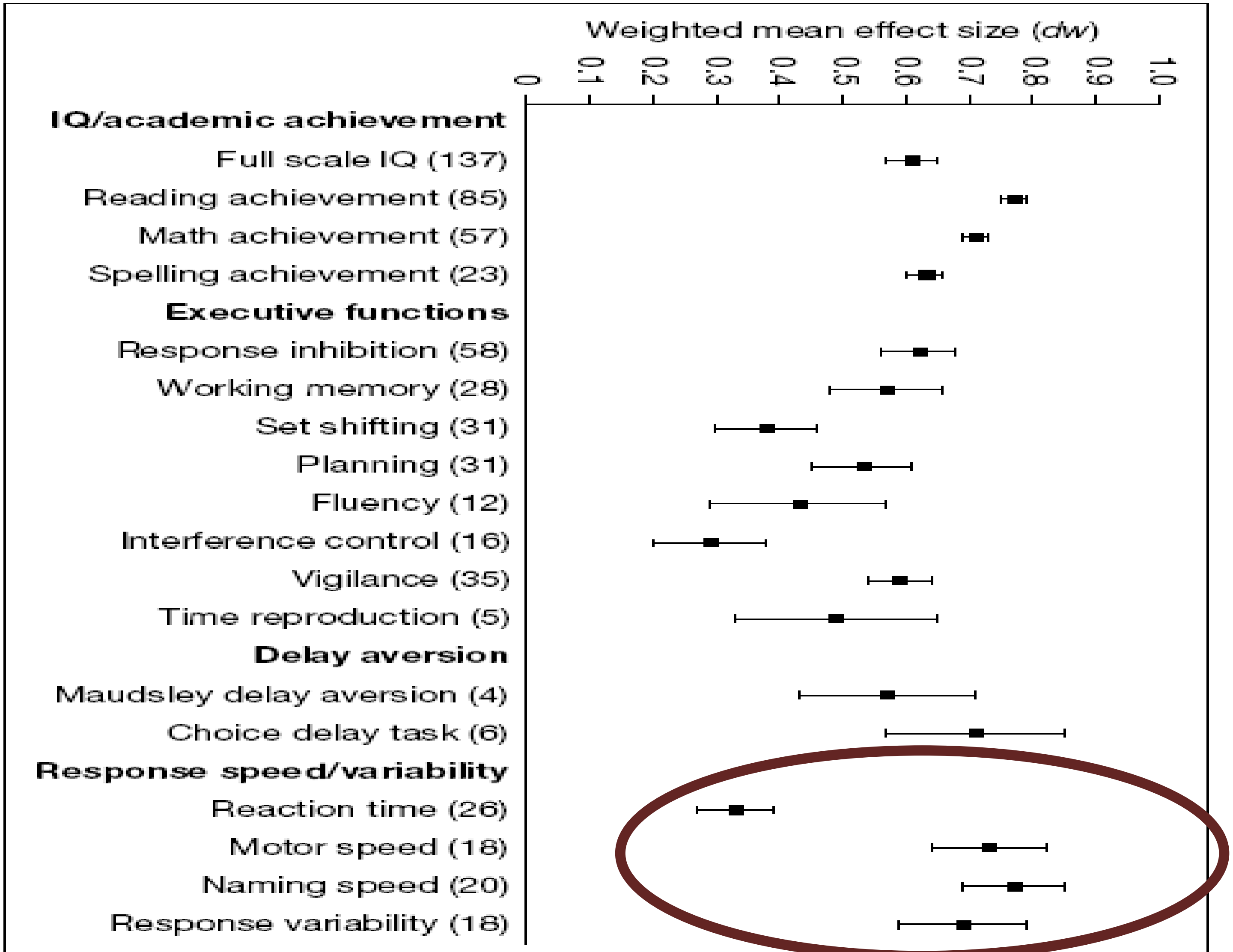


Delay aversion

- 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)
DAT1
D2
D1
?
?
SEVERE EARLY DEPRIVATION
MESO-LIMBIC REWARD CIRCUITS
MESO-CORTICAL CONTROL CIRCUITS
SEVERE EARLY DEPRIVATION
CULTURAL DELAY RELATED DEMANDS
SHORTENDED DELAY GRADIENT
INHIBITORY DYSFUNCTION
DELAY AVERSION
EXECUTIVE DYSFUNCTION
DISRUPTED TASK ENGAGEMENT
HYP/IMP
IA

