A Multiple Deficit Model of ADHD

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Collaborators

Colorado Learning Disability Research Center (CLDRC)

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Outline

I Single Deficit Models of ADHD

- A. Executive Inhibition
- B. State Regulation
- C. Delay Aversion

II Why Single Deficit Models Fail

- A. Review of Executive Inhibition Model: Inhibition deficit is associated, coheritable, but not pervasive in ADHD
- B. Tests of Motivational Effects
  1. Motivational Inhibition Tasks
  2. Manipulating Incentives on the Stop Task
  3. Delay Aversion
  4. Orbital Frontal Tasks: Object Reversal and Gambling

III What is the Multiple Deficit Model?

IV Multiple Deficit Model Applied to Comorbidity of ADHD and RD

- A. ADHD and RD have a genetic overlap
- B. ADHD and RD have a cognitive overlap

V. Conclusions

Cognitive Mechanisms in ADHD

Distinctive cognitive Profile — Douglas (1988)

Impairments in vigilance, systematic search, motor inhibition, tasks without extrinsic rewards.

Not impaired on basic verbal and nonverbal memory tasks.

Executive Deficits — Pennington & Ozonoff (1996)

Consistent for MFFT errors and Motor Inhibition Tasks, like Go No-Go, Stopping.

Not consistent for WCST, Fluency tasks

The Frontal Hypothesis in ADHD

Frontal Lobe Dysfunction

- Pontius (1973)
- Rosenthal & Allen (1978)
- Stamm & Kreder (1979)
- Gualtieri & Hicks (1985)
- Zametkin & Rapaport (1986)
- Mattes (1989)

Executive Dysfunction

- Douglas (1983)
- Conners & Wells (1986)
- Pennington (1991)
- Schachar, Tannock, & Logan (1993)
- Pennington & Ozonoff (1996)
- Barkley (1997)
- Nigg (2000)

Executive Inhibition Hypothesis

Key Idea: The PFC-mediated process of voluntary motor inhibition is impaired in ADHD.

Marker task: Stopping task (Logan, Cowan & Davis, 1984)

Fundamental Questions:

1) Inhibition deficits are found in other disorders.

2) If someone fails to inhibit, is it because top-down control is too weak, or because bottom-up impulses are too strong, or both?

State Regulation Models of ADHD

Sergeant & van der Meere (1990)
Douglas (1989)

Key Idea: In contrast to executive inhibition model, holds that core problem is in maintaining optimal state for task. For instance, manipulation of event rate can lessen inhibition deficits.

Marker tasks: Reaction time (RT) and RT variability (SDRT)

Fundamental Questions:

1) Slower and more variable RTs are pervasive in developmental disabilities.

2) Neuroimaging studies of RT and SDRT implicate PFC.

Delay Aversion (DA)

Sonuga-Barke (2005)
Sagvolden et al. (2004)

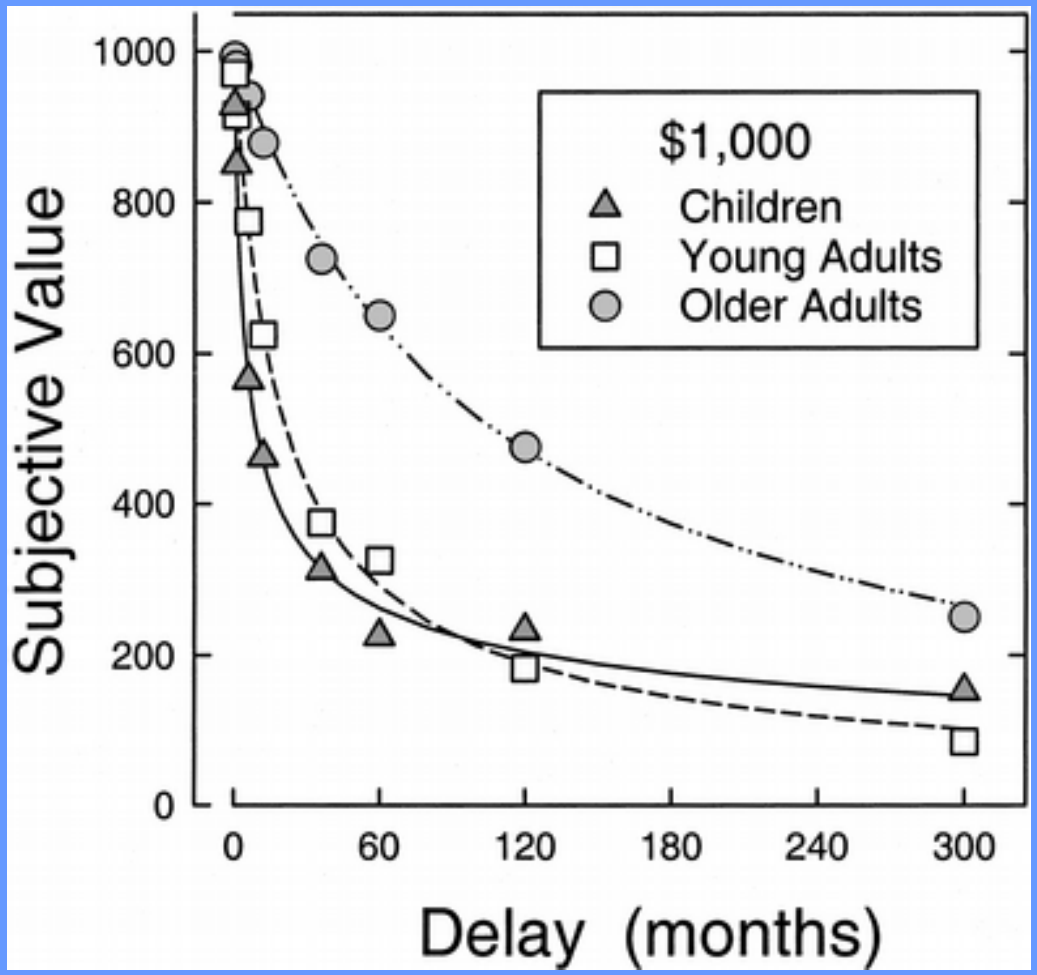
Key Idea: Prefer immediate small rewards to delayed larger rewards. Fall-off in reinforcement gradient is steep.

Related Constructs:
Delay of gratification (Mischel, et al. 1989)
Delay discounting (Green & Myerson, 2004)

Fundamental Questions:

1) Is DA more related to CD than ADHD?
2) How does DA deficit relate to state regulation and inhibition deficits?

Delay Discounting
(Green & Myerson, 2004)



The EF theory of ADHD

A core EF deficit is necessary and sufficient to cause ADHD (usually referring to the combined type)

Five criteria that must be met for EF weaknesses to be considered the core deficit of ADHD

I. Groups with ADHD must exhibit weaknesses on EF measures.

II. The group deficit must remain significant after controlling for IQ and symptoms of other disorders.

III. The group EF deficit must explain a large proportion of the variance in ADHD symptoms.

IV. EF weaknesses must be present in most individuals with ADHD, and absent in most individuals without ADHD.

V. EF weaknesses must be due to the same genes as ADHD.

Meta-analysis of EF and ADHD

(Willcutt, Brodsky, et al., 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005)

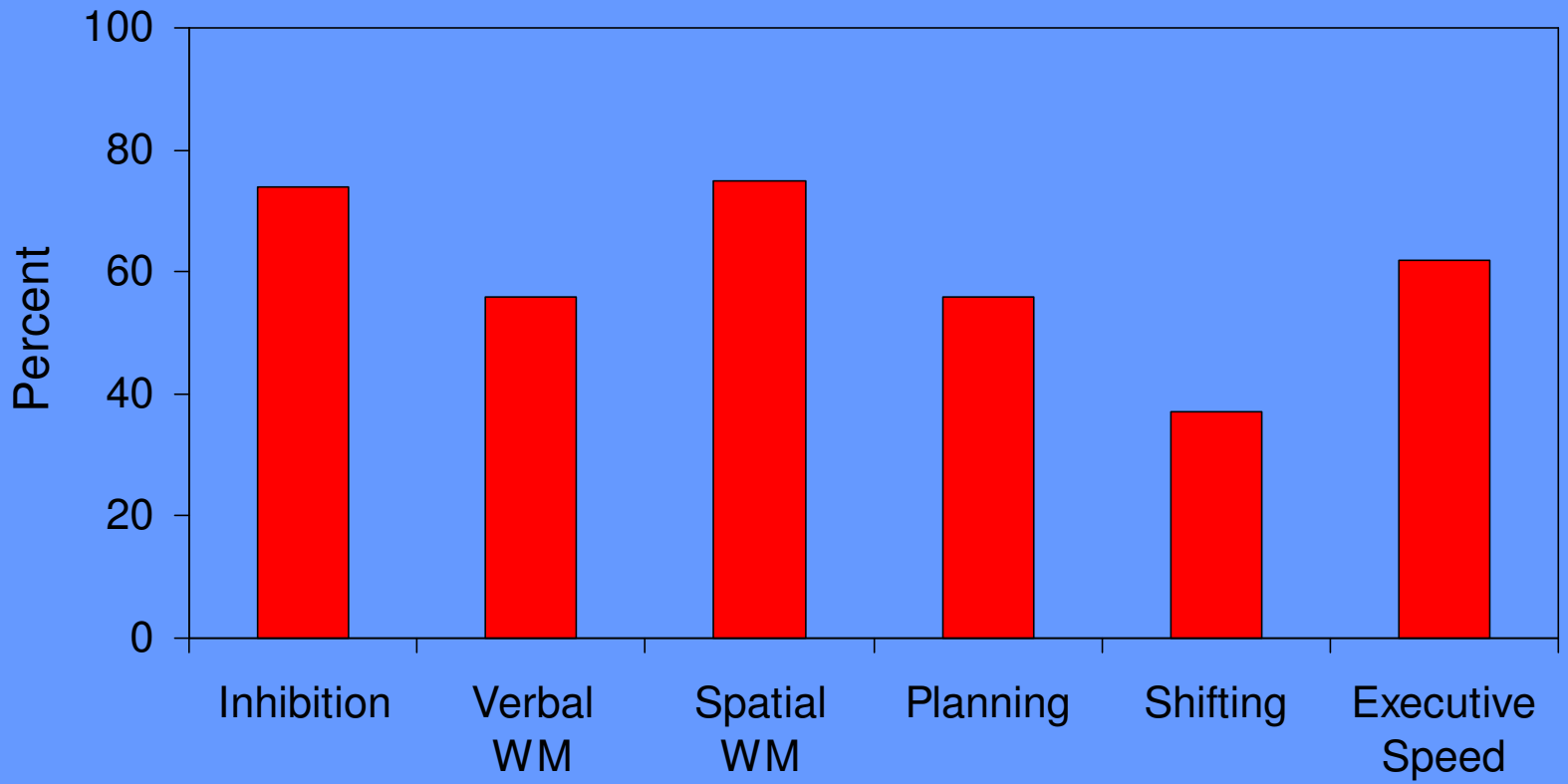
- One key measure of each core EF domain was identified
  - Inhibition: Stop-signal Reaction Time (25 studies)
  - Set shifting: Wisconsin Card Sort perseverative errors (25 studies)
  - Verbal working memory: sentence span (3 studies) and digits backward (6)
  - Planning: Tower of Hanoi / London (12 studies)
  - Interference Control: Clinical Stroop (9 studies)
  - Executive Processing Speed: Trailmaking Test Part B (13 studies)
- 100 new studies of EF measures have been published since the review by Pennington and Ozonoff (1996)
- 65 studies that administered at least one of these six measures were included (most studies combined type only)
- Total N = 3,374 with ADHD and 2,969 without ADHD

Testing the EF model of ADHD: Five Criteria for a core deficit

Criterion	Result
I. ADHD must be associated with EF weaknesses.	

