Conceptualising & Partitioning Heterogeneity in ADHD

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OUTLINE

- Old paradigm models of ADHD: The search for the common core deficit.
- *Executive Dysfunction: A necessary and sufficient condition for ADHD?*
- A paradigm shift in ADHD research: From common core deficits to multiple pathway models.
- Are EDf, DA and TD causal links?
- Clinical implications

ASSUMPTIONS IN SCIENCE

- inevitable
- necessary
- constraining

OLD PARADIGM ASSUMPTIONS & QUESTIONS

Disorders are: discrete

dysfunctional-endogenous-fixed-homogenous

Where is the common core dysfunction in the brains/minds of ADHD children that ‘causes’ the disorder?

AN EXECUTIVE DYSFUNCTION MODEL

CORTICO-DORSAL STRIATAL LOOP DISTURBANCE

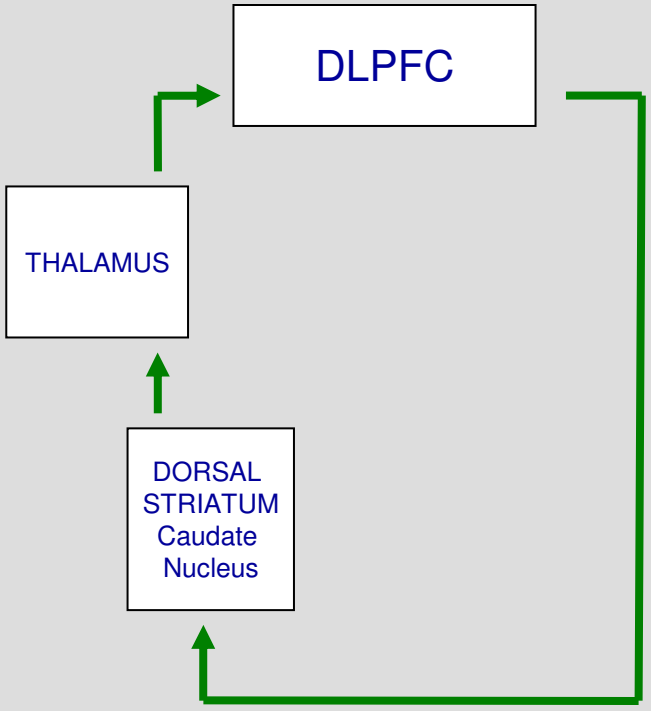
INHIBITORY DEFICITS

EXECUTIVE DEFICITS

ADHD

Adapted from Barkley, 1997

HYPOTHESIZED FUNCTIONAL NEUROANATOMY



EXECUTIVE DYSFUNCTION: A NECESSARY & SUFFICIENT CONDITION FOR ADHD?

There is a vast evidence base demonstrating a link between EDF and its neural substrate & ADHD.

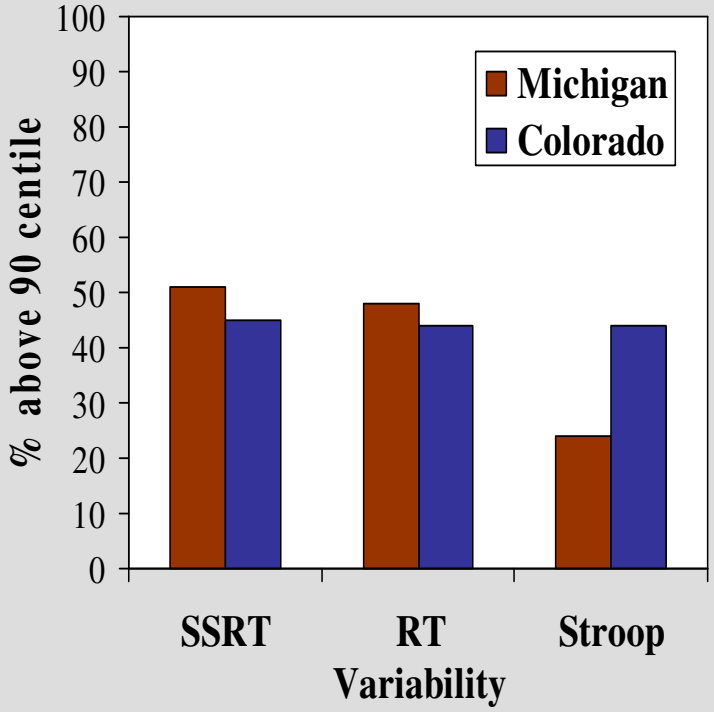
- Deficits in Working Memory, Attentional Flexibility, Planning etc.
- Inhibitory deficits may be a precursor
- Evidence implicating...
  - pre-fronto-striatal networks
  - dopamine, norepinephrine (Genes, Drugs)

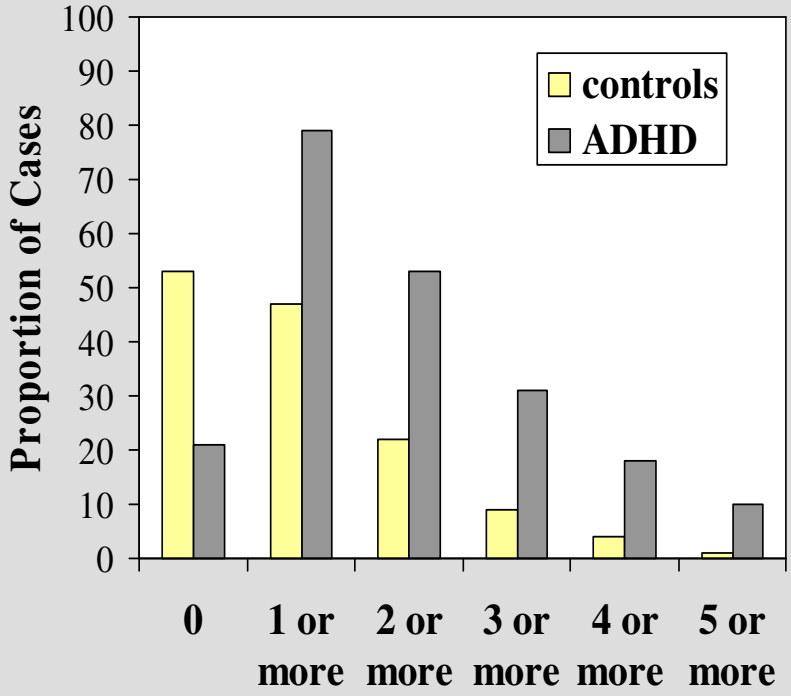
EXECUTIVE DYSFUNCTION: A NECESSARY & SUFFICIENT CONDITION FOR ADHD?