Weighted mean effect size of the difference between groups with and without ADHD

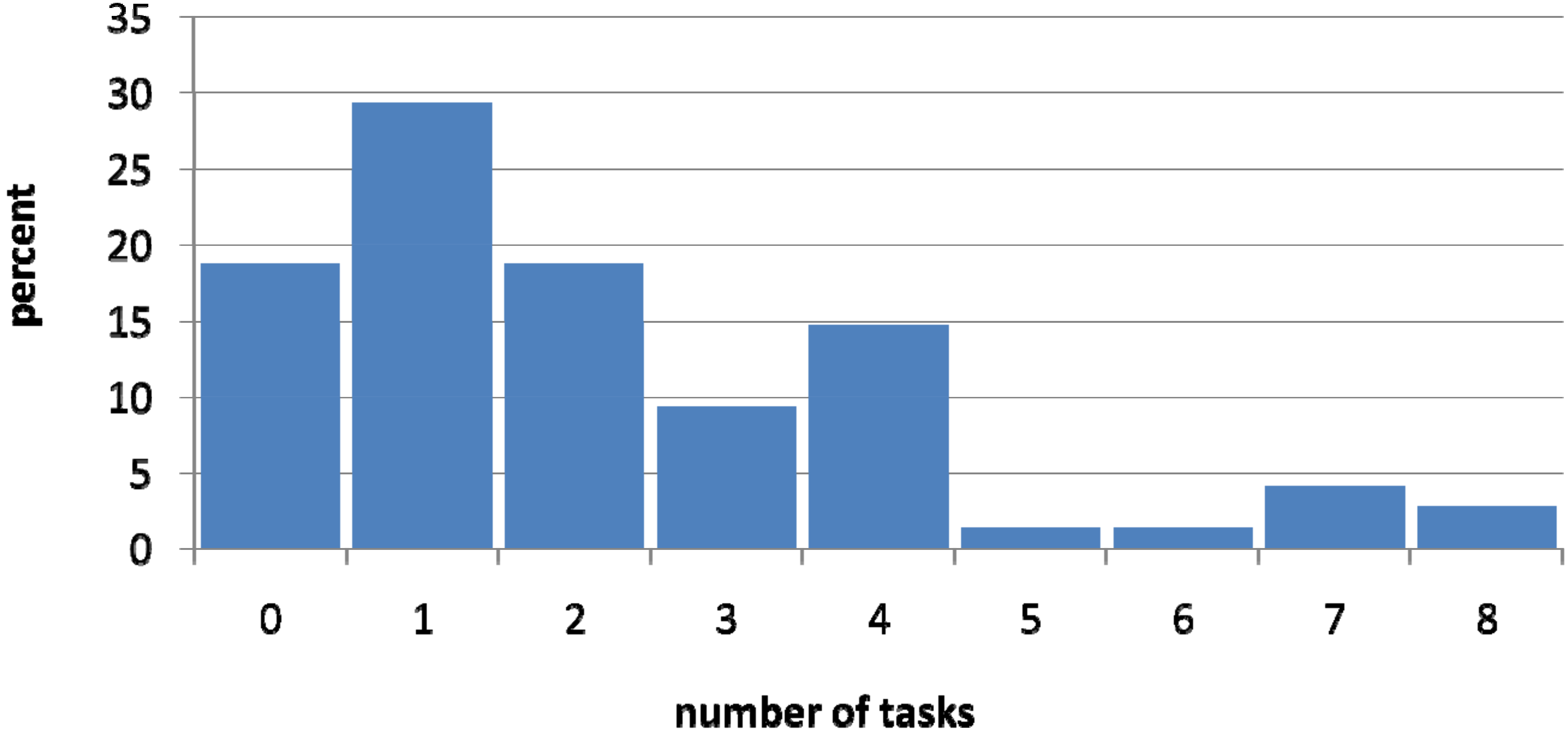


Hyperkinetic disorder vs controls effect size (d)	
Spatial Working Memory •BSE •Strategy	 0.75 0.70
Tower of London (Planning, working memory)	0.38
ID/ED Attentional Set Shifting	0.46
Spatial Span	0.60
Delayed Matching to Sample	0.92
Pattern Recognition	0.89
Spatial Recognition	0.72
PAL •Tot errors •Tot trials	 0.47 0.58
Reaction Time	0.71

Rhodes, Coghill & Matthews (2005) Psychological Medicine

Hyperkinetic disorder vs controls effect size (d)		Proportion ADHD cases with deficit (%)
Spatial Working Memory •BSE •Strategy	**0.75** **0.70**	**24** **15**
Tower of London (Planning, working memory)	**0.38**	**13**
ID/ED Attentional Set Shifting	**0.46**	**11**
Spatial Span	**0.60**	**11**
Delayed Matching to Sample	**0.92**	**39**
Pattern Recognition	**0.89**	**30**
Spatial Recognition	**0.72**	**28**
PAL •Tot errors •Tot trials	**0.47** **0.58**	**19** **21**
Reaction Time	**0.71**	**8**

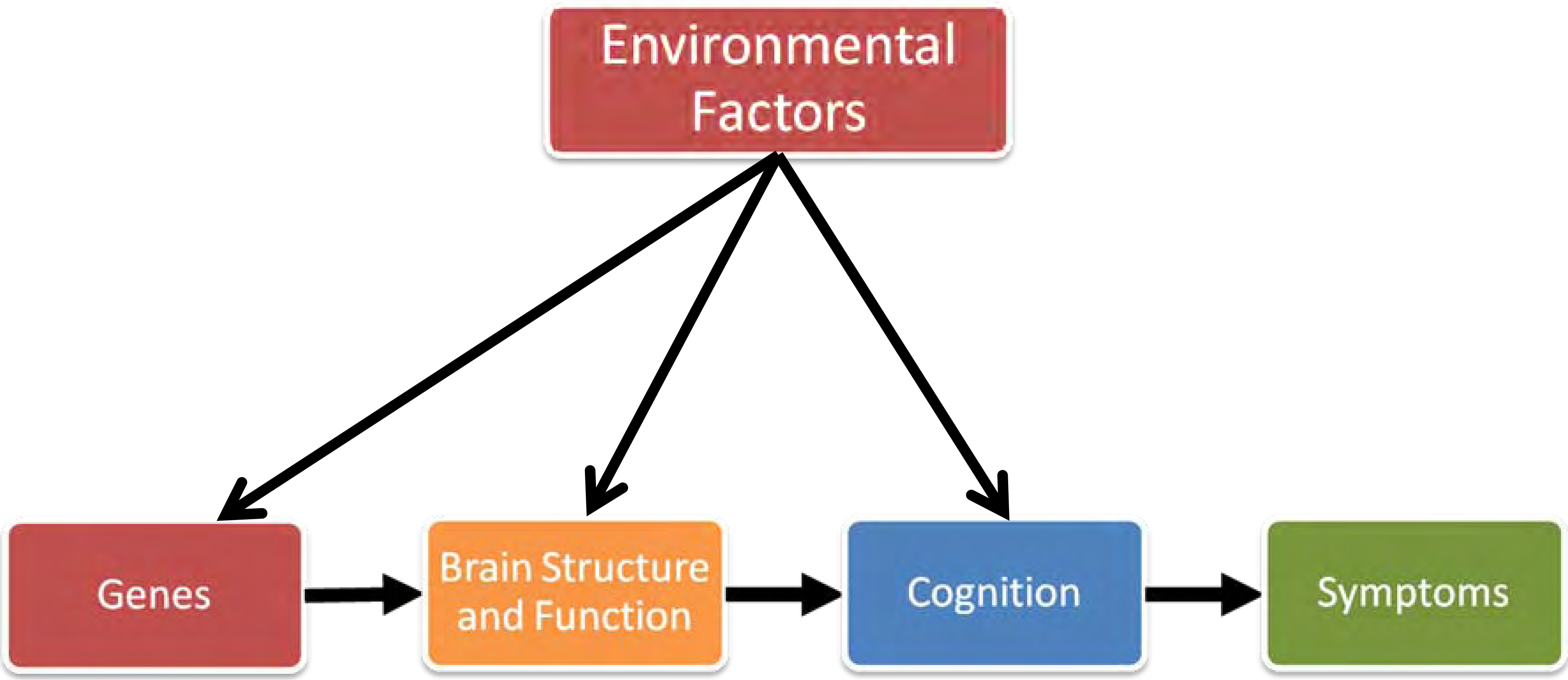
Variability of neuropsychological deficits in hyperkinetic disorder