Percentage of studies finding a significant difference between ADHD and control groups

(After Willcutt et al., 2005)



Testing the EF model of ADHD: Criteria for a core deficit

Criterion	Result
I. ADHD must be associated with EF weaknesses.	Supported

Testing the EF model of ADHD: Criteria for a core deficit

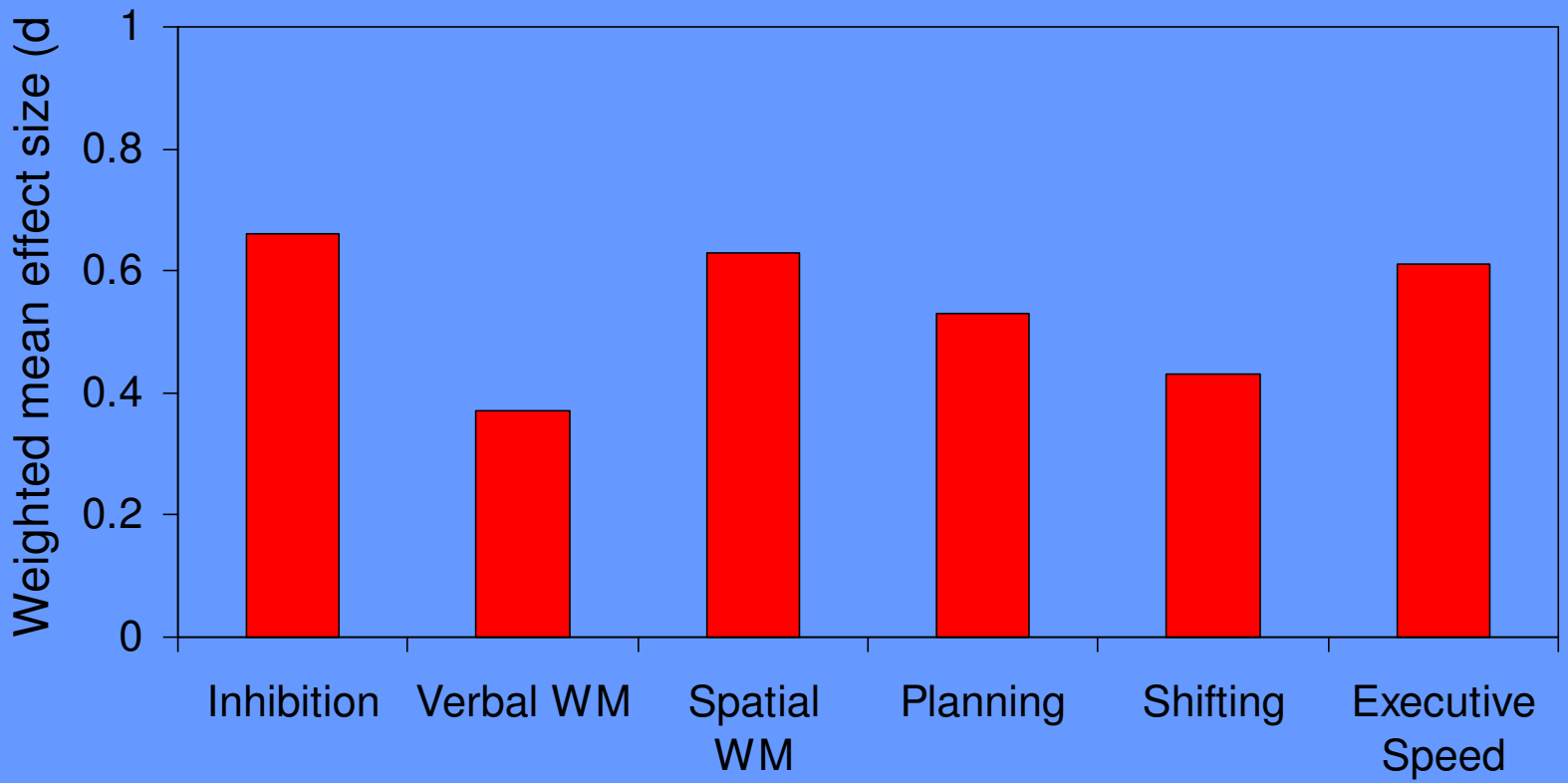
Criterion	Result
I. ADHD must be associated with EF weaknesses.	Supported
II. EF weaknesses must not be explained by group differences in IQ or comorbid symptoms.	Supported

Testing the EF model of ADHD: Criteria for a core deficit

Criterion	Result
I. ADHD must be associated with EF weaknesses.	Supported
II. EF weaknesses must not be explained by group differences in IQ or comorbid symptoms.	Supported
III. The EF deficit must be large enough to be a core deficit.	

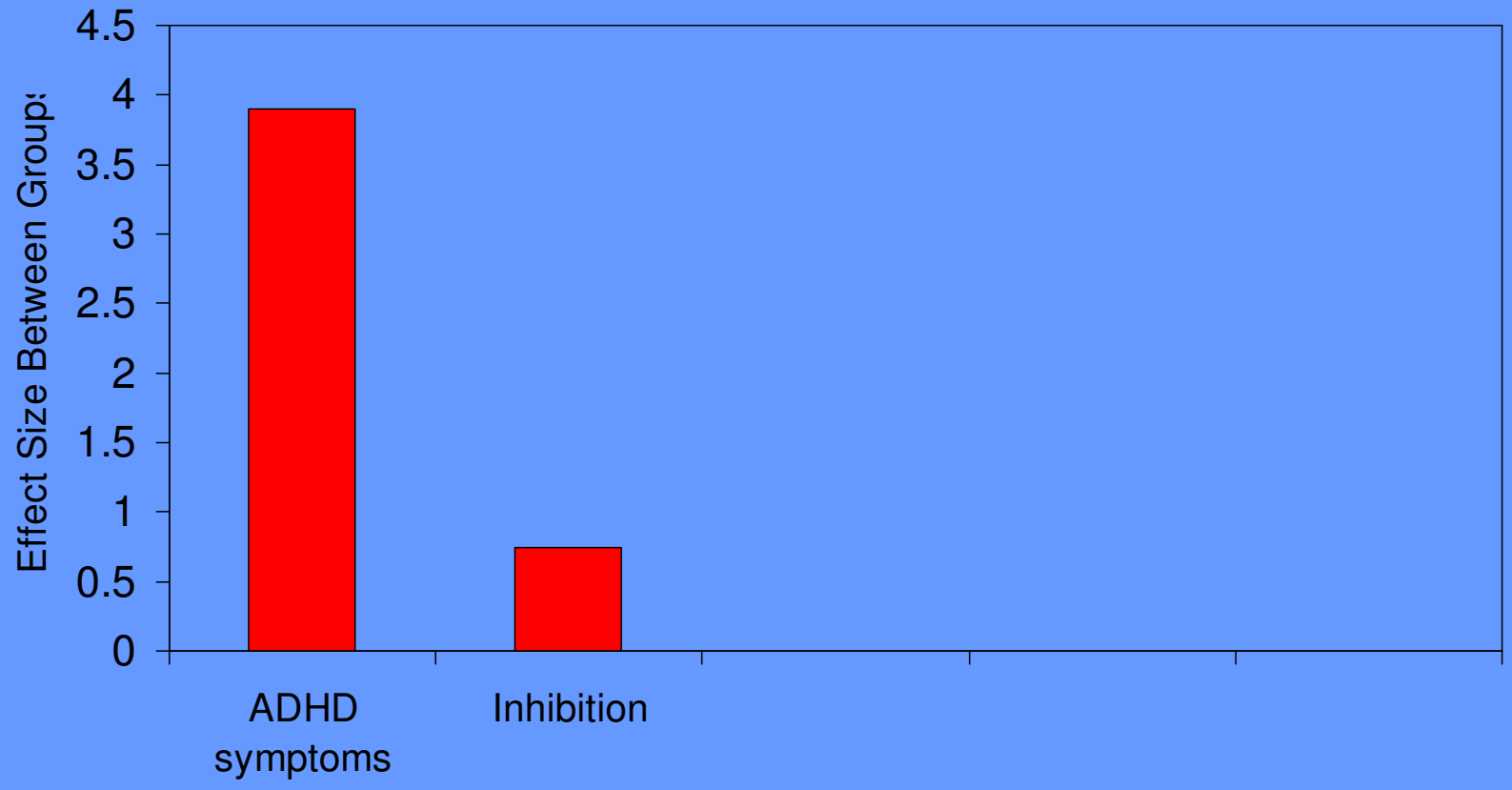
Mean effect size of the group difference on each EF measure

(After Willcutt et al., 2005)



Comparison of the effect sizes for the hypothesized "core deficit" in Reading Disability and ADHD

(Willcutt et al., 2001[28])



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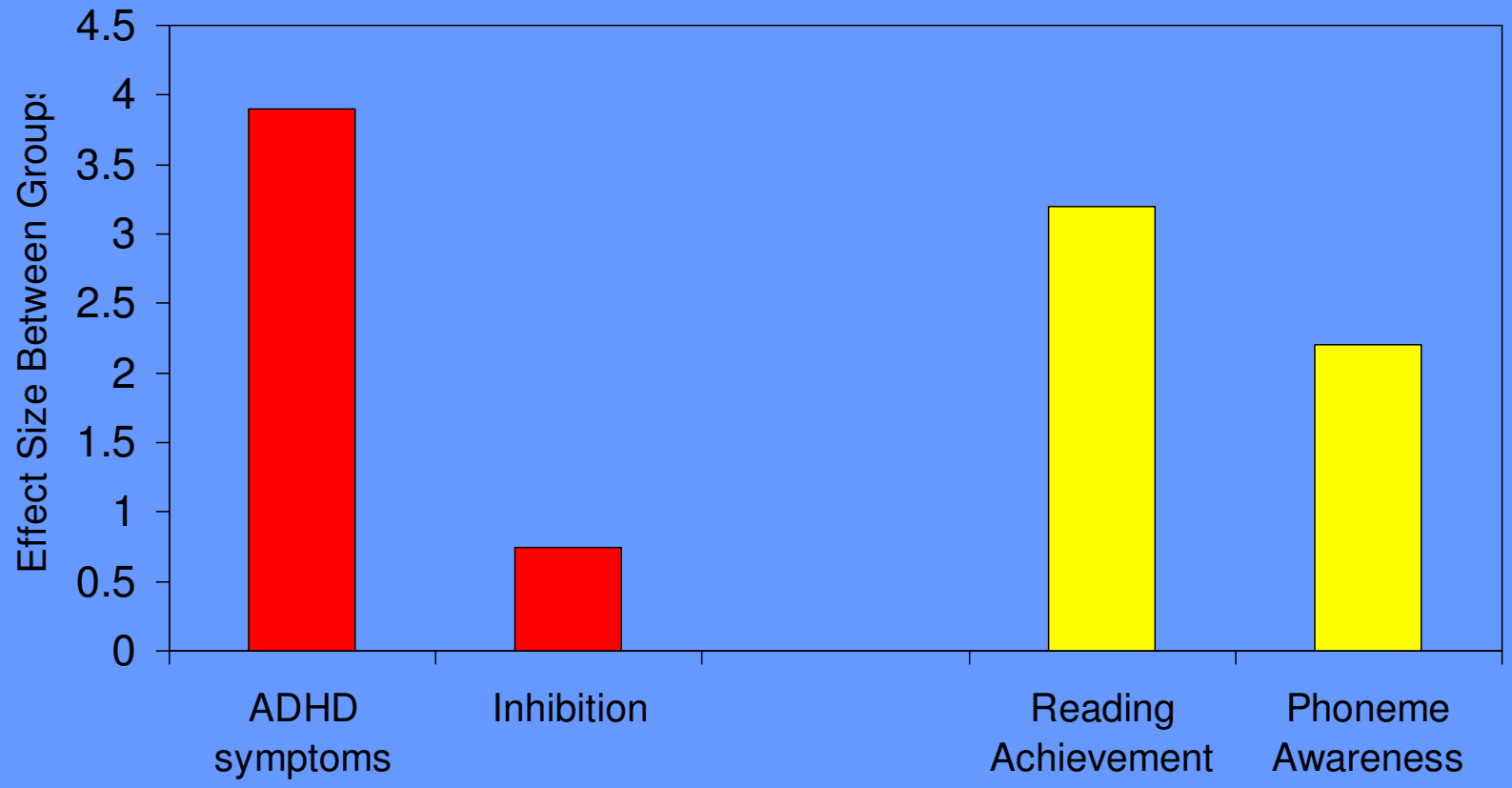