- But…
  - only a proportion of children with ADHD have EDF.
  - many children without ADHD have EDF.
  - EDF in ADHD nearly always presents in partial and fragmented way.

PERVASIVE EDf AFFECTS ONLY A MINORITY OF PATIENTS

Nigg, Doyle, Willcutt & Sonuga-Barke, 2005





WHAT 'CAUSES' ADHD IN 'UNAFFECTED' CHILDREN?

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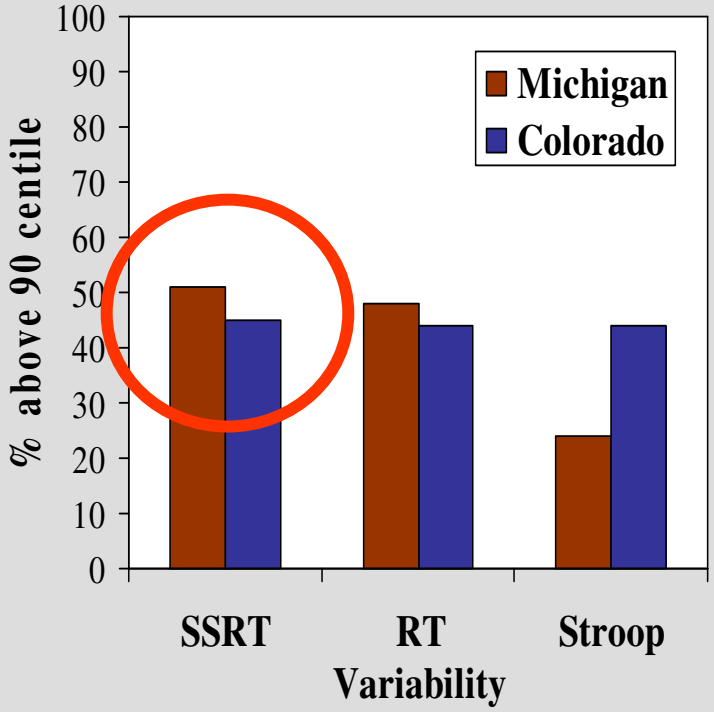