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

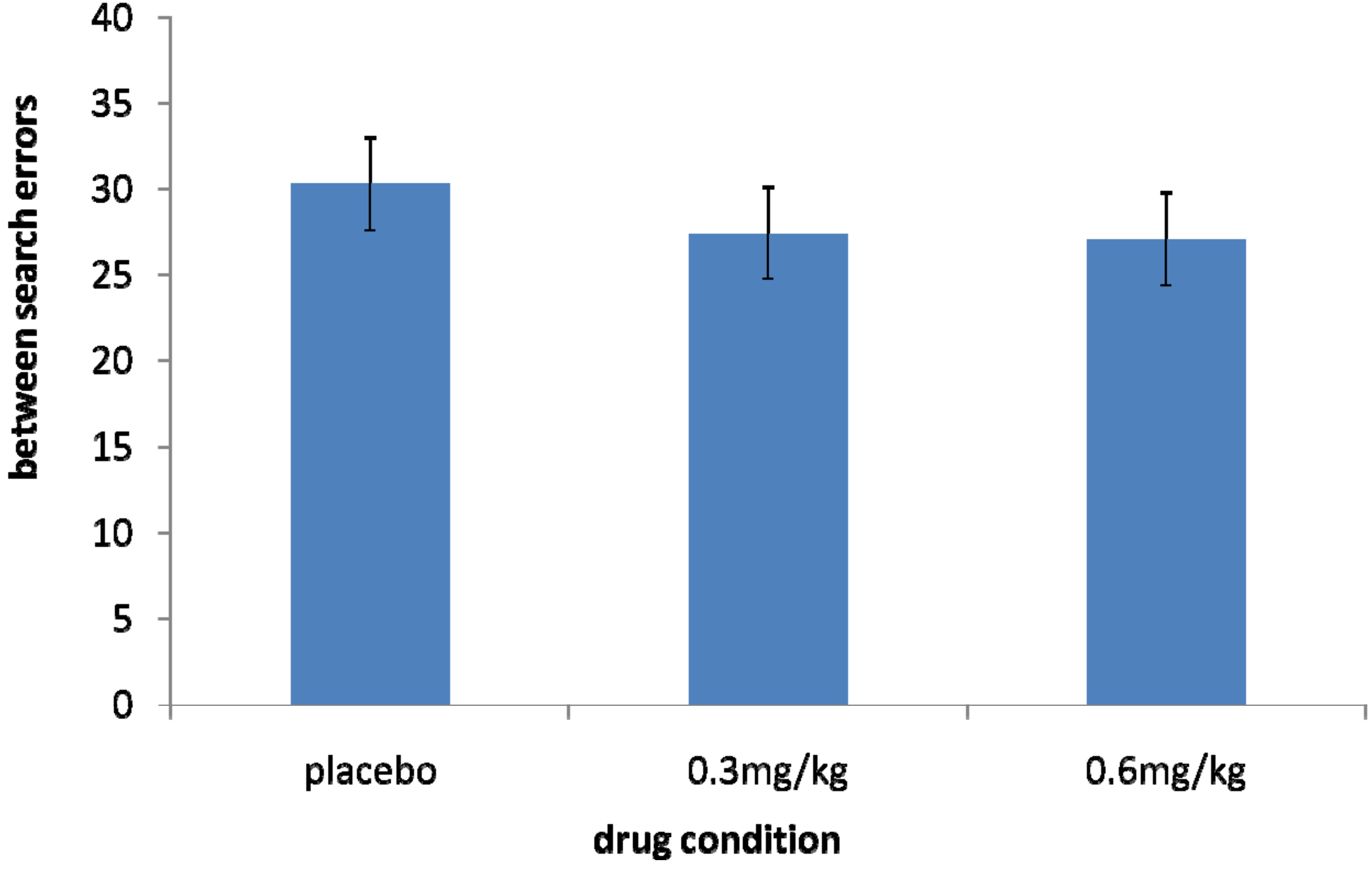
Do these neuropsychological deficits respond to treatment with stimulants?