Testing the EF model of ADHD: Criteria for a core deficit

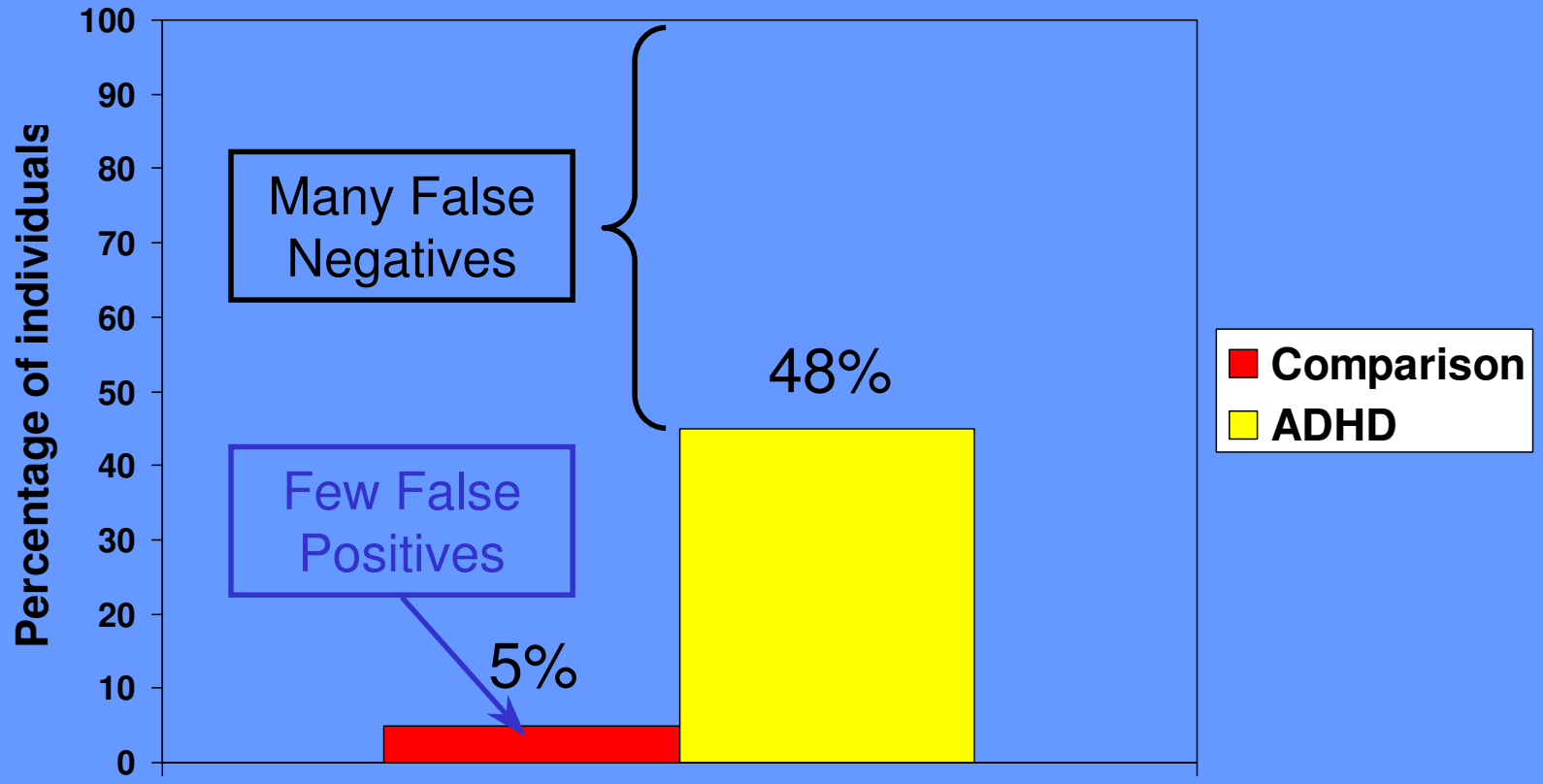
Criterion	Result
I. ADHD must be associated with EF weaknesses.	Supported
II. EF weaknesses must not be explained by group differences in IQ or comorbid symptoms.	Supported
III. The EF deficit must be large enough to be a core deficit.	Not Supported

Testing the EF model of ADHD: Criteria for a core deficit

Criterion	Result
I. ADHD must be associated with EF weaknesses.	Supported
II. EF weaknesses must not be explained by group differences in IQ or comorbid symptoms.	Supported
III. The EF deficit must be large enough to be a core deficit.	Not Supported
IV. EF deficits must be present in most individuals with ADHD and absent in most individuals without ADHD.	

Percentage of individuals with scores above the 95th percentile on the response inhibition factor

(after Nigg, Willcutt, et al., in press[12])



Testing the EF model of ADHD: Criteria for a core deficit

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Testing the EF model of ADHD: Criteria for a core deficit

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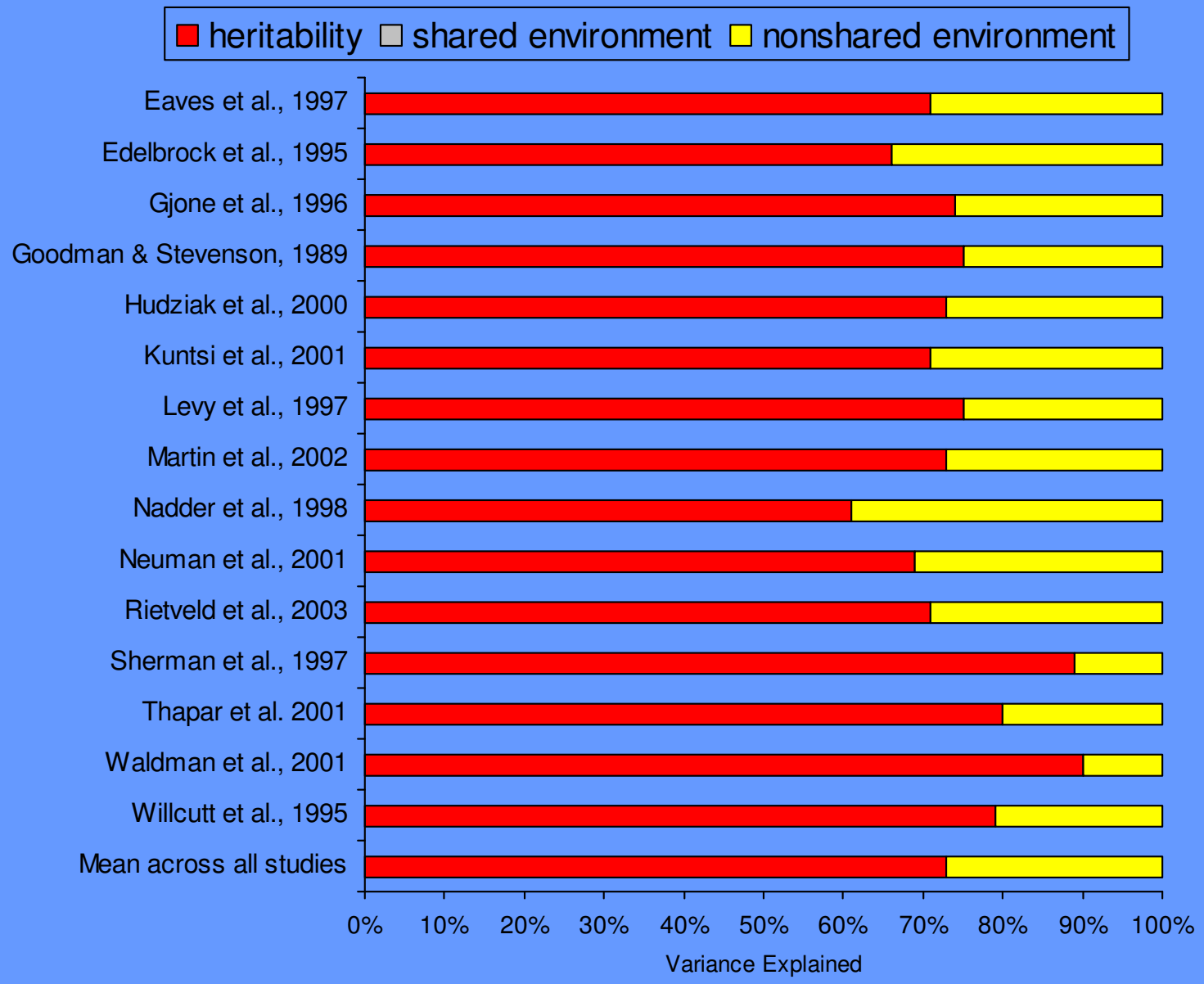
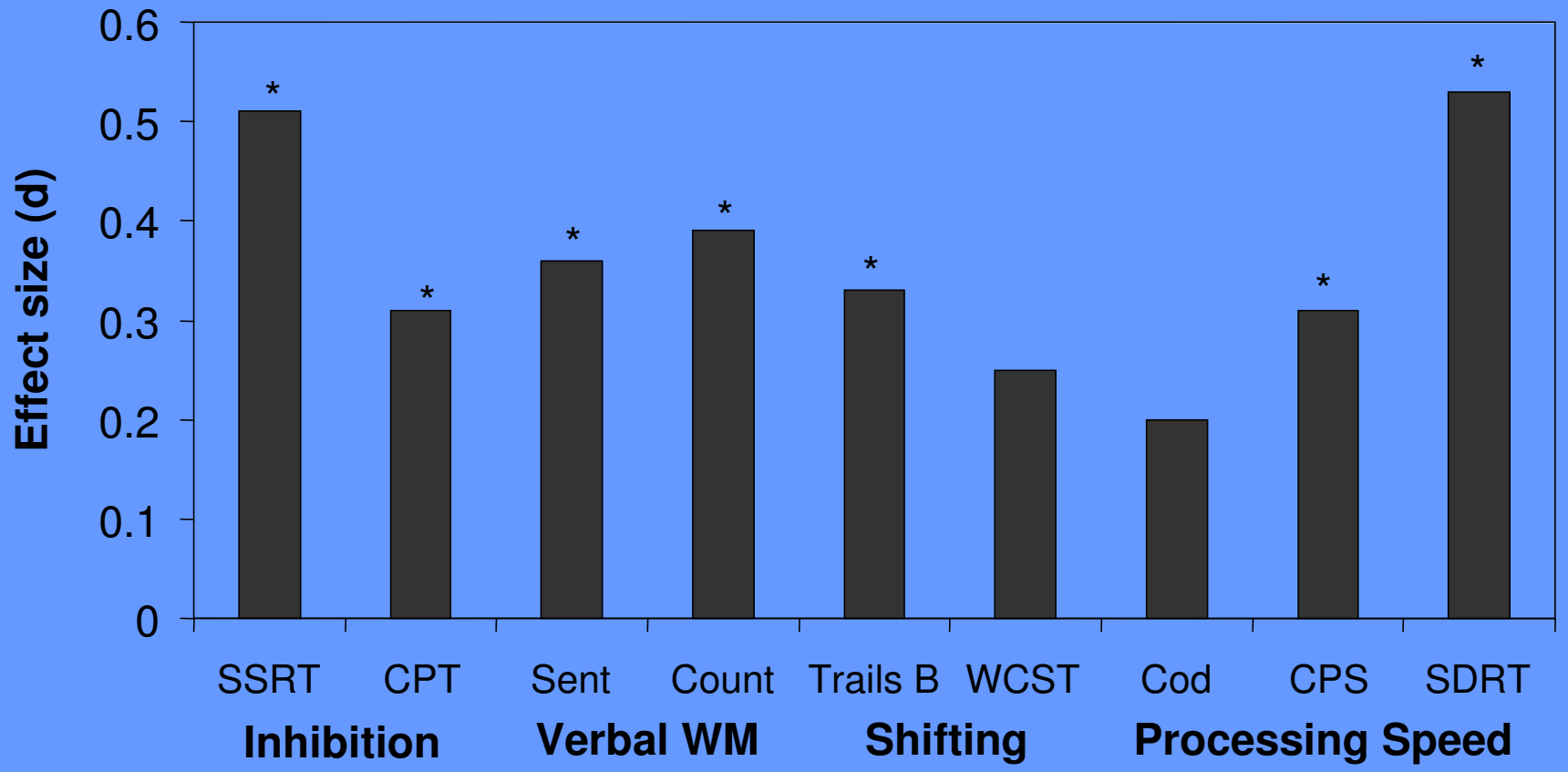
II. EF weaknesses must not be explained by group differences in IQ or comorbid symptoms.	Supported
III. The EF deficit must be large enough to be a core deficit.	Not Supported
IV. EF deficits must be present in most with ADHD and absent in most without ADHD.	Not supported Supported
V. EF deficits must be co-heritable with ADHD	

Twin studies of individual differences in ADHD symptoms (N > 10,000 twin pairs)



Familiality of Deficits (Bidwell et al., in press)