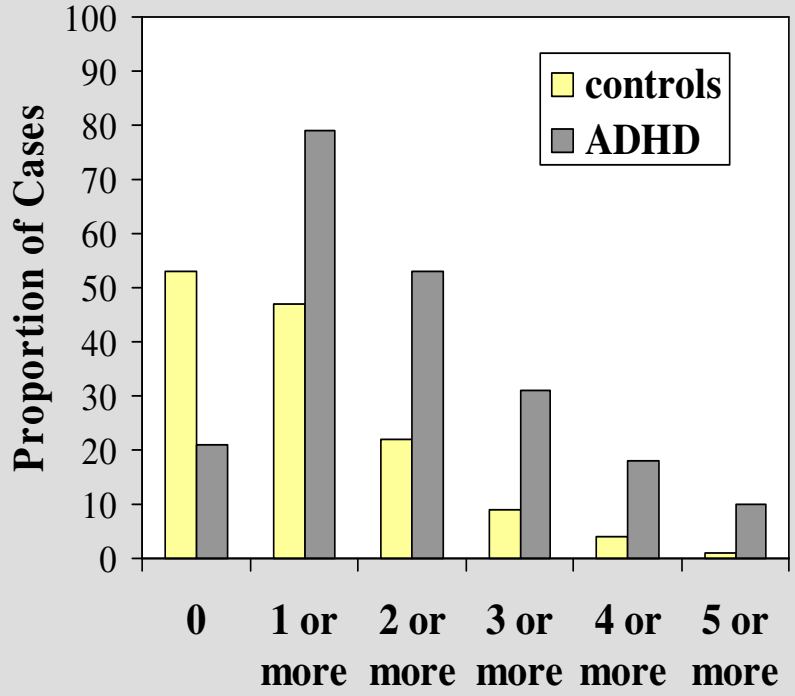

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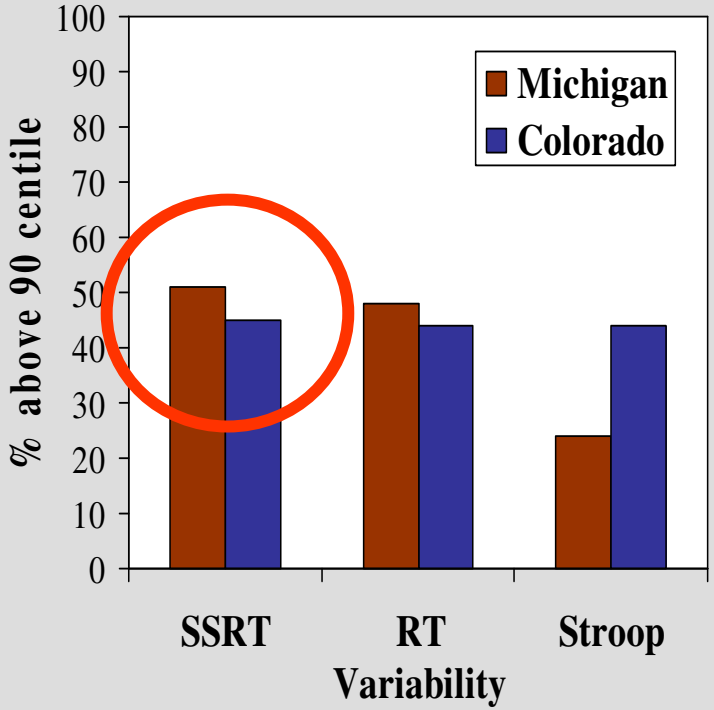
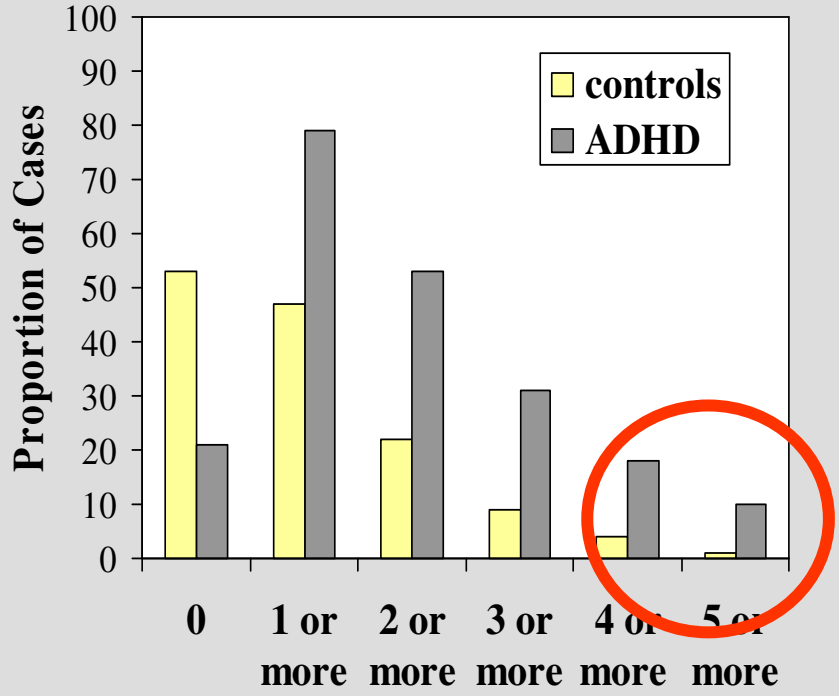




WHAT 'CAUSES' ADHD IN 'UNAFFECTED' CHILDREN?

SCIENTIFIC STRATEGY IN THE LIGHT OF NIGG ET AL (2005)

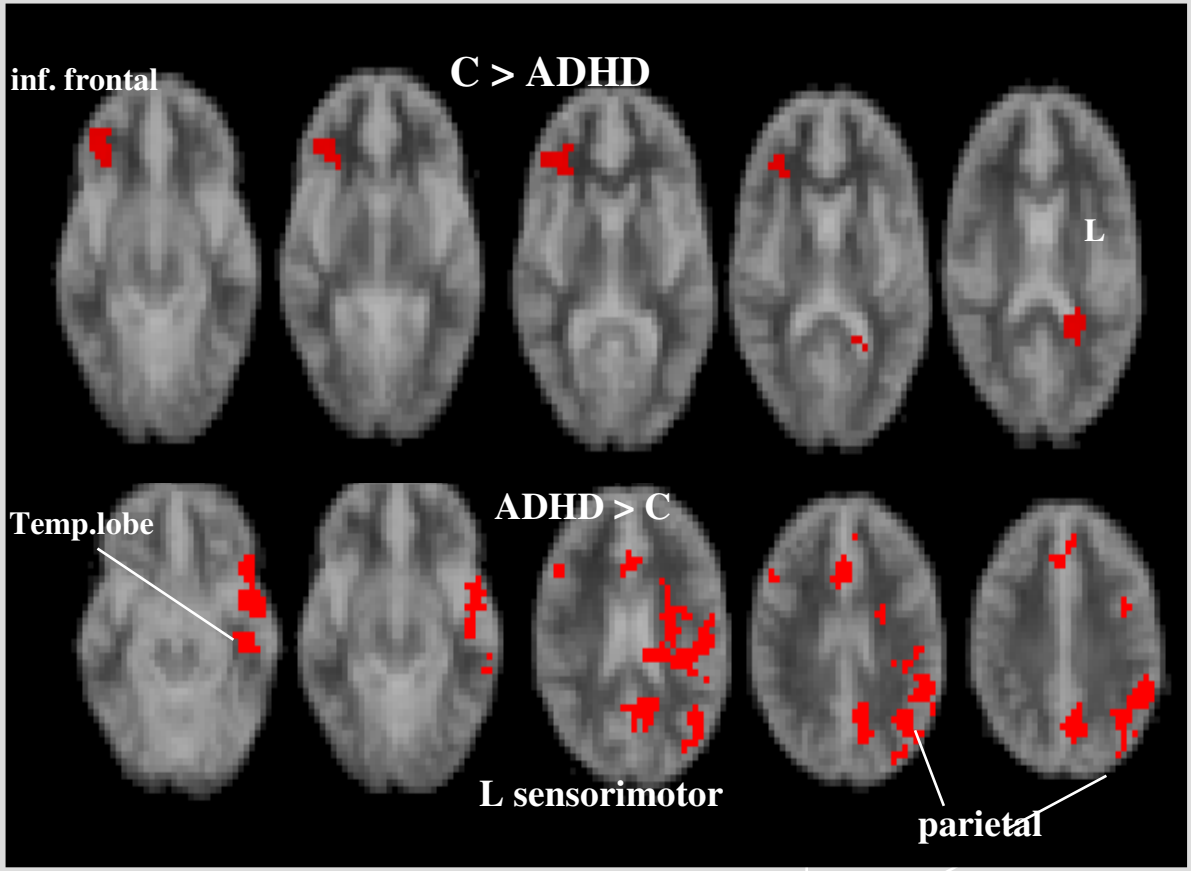
- ***Working within old paradigm***
  - Doggedly pursue EDF.
  - Supplant EDF with an alternative common core deficit.