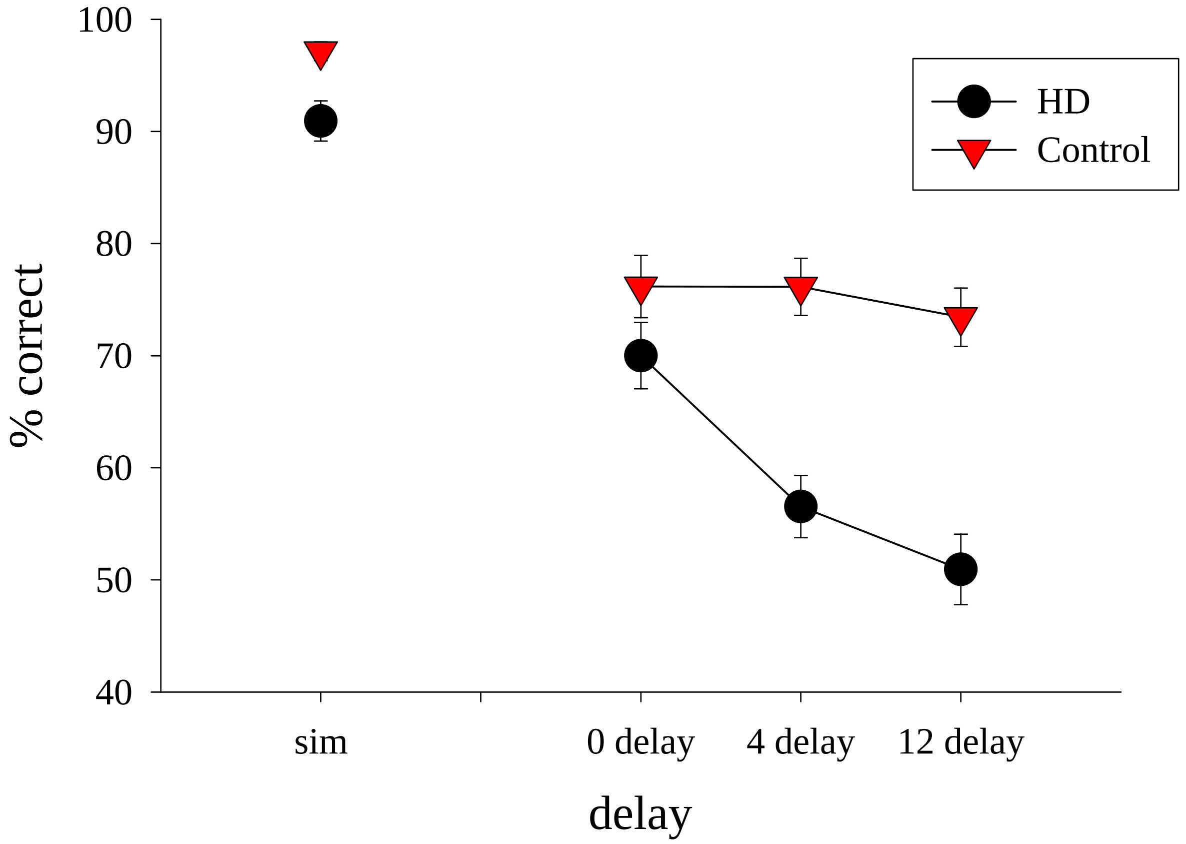
If medication effective in the treatment of ADHD would expect it to improve performance on the task

And for any reduction in symptoms to be related to this improvement in task performance.