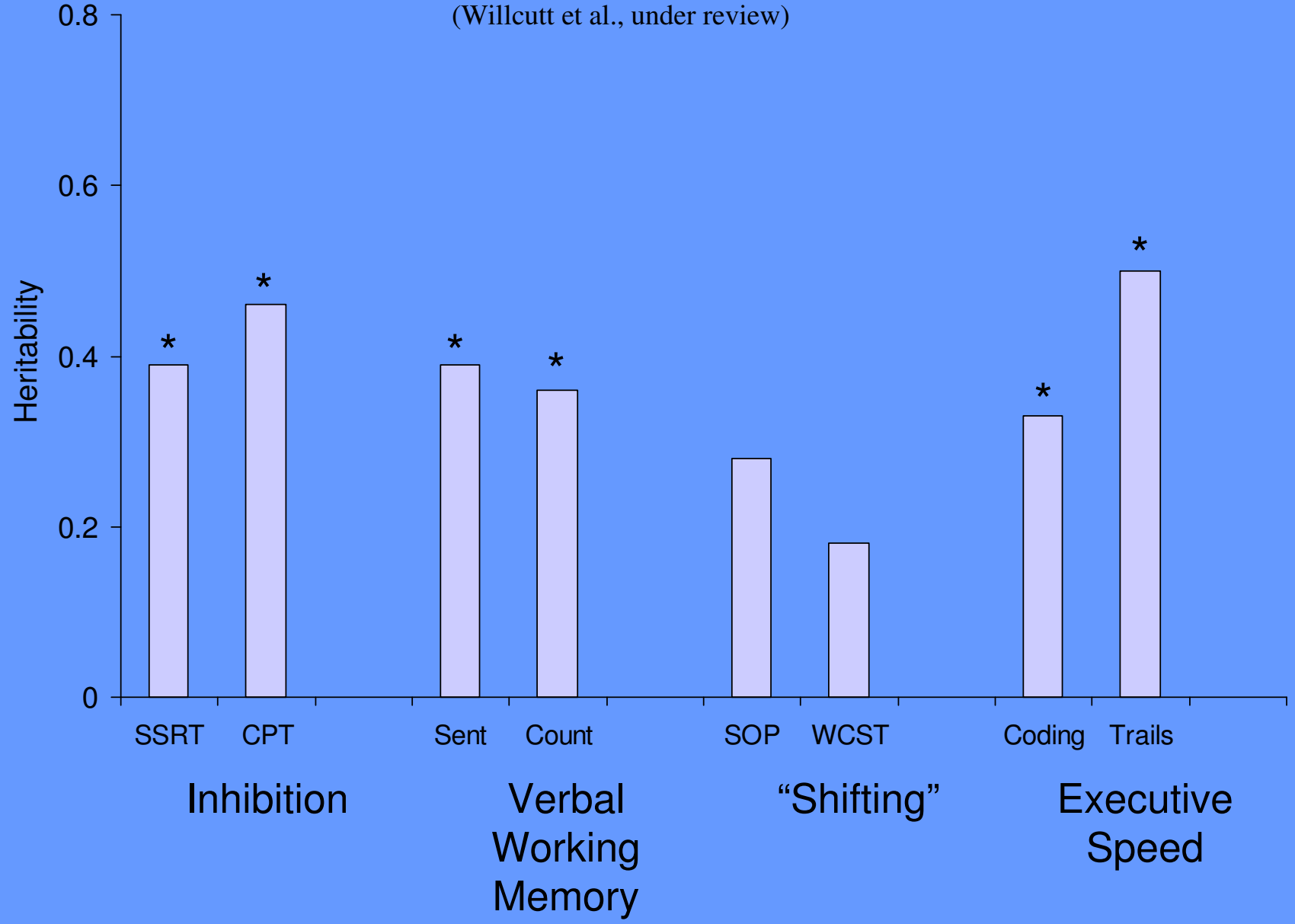
Method: Compare unaffected DZ cotwins (n = 228) to control DZ twins (n = 332)



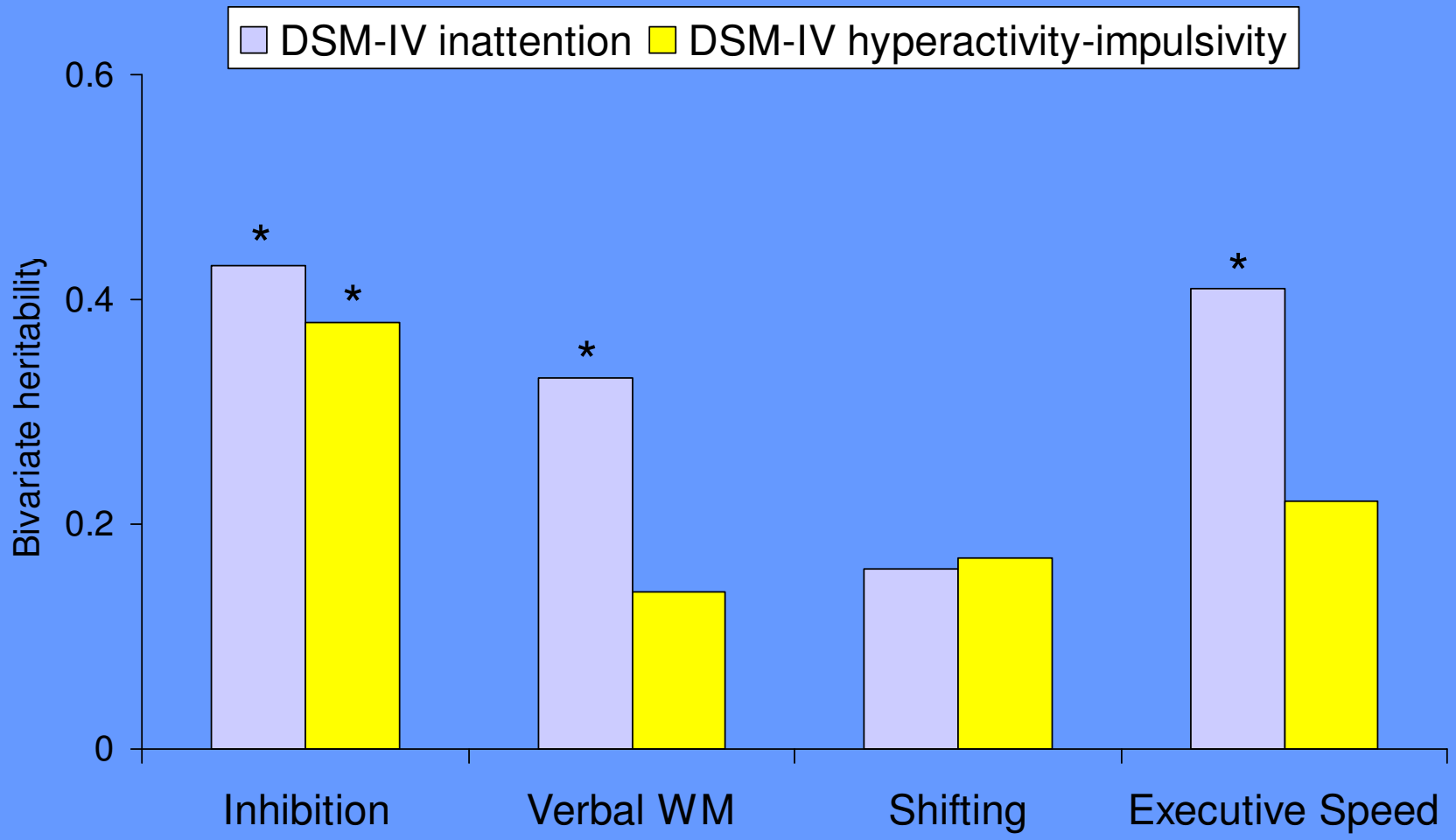
* Significant after covarying ADHD symptoms

Heritability of EF deficits in the Colorado Learning Disabilities Research Center twin study

(Willcutt et al., under review)



Bivariate heritability of ADHD symptoms and EF factor scores



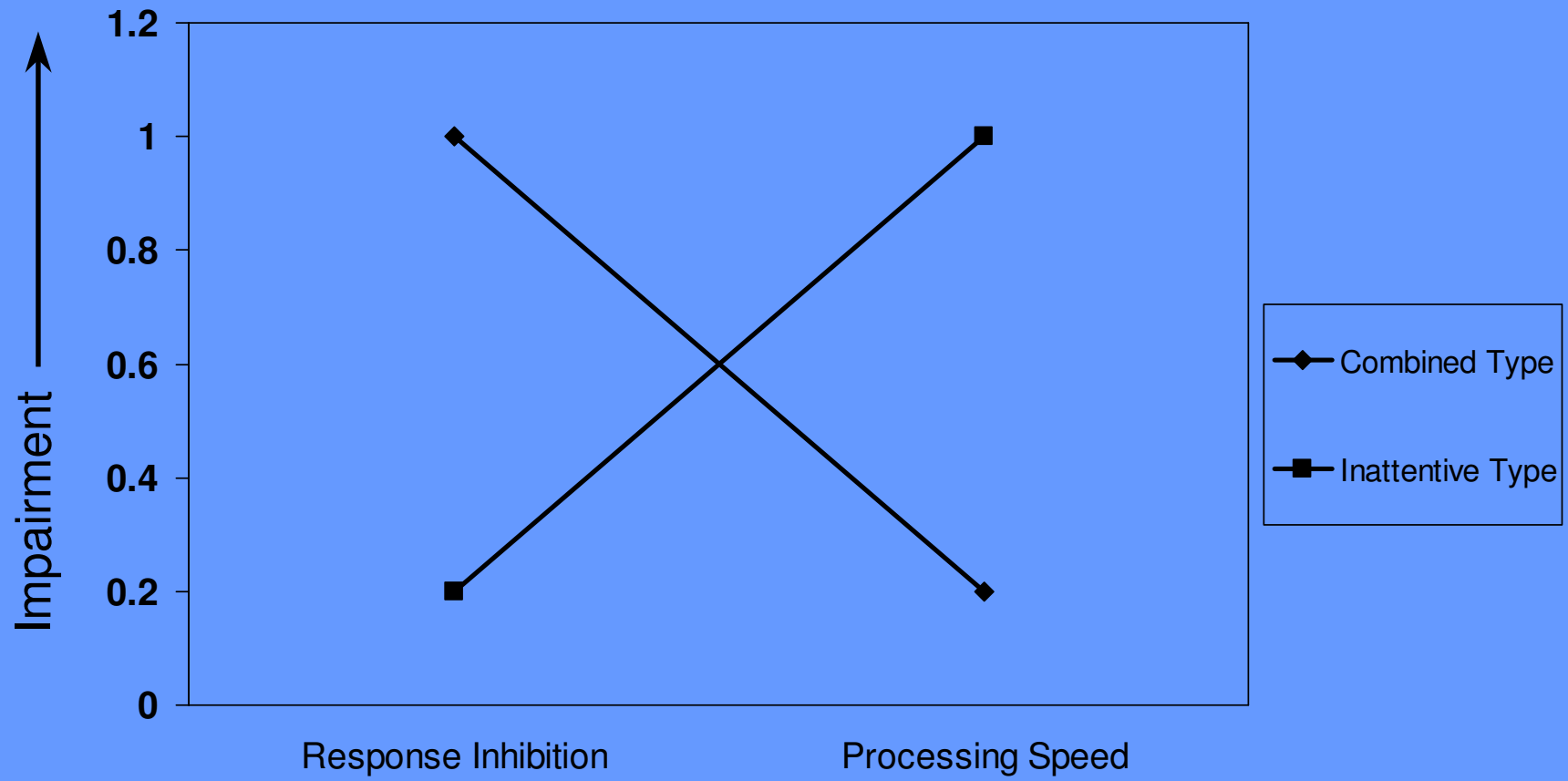
Testing the EF model of ADHD: Criteria for a core deficit

Criterion	Result
I. ADHD must be associated with EF weaknesses.	Supported
II. EF weaknesses must not be explained by group differences in IQ or comorbid symptoms.	Supported
III. The EF deficit must be large enough to be a core deficit.	Not Supported
IV. EF deficits must be present in most with ADHD and absent in most without ADHD.	Not supported Supported
V. EF deficits must be co-heritable with ADHD	Supported, but small common genetic effect

Why didn’t we find a core EF deficit?