- posterior parietal - orienting (Brandeis et al., 1998)
- Cerebellum - timing (Toplak & Tannock, 2003)
- OFC/NAcc – motivation/sensitivity to reward delay (Sagvolden et al., 2005)

Evidence for each candidate

but with moderate effect sizes - only subgroups are affected

FUNCTIONAL NEUROANATOMY OF SIMPLE COGNITIVE MODEL



Rubia et al., 1999

SCIENTIFIC STRATEGY IN THE LIGHT OF NIGG ET AL (2005)

- ***ADHD in new light (shift paradigm)***
  - Accept that ADHD represents a heterogeneous grouping consisting of diverse deficits.

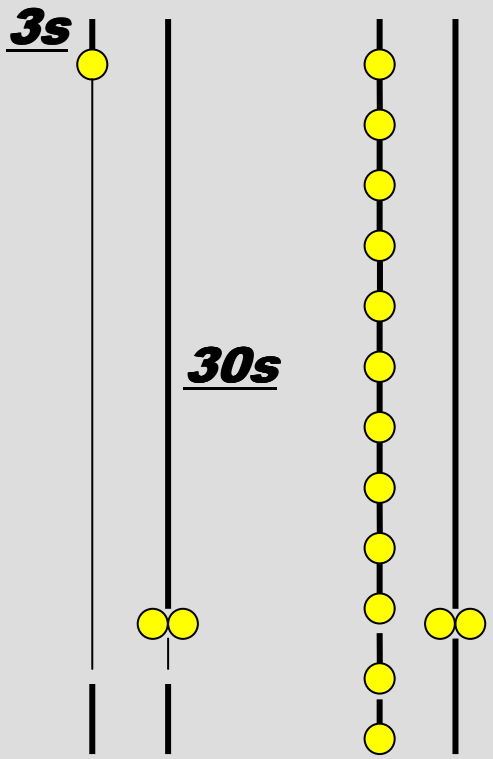
Which/how many neuropsychological pathways/types are subsumed within ADHD? Which particular dysfunction does a particular child with ADHD have?

PROPOSED MOTIVATIONAL ABNORMALITIES

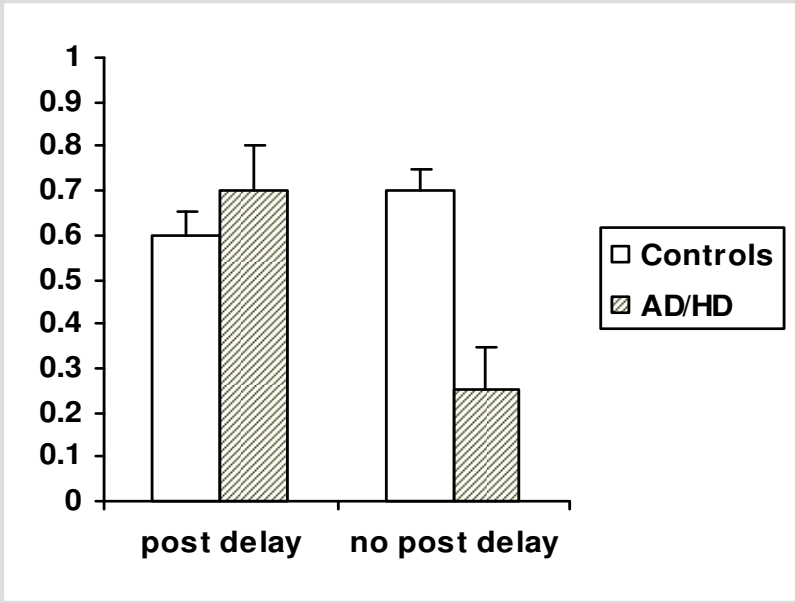
- Undersensitivity
  - Reinforcer effects (Haelein & Caul, 1987) (3/9 positive studies[1])
  - Changes in contingencies (Kollins et al., 1997) (1/1)
  - History of reinforcement (Tripp et al. 1999) (1/1)
  - Punishment (0/6[1]), partial reinforcement (Quay, 1988) (0/3[1])
- Oversensitivity
  - Punishment (van Meel et al, 2005) (1/1)
  - Frustrative non-reward (Douglas, 1999) (1/3[1])
  - Imposition of delay/'delay aversion' (Sagvolden et al, 2005; Sonuga-Barke, 2005) (see ahead)
- Inefficient Decision Making (Toplak et al., 2005) (2/4).

1. Luman M, Oosterlaan J, Sergeant JA (2005). The impact of reinforcement contingencies on AD/HD: A review and theoretical appraisal. *Clin Psychol Review* 25: 183-213.