Spatial Working Memory

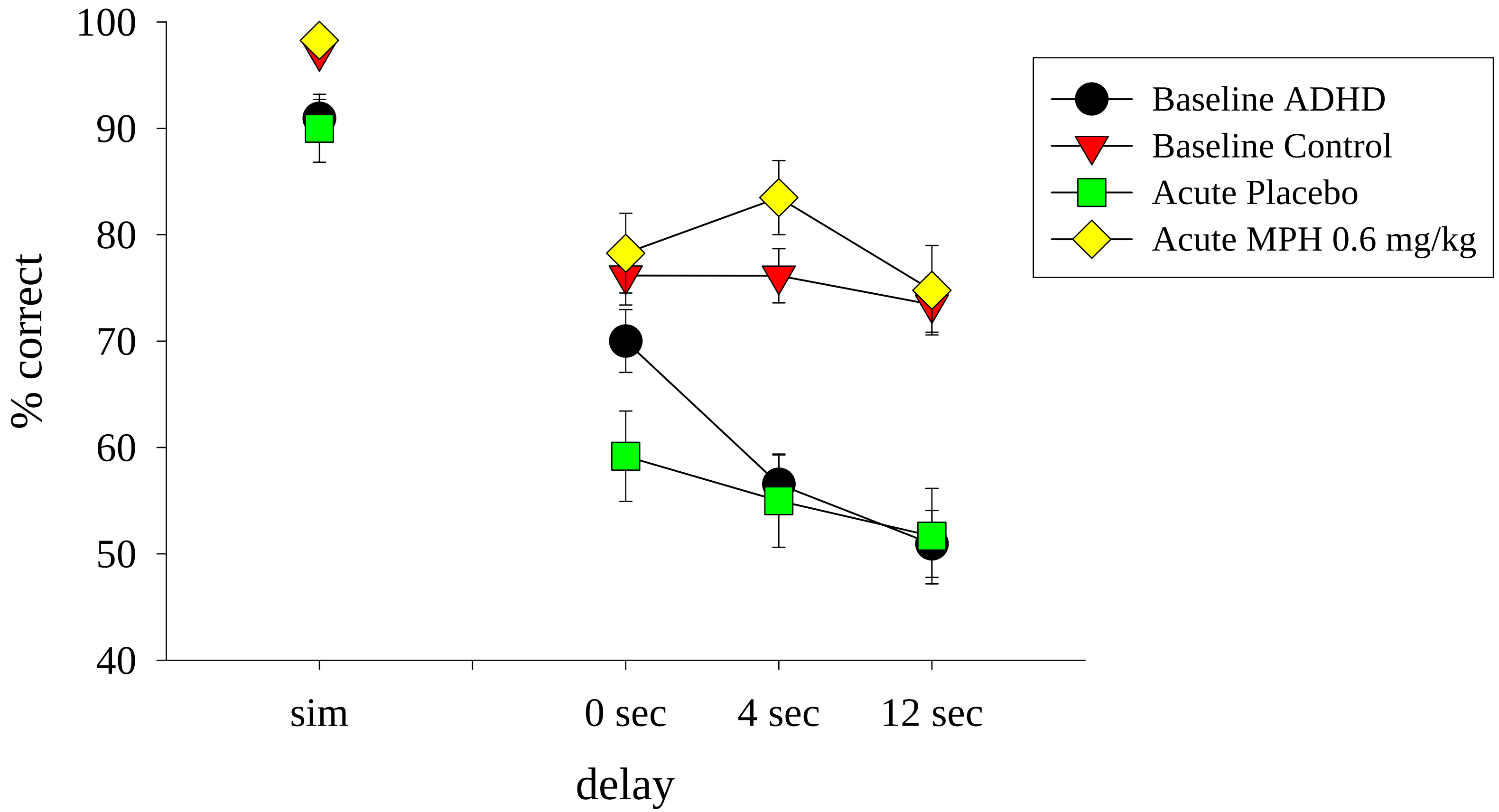


DMTS: ADHD vs Control (Drug Naive)



Rhodes, Coghill & Matthews (2004) Psychopharmacology

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



Rhodes, Coghill & Matthews (2004) Psychopharmacology

Neuropsychological Test	Effect of chronic methylphenidate
Spatial Working Memory	No significant effect of MPH on any measure
Stockings of Cambridge	No significant effect of MPH on any measure
ID/ED (attentional set-shifting)	No significant effect of MPH on any measure
Spatial Span	No significant effect of MPH on any measure
Delayed Matching to Sample	0.3 & 0.6mg/kg MPH improved performance on simultaneous & delay conditions
Pattern Recognition	0.3 & 0.6mg/kg MPH improved performance
Spatial Recognition	0.3 & 0.6mg/kg MPH improved performance
Paired Associates Learning	No significant effect of MPH on any measure
Reaction Time	No significant effect of MPH on any measure

Coghill, Rhodes & Matthews (2007) Biological Psychiatry

ADHD: Impact of Untreated & Undertreated ADHD continues through adolescence and into adulthood

Healthcare System

50% ↑ in bike accidents[1]

33% ↑ in ER visits[2]

2–4 x more motor vehicle crashes[3-5]

Patient

Family

3–5 x ↑ parental divorce or separation[11,12]

2–4 x ↑ sibling fights[13]

School & Occupation

46% expelled[6]

35% drop out[6]

Lower occupational status[7]

Society

Substance use disorders:

2 x risk[8]

Earlier onset[9]

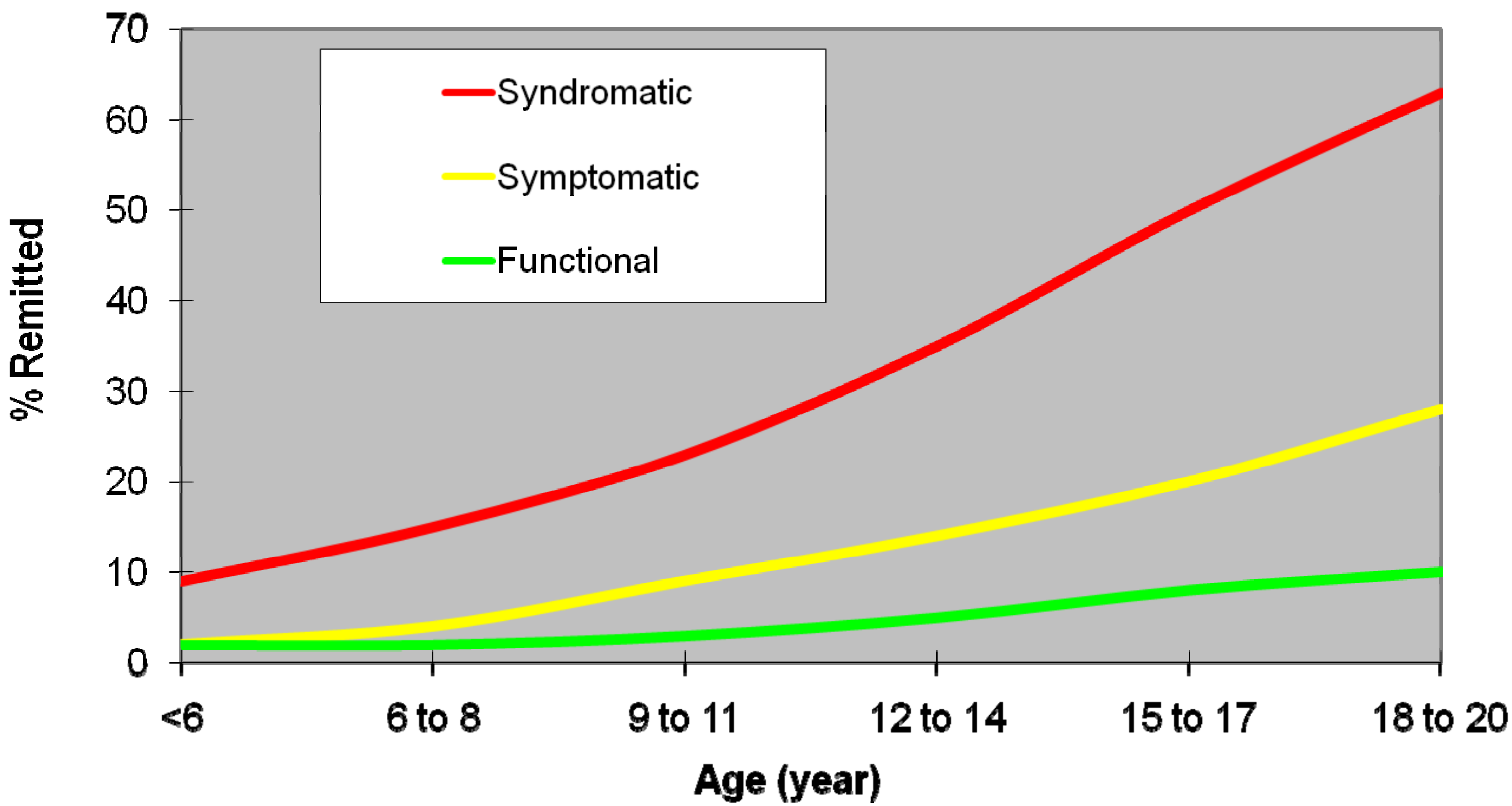
Less likely to quit in adulthood[10]