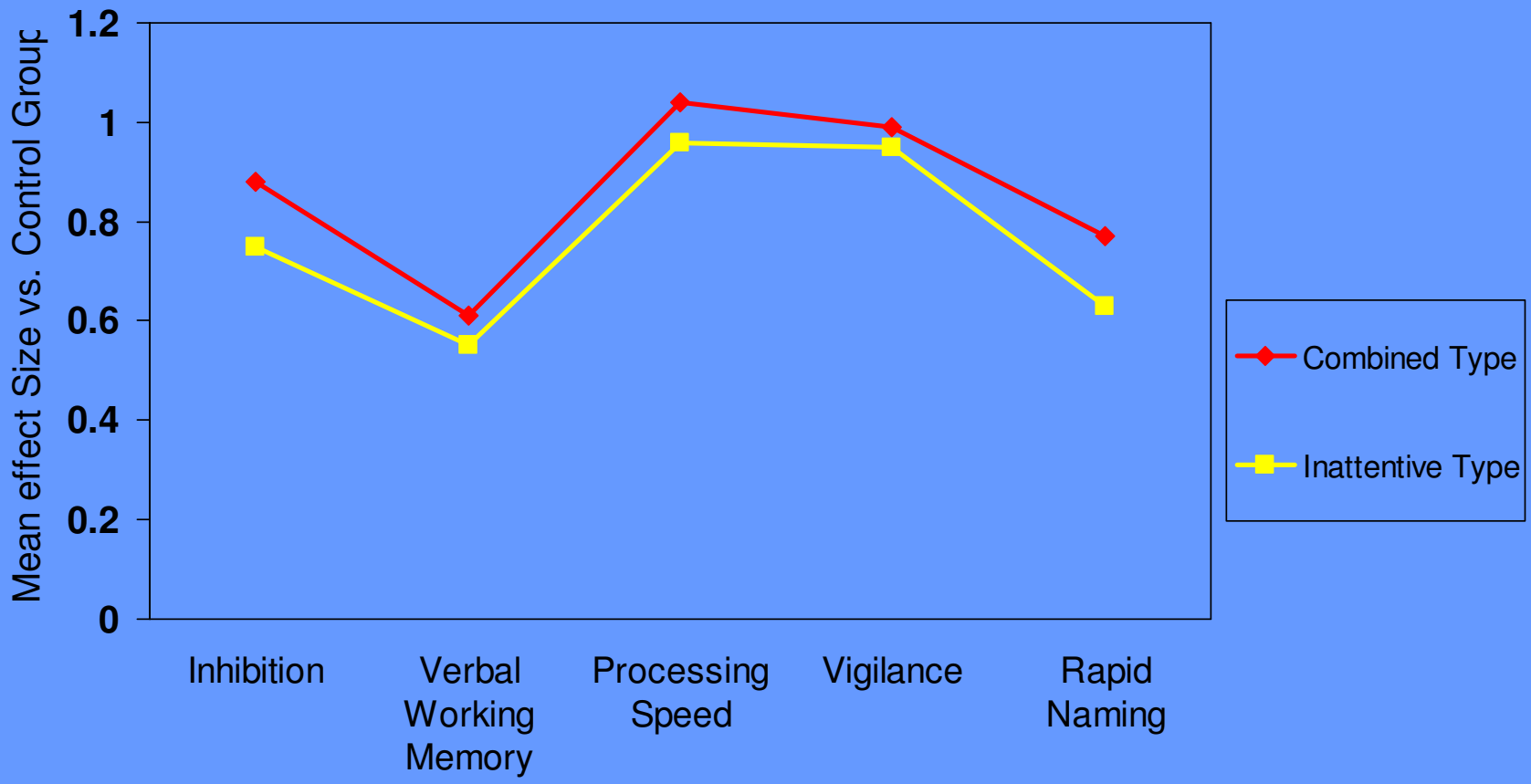
Did diagnostic heterogeneity attenuate the effect?

Predicted Double Dissociation between the Combined and Inattentive Subtypes



Performance of the DSM-IV Inattentive and Combined types on measures of neuropsychological functioning

(after Chhabildas et al., 2001[1]; Willcutt et al., in press[30])



Meta-analysis of performance of the DSM-IV subtypes on measures of neuropsychological functioning

(10 studies; Willcutt et al., under review[25])

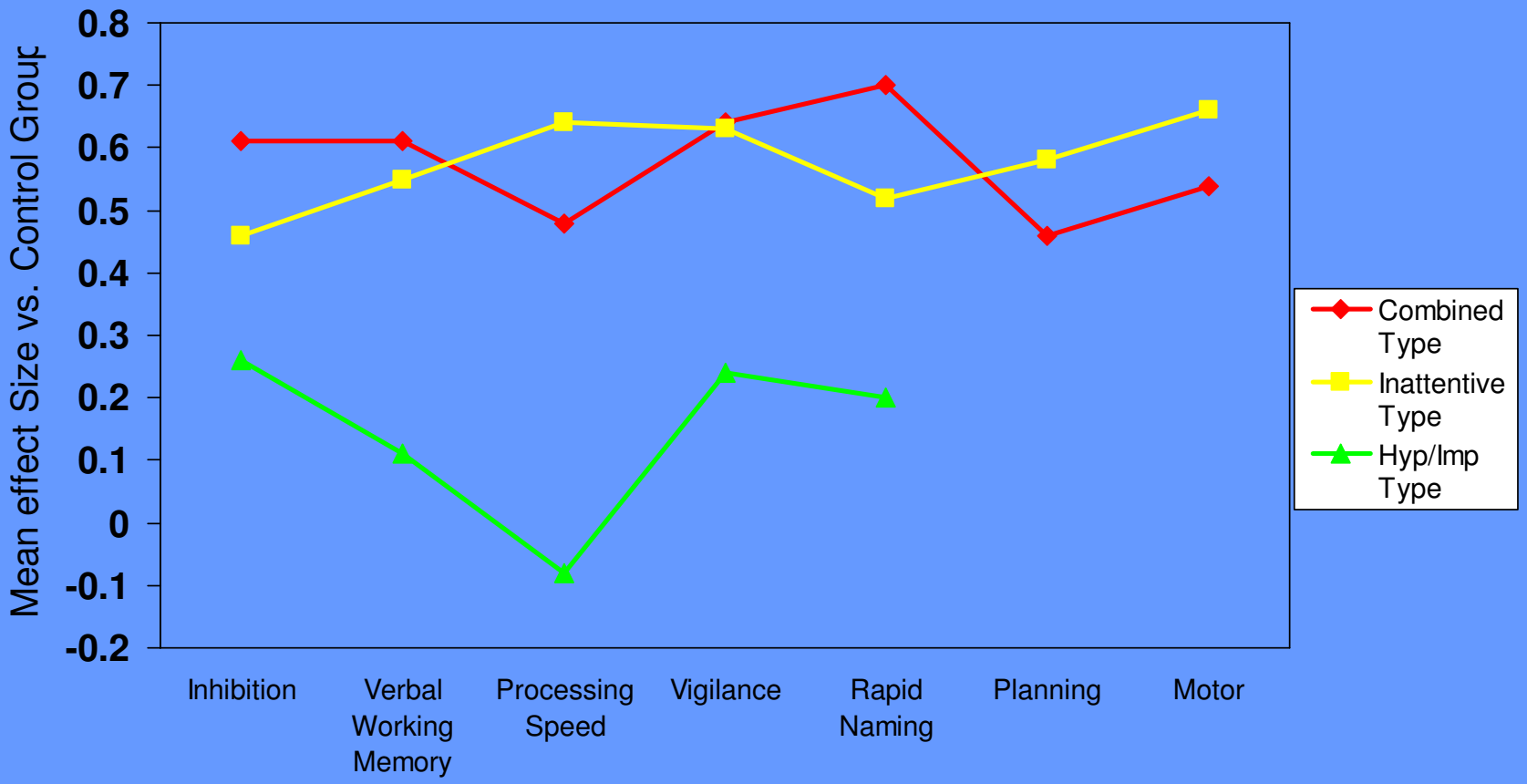
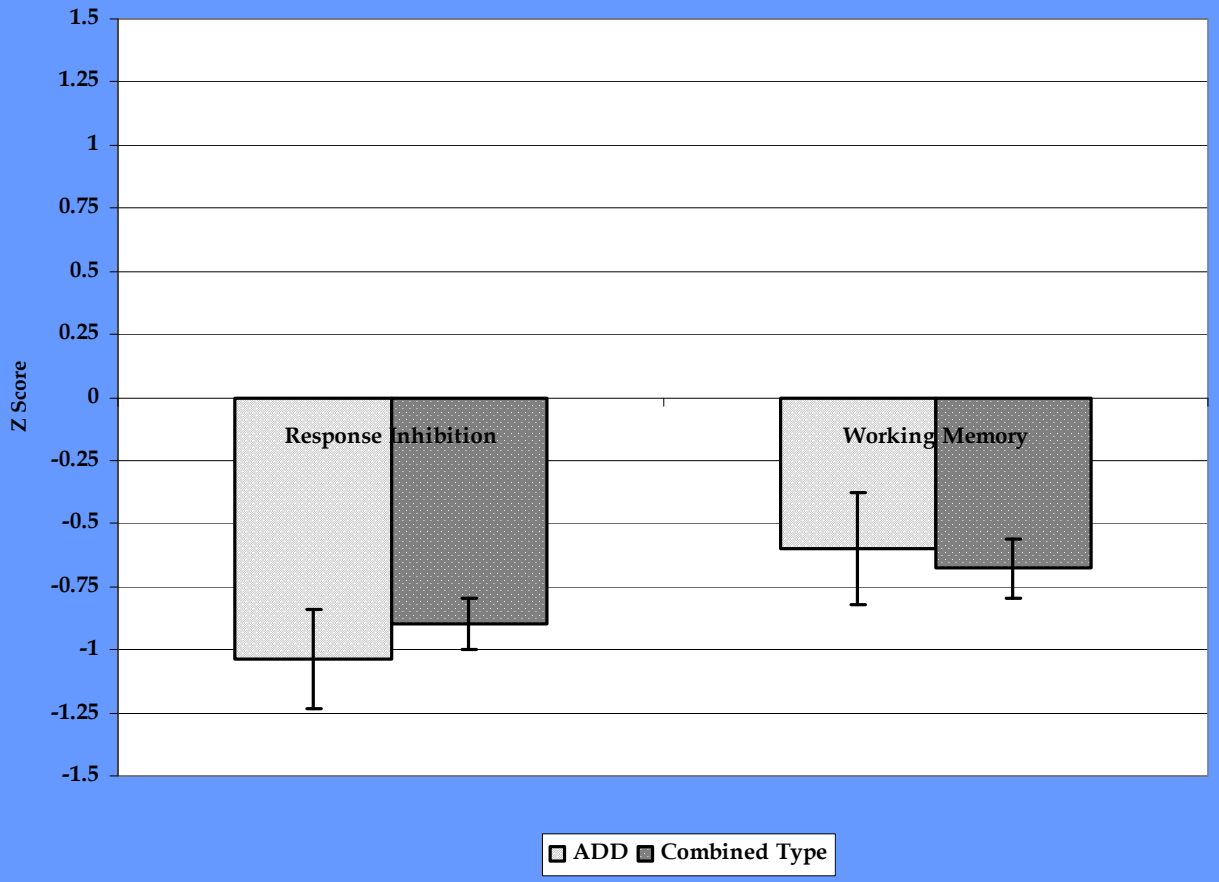


Figure 3: Estimated Marginal Means of "Pure" ADD vs. Combined Type



A paradigm shift:
The need for a multifactorial model

- ADHD is not attributable to a single core deficit in EF or anything else.
- EF deficits are one important part of a model that includes several other weaknesses.
- Other possible weaknesses:
  - Delay Aversion: hypersensitivity to delay expressed as behaviors devoted to minimizing the experience of delay (Sonuga-Barke, 2003)
  - Arousal ("state") regulation: fluctuations in arousal/activation lead to suboptimal performance (Sergeant et al., 2003)
  - Cognitive Speed
    - Naming speed (Rucklidge & Tannock, 2002)
    - Processing speed (Willcutt et al., in press)
  - Temporal processing
    - Durations > 2 seconds (Barkley et al., 2001)
    - Durations < 1 second (Castellanos & Tannock)
- Some weaknesses may be shared with comorbid disorders and some may be specific to ADHD.