CHOICE OF SMALL IMMEDIATE REWARD HAS ECONOMIC ELEMENTS



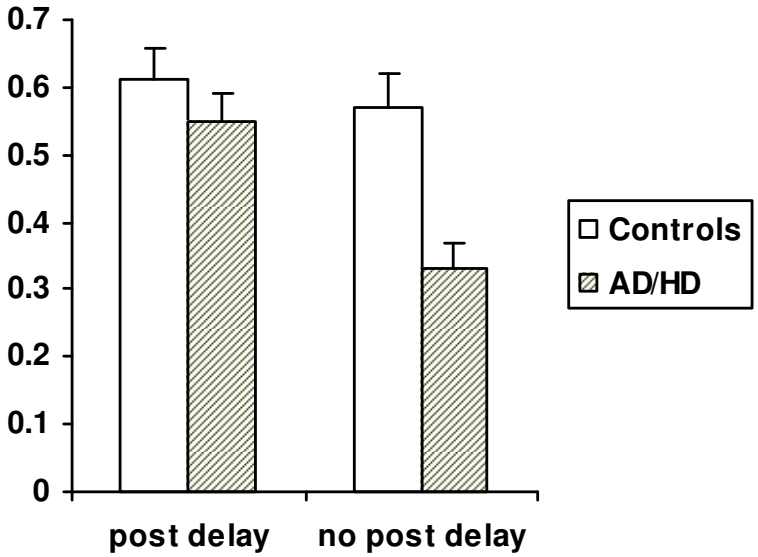
Only 20 trials – so more rewards overall if you choose the large delayed reward



A RECENT REPLICATION IN PRESCHOOLERS

Dalen et al (2004) Neural Plasticity

- ADHD children will choose immediacy to reduce delay even at the expense of rewards



No post reward delay – SS reduces trial delay
Post reward delay - SS has no effect on trial delay

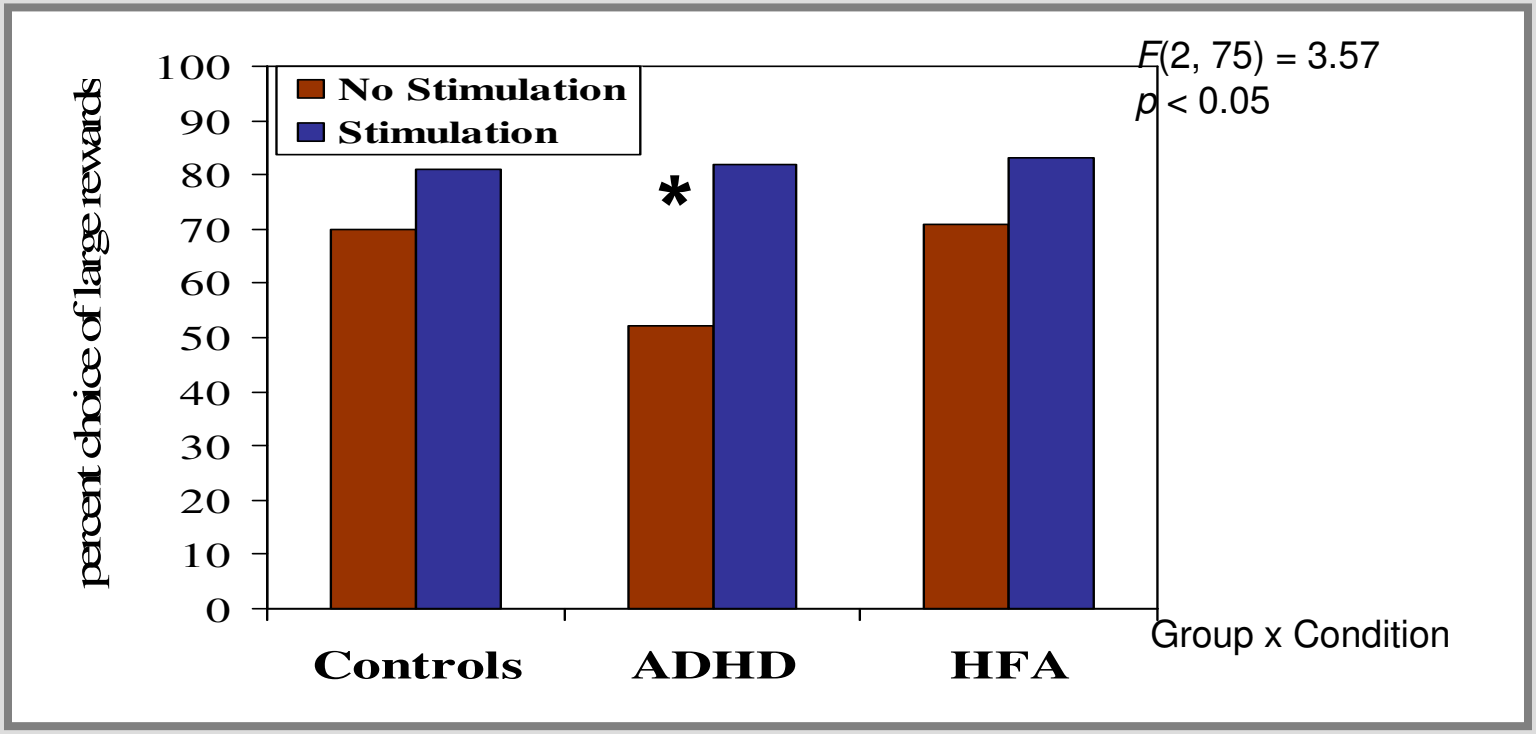
IMPULSIVE ONLY WHEN IN LOW STIMULATION ENVIROMENTS

Antrop et al (2006)

Subjects - 29 ADHD - 26 HFA - 29 Controls

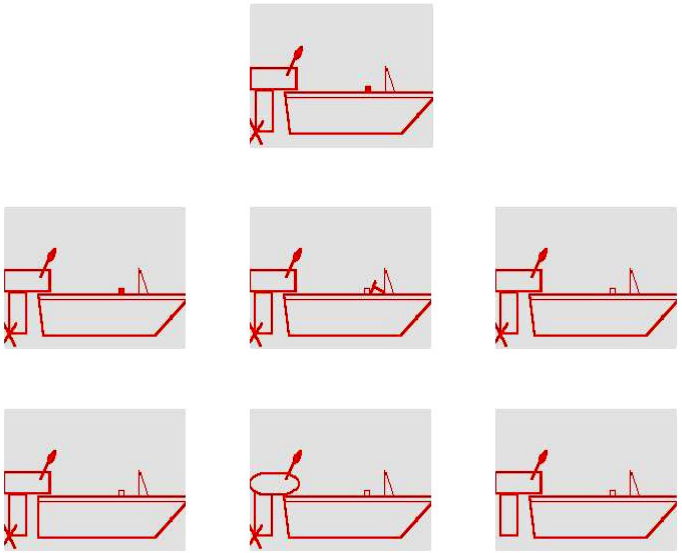
Design - Maudsley Index of Delay Aversion – (1 in 2 secs vs 2 in 30s).