Employer

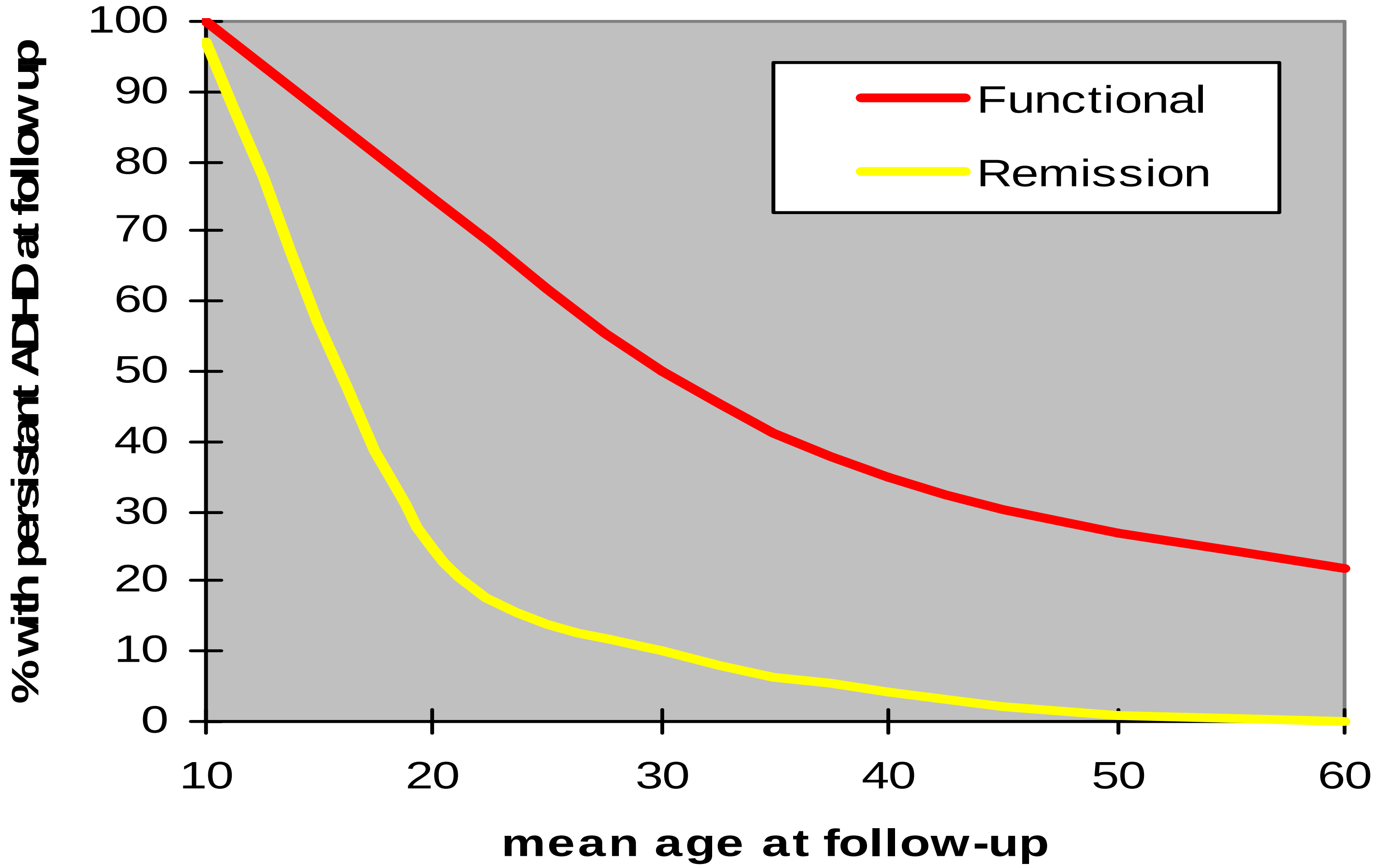
↑ parental absenteeism and productivity[14]

[1]DiScala et al, 1998.
[2]Liebson et al, 2001.
[3]NHTSA, 1997.
[4-5]Barkley et al, 1993, 1996.
[6]Barkley et al, 1990.
[7]Mannuzza et al, 1997.
[8]Biederman et al, 1997.
[9]Pomerleau et al, 1995.
[10]Wilens et al, 1995.
[11]Barkley et al, 1991.
[12]Brown & Pacini, 1989.
[13]Mash & Johnston, 1983.
[14]Noe et al, 1999.