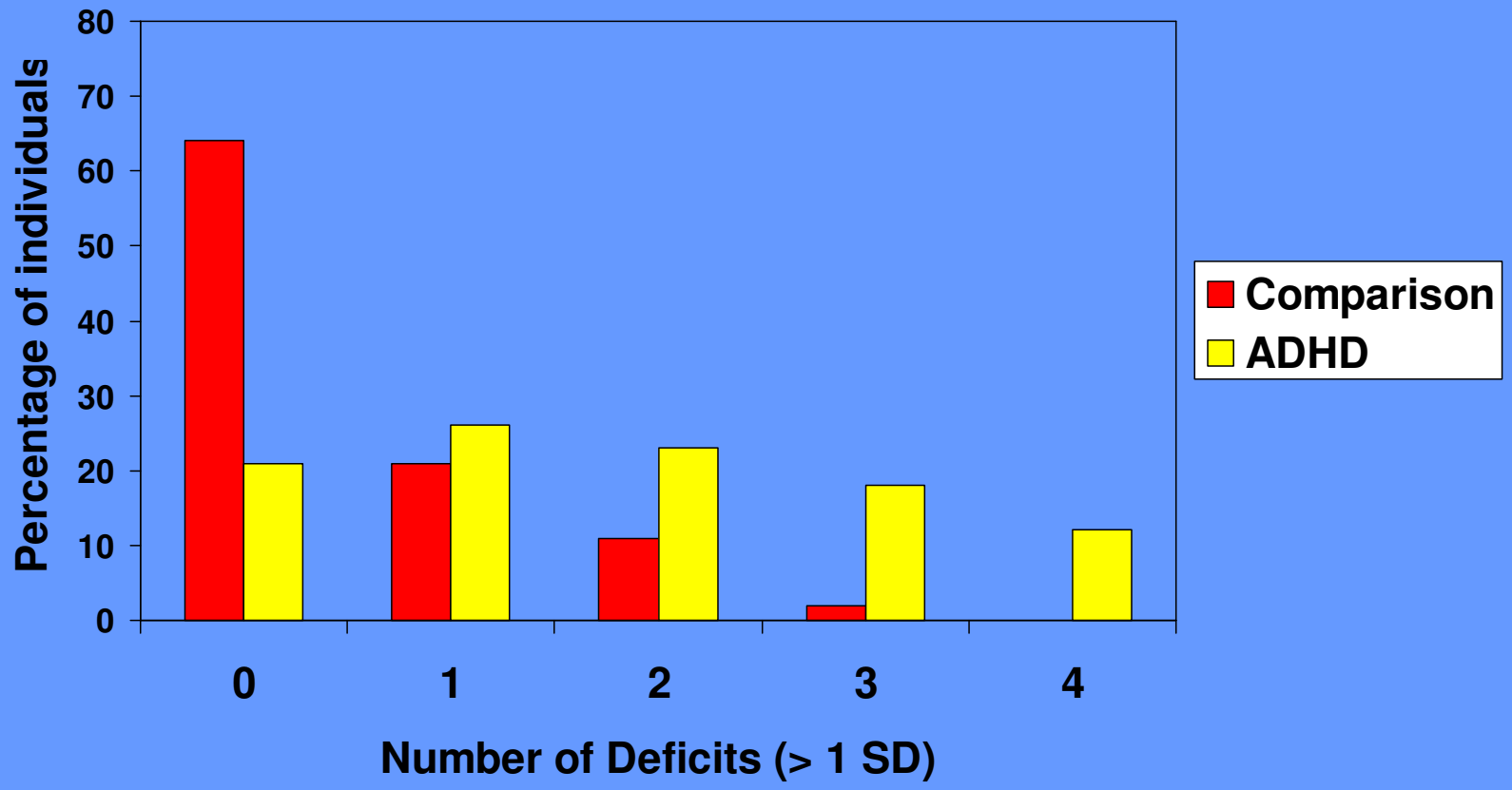
Logistic regression predicting ADHD simultaneously with all EF/neurocognitive composites

(Willcutt et al., in preparation)

Composite	Wald	P
Inhibition	6.54	.01
Working Memory	6.31	.01
Vigilance	4.49	.03
Processing Speed	21.8	<.001

Number of neurocognitive deficits exhibited by children with and without ADHD

(Domains assessed: inhibition, set shifting, processing speed, vigilance)



Tests of Motivational Effects in CLDRC

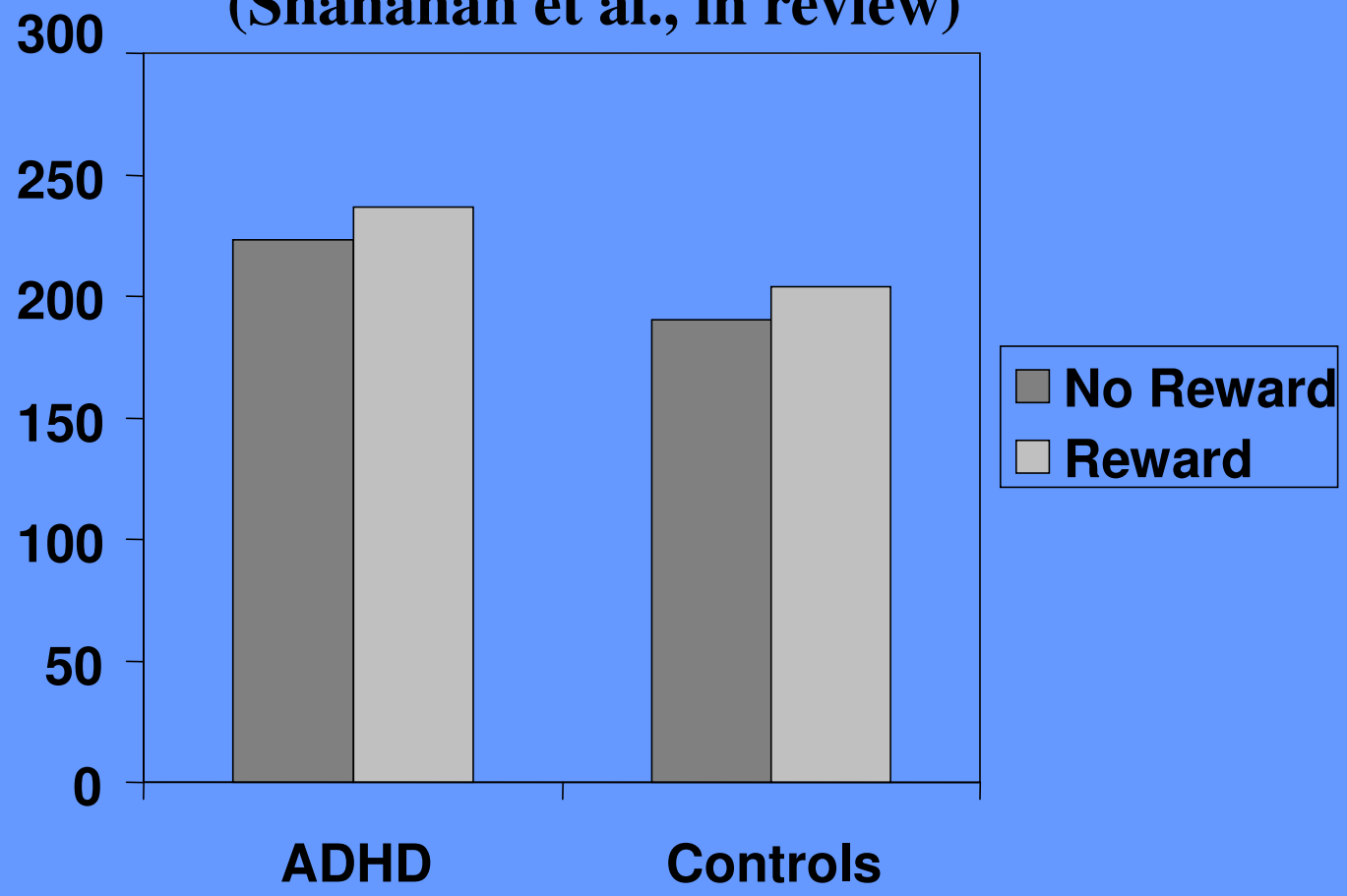
A. Motivational Inhibition (Hartung, in preparation)
   1. Newman's Go No Go Commissions
      d= .38*
   2. Doors task
      d= .15, ns
B. Manipulating Incentives on Stop Task
   (Shanahan et al., in revision)
   No group x incentives interaction

C. Delay Aversion : Effects in younger age group

D. Orbital Frontal Tasks (Object Reversal and Gambling)
   Evidence for multiple deficits

Effects of Incentives on Stop Task: SSRT

(Shanahan et al., in review)



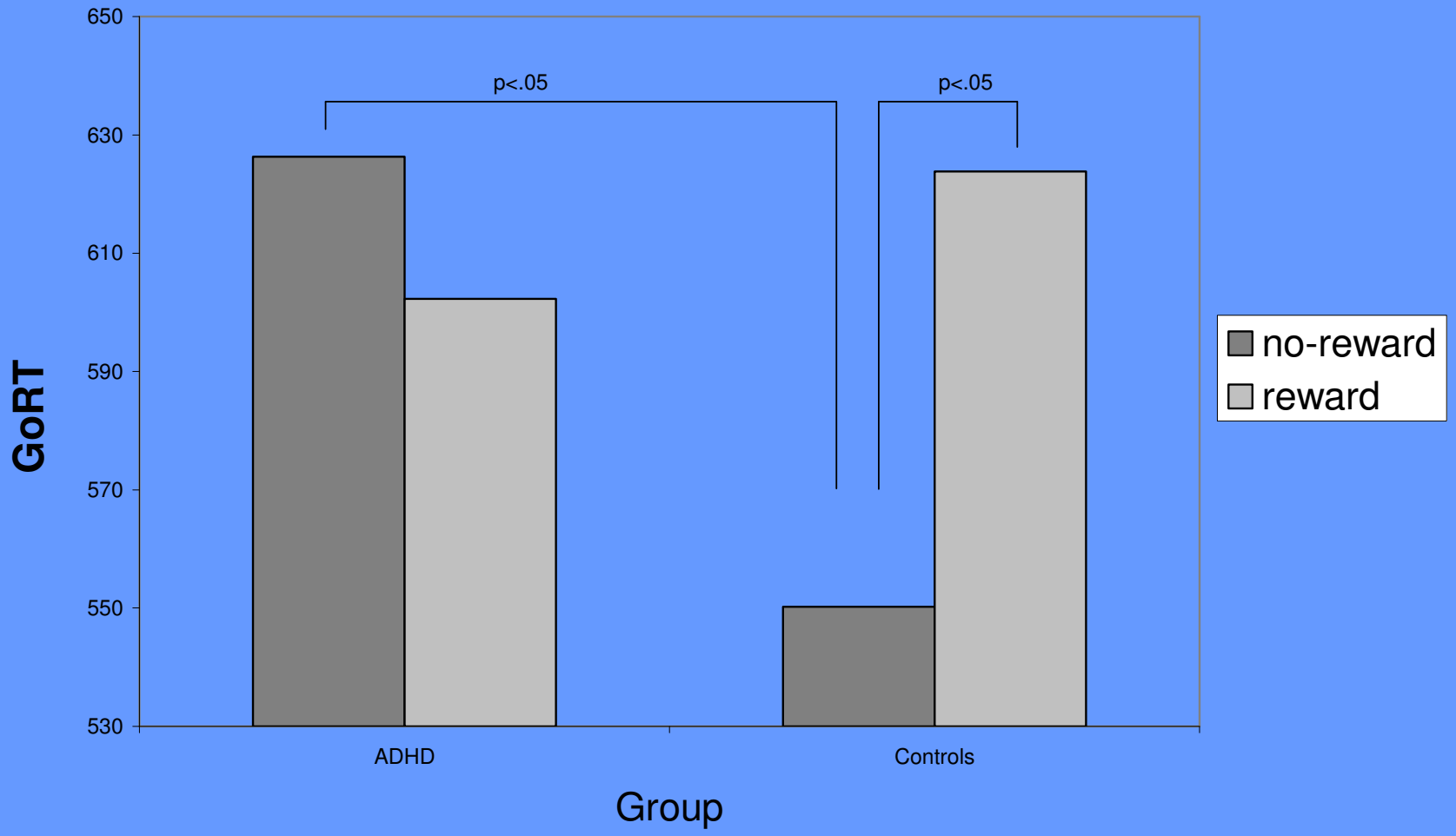
Main effect of Group ($F(1, 54) = 5.12$, $p < .05$

No Main effect of Reward

No Group by Reward Interaction

Effects of Incentives on Stop Task: Go RT
(Shanahan et al, in review)

Group by Incentives Interaction



Delay Aversion Results in CLDRC:
Age Differences

8-11 years

Controls (n=129)	31.9 (5.4)
ADHD (n=65)	30.5 (5.1)

d= .26, p<.10

12-18 years

Controls (n=70)	32.9 (5.7)
ADHD (n=29)	35.2 (5.2)

d= -0.43, p=.06

Group Differences in Executive and Motivational Tasks

Task	*F (1,70)*	*p value*
Inhibition		
SSRT	11.45	p<.001
GDS-Commission Errors	3.27	p=.07
Motivational		
CGT- Quality of Decision Making	13.5	p<.001
CGT- Deliberation Time	3.89	p=.05
Object Reversal - Total Errors	5.2	p<.05
Object Reversal - Total Points	3.9	p=.05
Object Reversal - Total Trials	5.79	p<.05

Note. Children with ADHD performed significantly worse on all of these variables.
Note. When Full Scale IQ was covaried from the analyses, the same overall pattern remained.