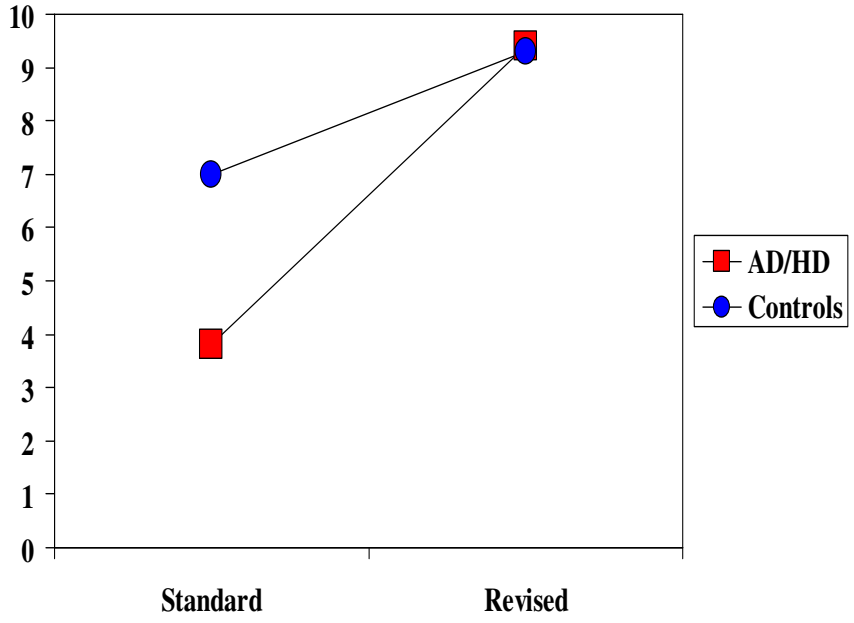
» no access to stimulation *v* access to stimulation



IMPULSIVE ONLY WHEN ESCAPE FROM DELAY IS POSSIBLE

Sonuga-Barke et al (1994)



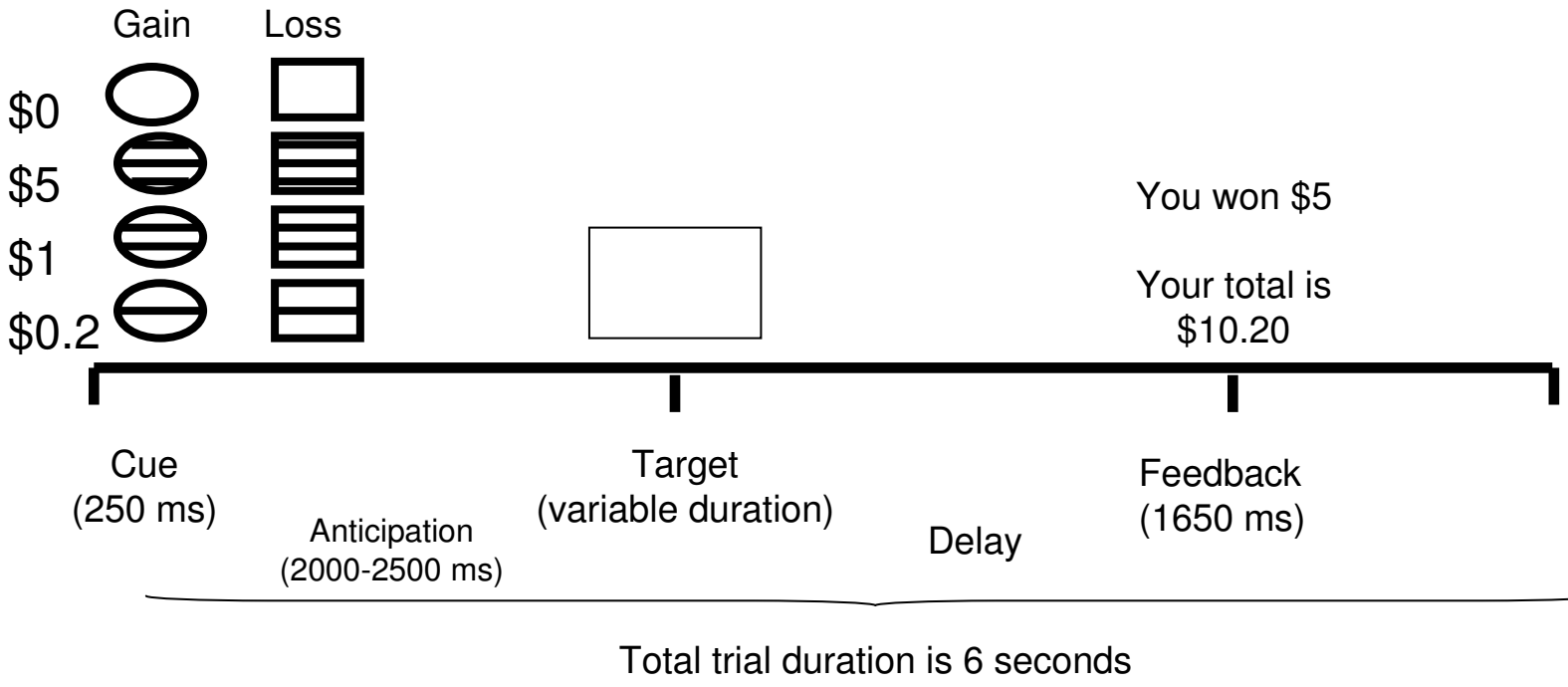


Standard – variable trial – Revised – fixed trial (45 mins)