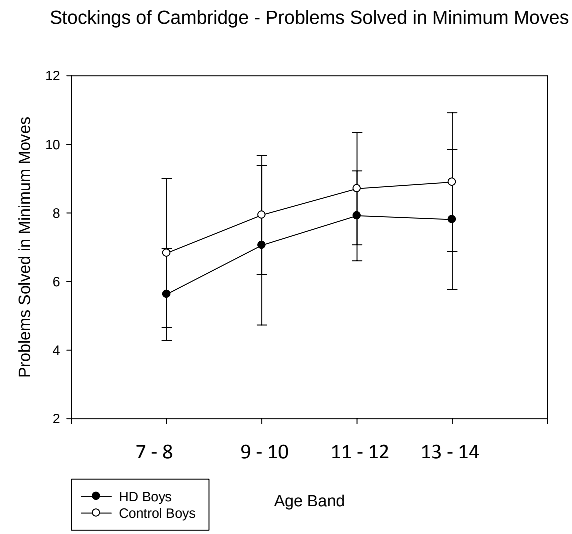
Patterns of ADHD across development

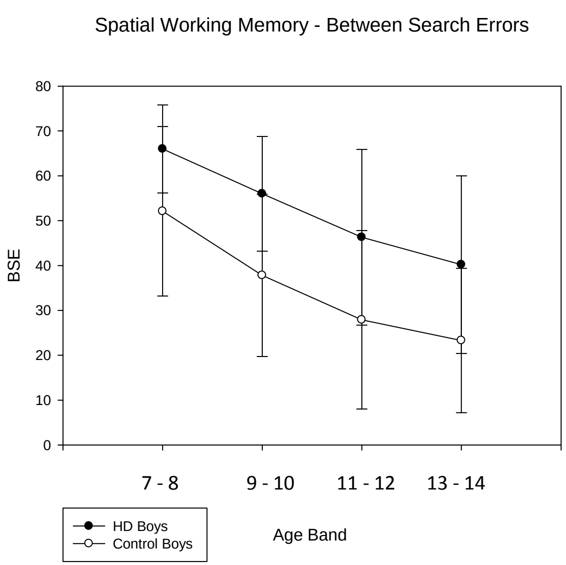


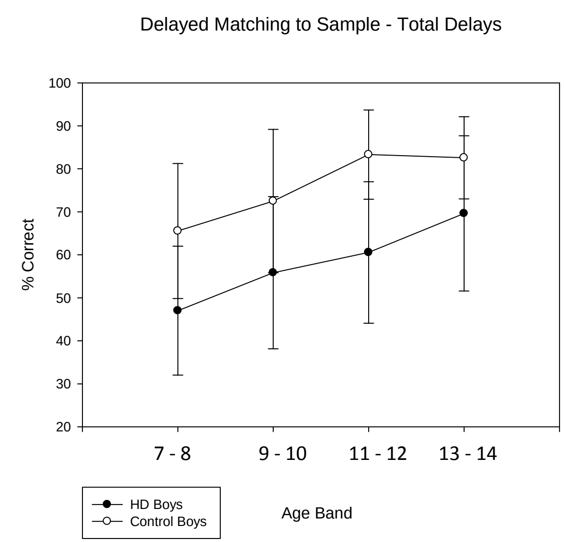
Patterns of ADHD across development



The development of cognitive abilities in ADHD

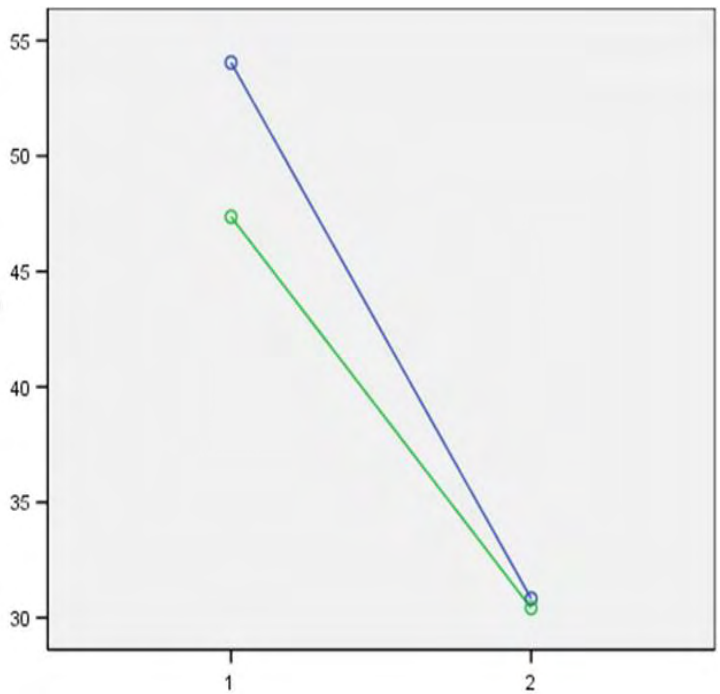




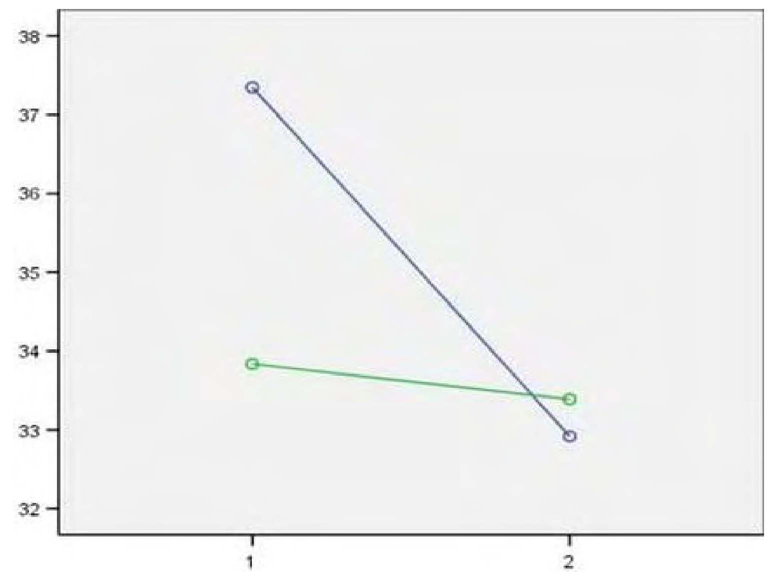


The development of Spatial Working Memory in ADHD

Between Search Errors
Effect of age
No effect group
No interaction