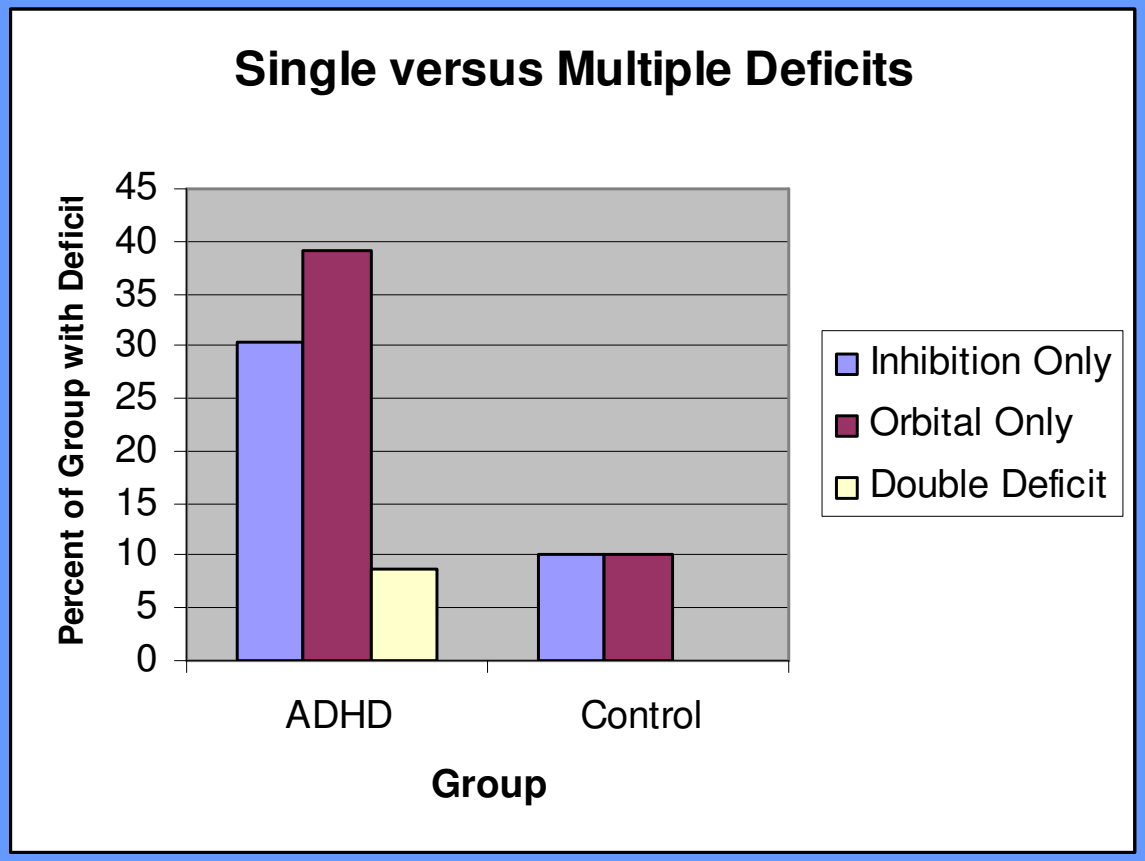
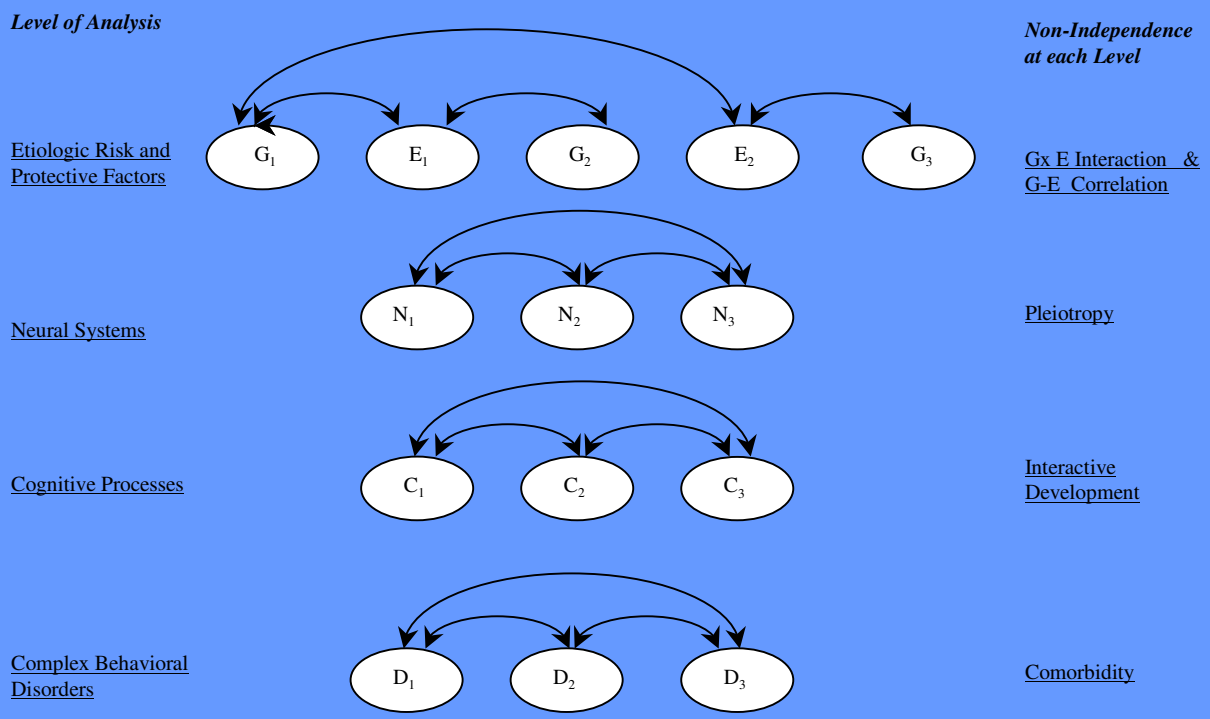

Single versus Multiple Deficits
Percent of Group with Deficit
45
40
35
30
25
20
15
10
5
0
ADHD
Control
Group
Inhibition Only
Orbital Only
Double Deficit

Figure 2. Multiple Deficit Model
Pennington, 2006



KEY
G = genetic risk or protective factor, E = environmental risk or protective factor,
N= neural system, C= cognitive process, D= disorder

RD and ADHD are Comorbid: Why?

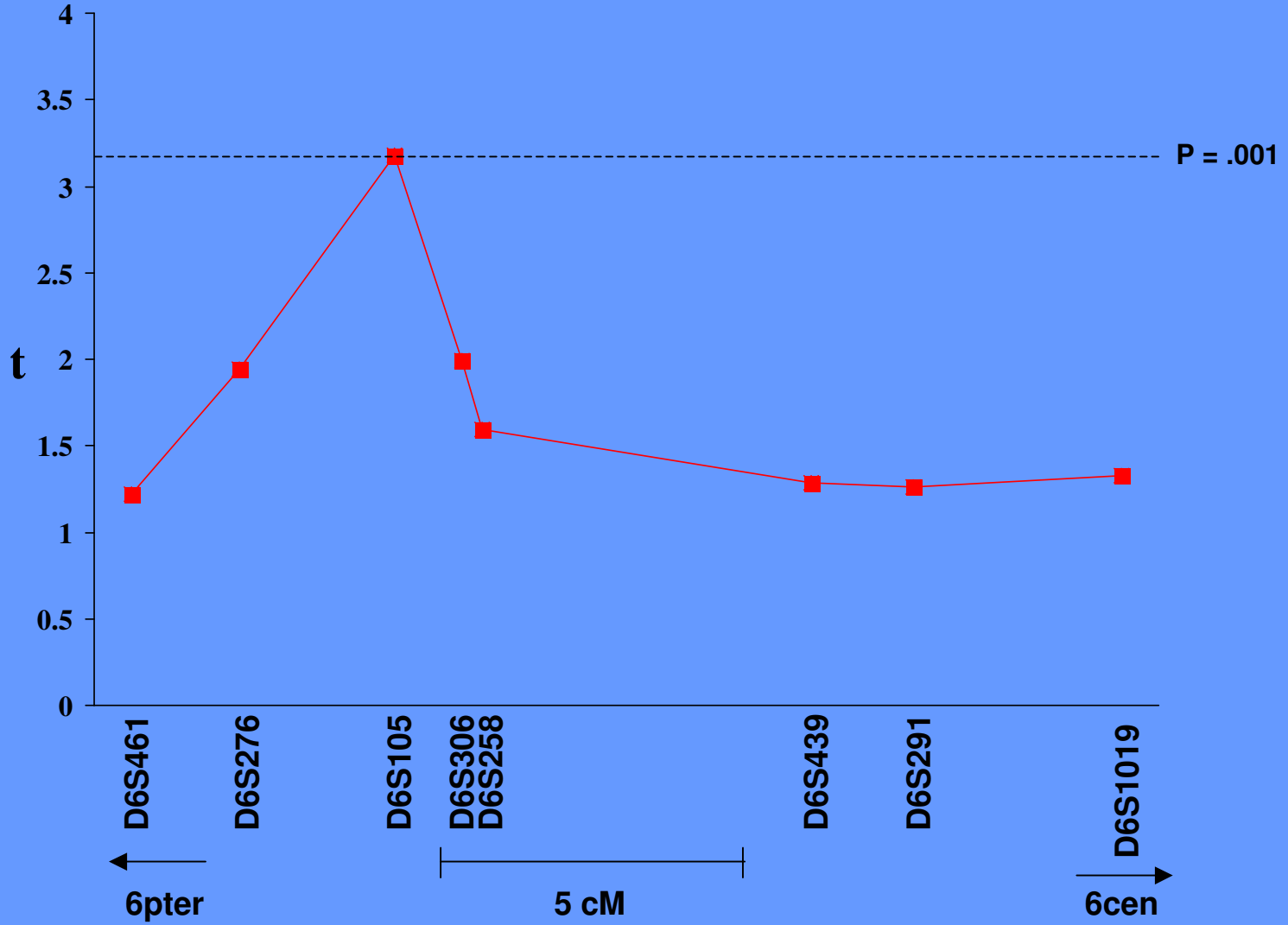
Rejected Hypotheses

- Not a selection artifact: Comorbidity found in population samples (eg Willcutt & Pennington, 2000)
- Not a secondary phenocopy: Comorbid subjects have both EF and PA deficits (Willcutt et al, 2001), contrary to Pennington et al (1993)
- Not cross-assortment (Friedman et al, 2003)

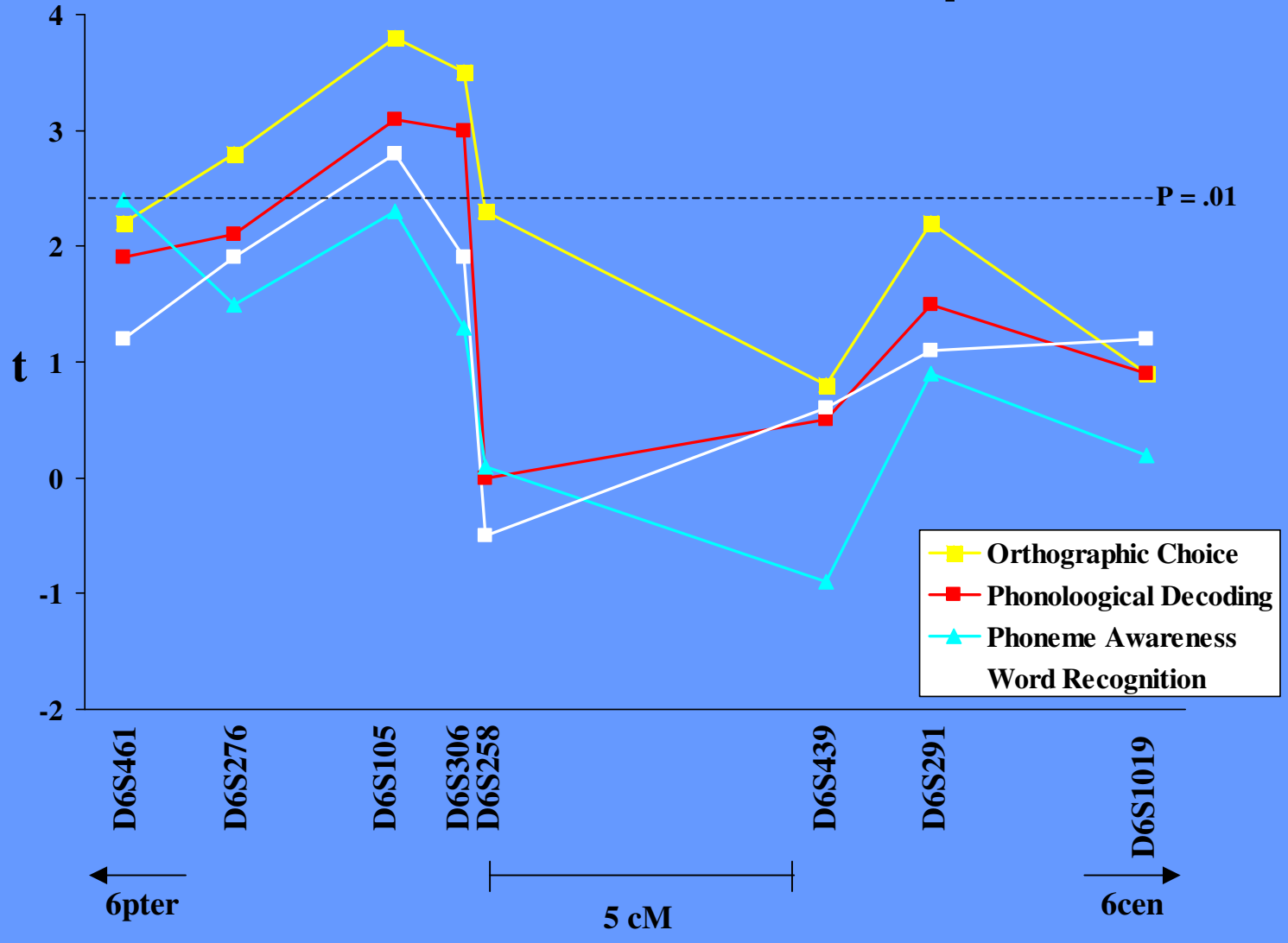
Supported Hypothesis: Shared Etiological Influences