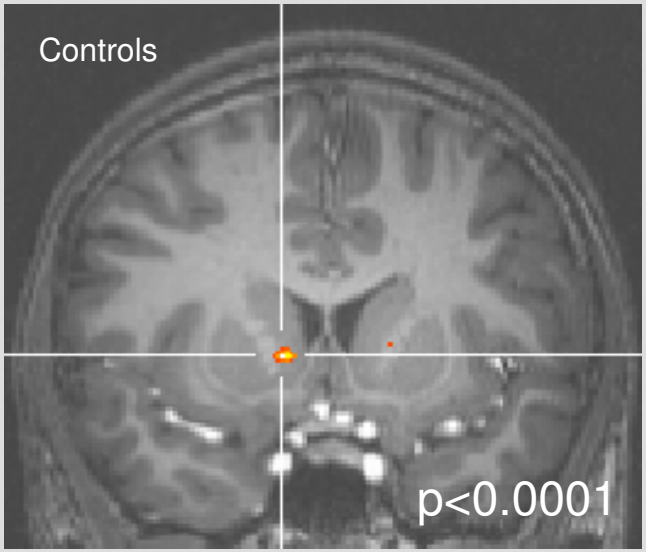
FUNCTIONAL ANATOMY OF MOTIVATIONAL MODEL

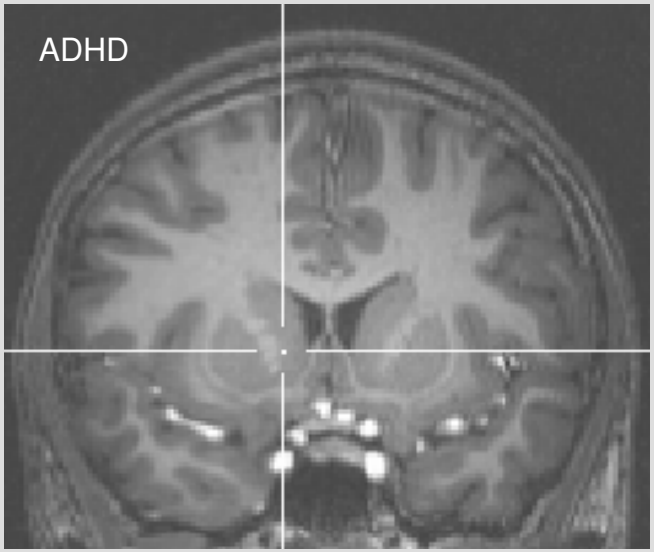
SCHERES ET AL (2006)

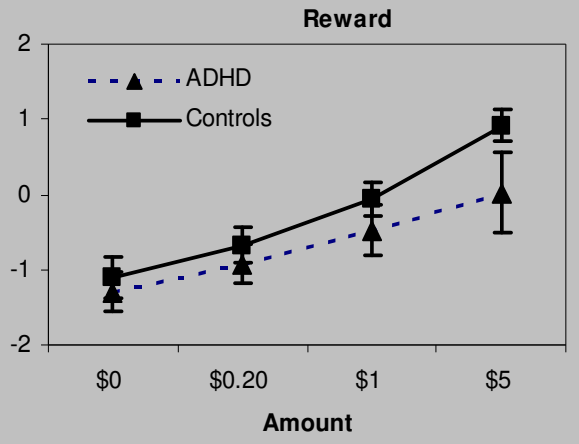
- Adolescents ages 12-17 (N = 22)
  - 11 ADHD (2 girls; 9 boys -4 ADHD-I, 7 ADHD-C)
  - 11 NC (3 girls; 8 boys)

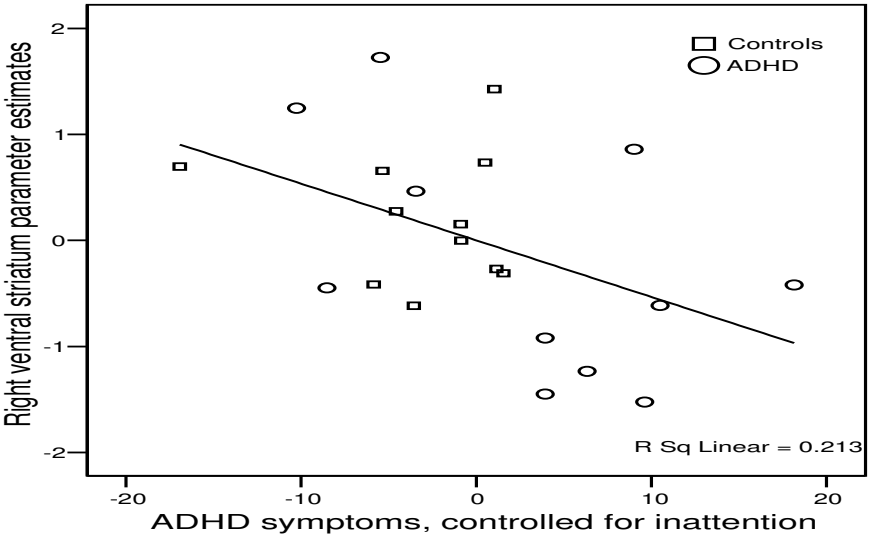


BOLD ACTIVATION DURING REWARD ANTICIPATION IN STRIATUM









DELAY AVERSION IN ADHD: INTERPRETING THE EVIDENCE

- Respond inappropriately to unexpected imposition of delay (Bitsakou et al, 2006) and extinction (Sagvolden et al., 1998).
- Prematurely disengage from long and challenging tasks (Scime et al., 2006).
- Differentially active during delay (Antrop et al., 2002).
- Biased towards task responses tied to immediate rewards (Tripp et al, 2003).
- Vigilant to environmental delay cues (Sonuga-Barke et al., 2004).
- Prefer reward immediacy to high reward rate or task ease (Neef, 2005).
- Discount future hypothetical rewards (Barkley, 2001; Scheres et al., 2006 for counter case).
- Differential effect of slow event rates/sparse schedules (Wiersema et al, 2006; Aase et al, 2006).
- Choose SS over LL rewards (see ahead).