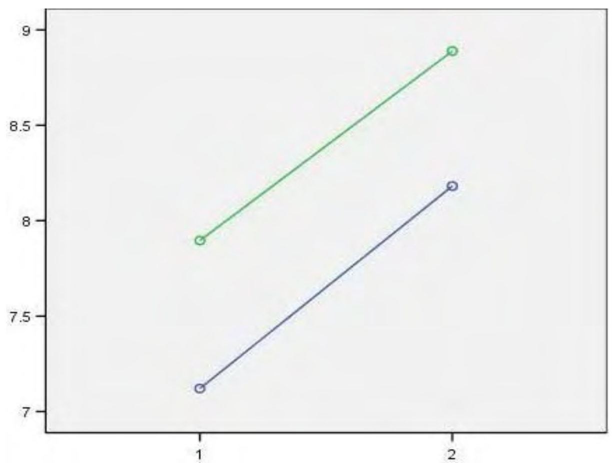
Strategy Score
Effect of age
Effect of group
Interaction between age and group



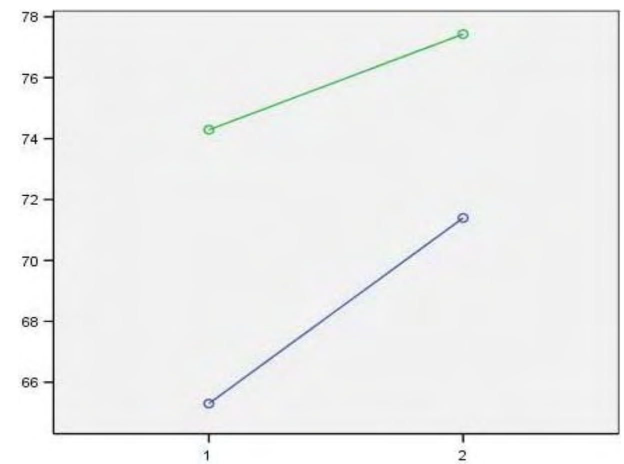
Mean Age at T1 ≈ 10 years , Mean age at T2 ≈ 14 years

The development of other neuropsychological functions in ADHD

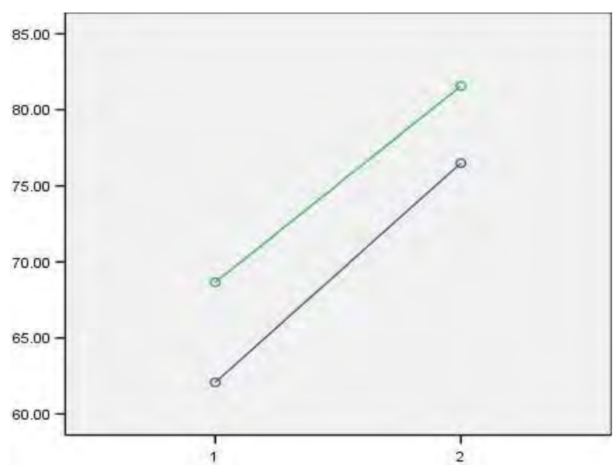
ID / ED Shift



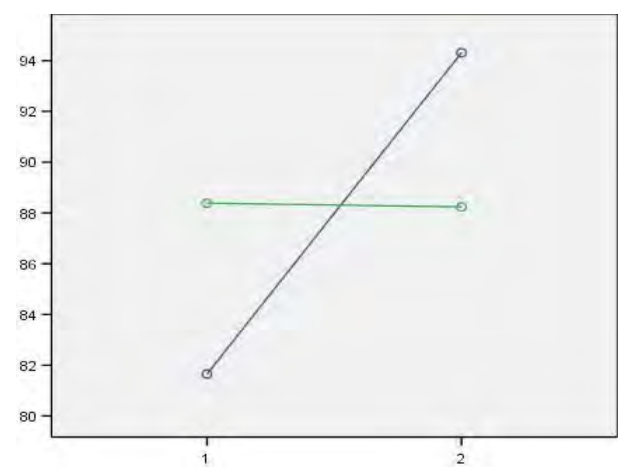
Spatial Recognition



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.