- Bivariate h^2g for RD and ADHD (Stevenson et al, 1993; Light et al, 1995)
- Bivariate h^2g for RD and Inatt is about .40, whereas NS for RD and HI (Willcutt et al, 2000)
- QTL for RD on 6p21.3 is also linked to ADHD and shows bivariate linkage with RD phenotypes (Willcutt et al, 2002)

Linkage of ADHD to markers on chromosome 6



Bivariate linkage of RD and ADHD to markers on chromosome 6p



Genome Scans for Shared Risk Loci For RD and ADHD

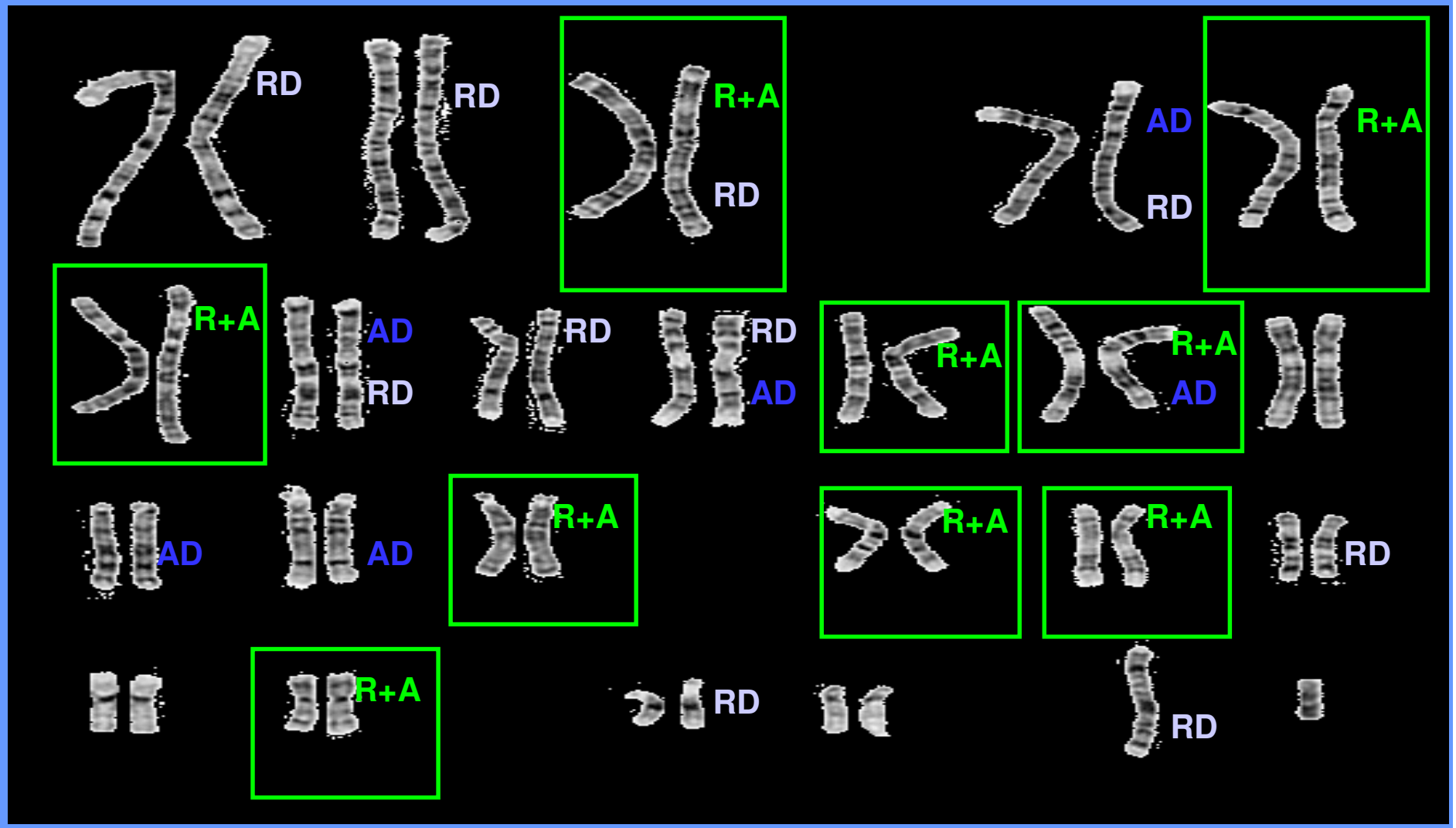
Start with ADHD Sample, Test Linkage to RD

Lou et al. (2004)

Start with RD Sample, Test Linkage to ADHD

Gayan et al. (2005)

Possible Locations of Genes That Influence RD, ADHD, or both RD and ADHD



Measures

Latent Variable	Measures Used to Predict Latent Variable
Reading Ability	*Time limited word recognition task, PIAT Reading Recognition, & PIAT Spelling*
Inattention Symptoms	*Mother, Father, Teacher, & Examiner Ratings*
Hyperactive/Impulsive Symptoms	*Mother, Father, Teacher, & Examiner Ratings*
PA	*Phoneme Deletion (% correct, blocks 1 & 2), Pig Latin test, & the Lindamood Auditory Conceptualization task*
VR	*Information, Similarities, Vocabulary, & Comprehension from the WISC-R*
WM	*Nonword Repetition, Digit Span (Forward & Backward), Sentence Span & Counting Span*
Inhibition	*Gordon Diagnostic System commission errors (Vigilance & Distractibility), & Stop Signal Reaction Time from the Stop Task*
PS	*WISC-R Coding, WISC-III Symbol Search, Colorado Perceptual Speed Task,Identical Pictures, Trailmaking Test, Rapid Automatized Naming Task (Colors, Numbers, Letters, & Pictures) & Stroop Task (Word Naming & Color Naming)*

Note. For ADHD, mean severity ratings from each rater were used as the indicators. This strategy allows for more variance than the more typical strategy of defining ADHD using symptom counts.

Note. Errors from the same instrument (e.g., WISC Coding and Symbol Search) were allowed to correlate in both measurement models.

Results

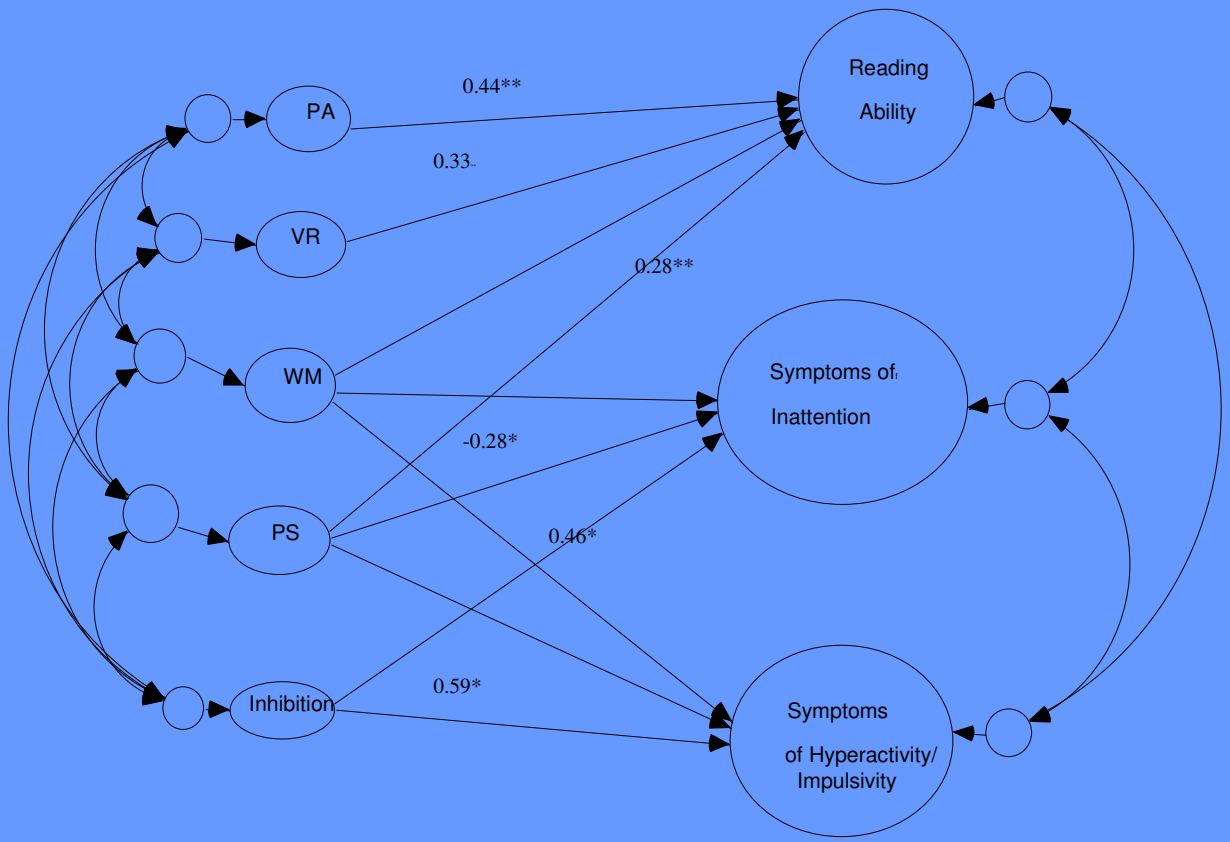
Measurement Model

The best fitting measurement model was one which created separate latent variables for the continuous symptoms of inattention and symptoms of hyperactivity/impulsivity ($\chi 2$ /df= 2.303, CFI= 0.986, RMSEA=0.045).

The measurement model for the latent variables of the the cognitive constructs was also a good fitting model ($\chi 2$ /df= 3.187, CFI= 0.915, RMSEA=0.059).

Full SEM Model

The full SEM model was also a good fit ($\chi 2$ /df= 2.63, CFI= 0.918, RMSEA=0.05



Summary of Results and Discussion

✓ This model accounted for 82% of the variance in RD, 39% of the variance in symptoms of inattention, and 22% of the variance in symptoms of hyperactivity/impulsivity.

✓ Furthermore, it reduced the relationship between RD and inattention symptoms from a zero-order correlation of -0.425 to a non-significant partial correlation of -0.08, which implies that PS explains a significant amount of their overlap.

✓ It also reduced the relationship between RD and hyperactivity/impulsivity from -0.215 to -0.12, suggesting that PS partially explains this relationship.

✓ Contrary to prediction, WM did not contribute uniquely to either RD or ADHD symptoms.

✓ These results indicate that PS is a shared cognitive risk factor for RD and ADHD, especially between RD and Inattention symptoms.

✓ Moreover, by using latent traits of symptoms of inattention and hyperactivity/impulsivity and their neuropsychological predictors, we were able to explain a much greater amount of the variance (24-39%) of the symptoms of ADHD than is typically found in the literature (10-12%).

Correlations Among Constructs (N=444)

	Inhibition	Processing Speed	SDRT
Delay Aversion	.05	.05	.03
SDRT	**.46**	**.43**	
Processing Speed	**.37**		

Bold = p<.01

Predicting ADHD Symptoms (N=444)

	Adjusted R^2	R^2 Change	p
Processing Speed	.135	.137	.000
Inhibition	.174	.041	.000
SDRT	.187	.015	.006
Delay Aversion	.191	.006	<.10

Conclusions

1. No single cognitive deficit model of ADHD appears adequate.

2. DSM-IV subtypes are not cognitively distinct, nor is pure Inattentive subtype.

3. Some combinations of executive and motivational deficits appear promising, but more work is needed.

4. A multiple cognitive deficit model helps explain ADHD's comorbidity with dyslexia.

5. More work is needed on relations among key constructs: executive inhibition, state regulation, and delay aversion.