DELAY SENSITIVITY & EXECUTIVE DYSFUNCTION HEAD-TO-HEAD

Solanto et al, (2001) Journal of Abnormal Child Psychology, 29, 215-228.

Question: What is the core 'deficit' in ADHD?

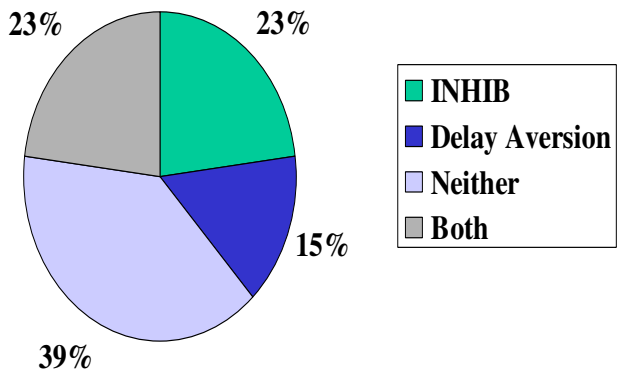
Methods:

- Both theoretical camps involved
- Independently Designed and Instigated
- "Pick your best task!" - choice delay vs stop signal

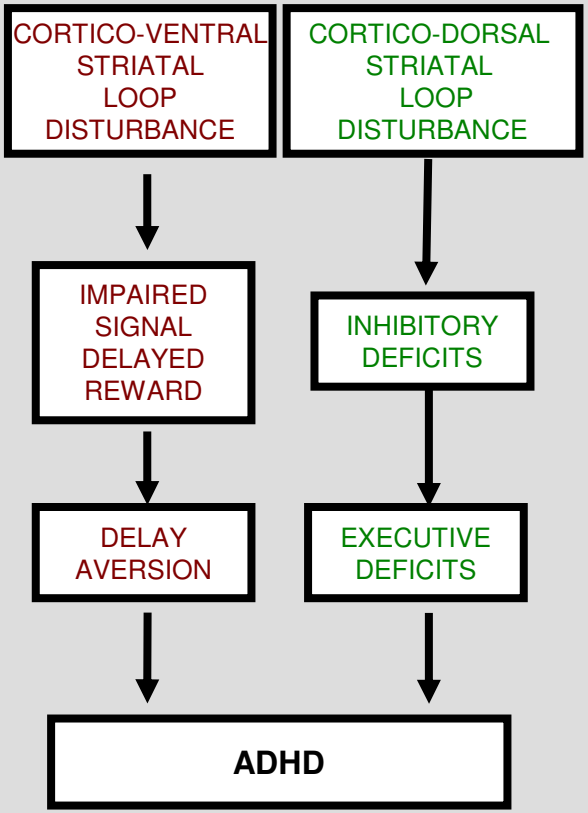
Results:

Delay Aversion and Inhibition uncorrelated

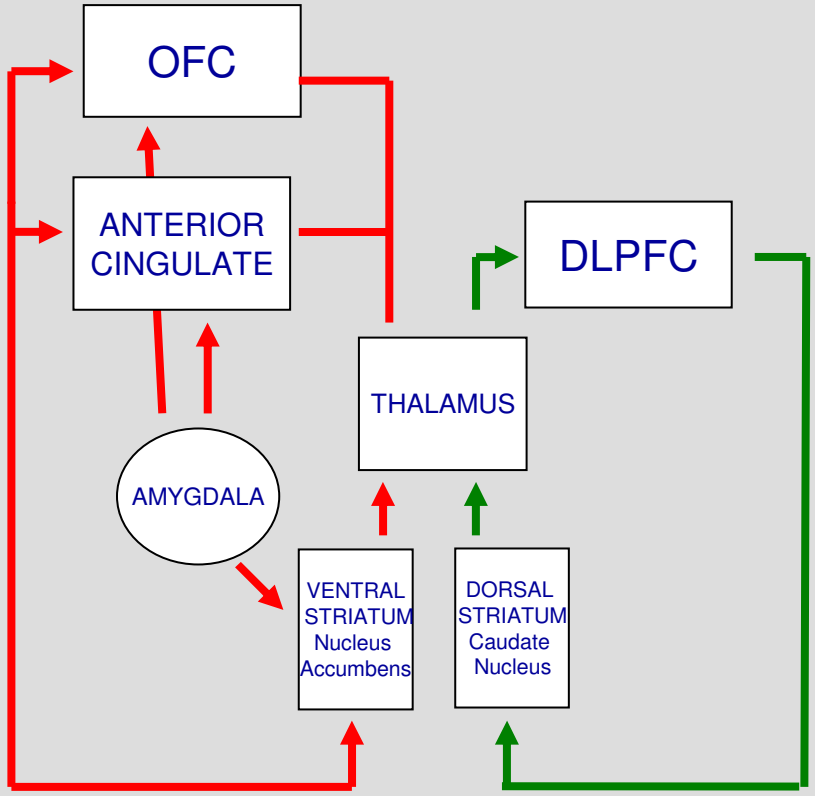
Groups differed significantly on both measures.



A DUAL PATHWAY MODEL EFD & DELAY AVERSION



HYPOTHESIZED FUNCTIONAL NEUROANATOMY



Motivational (delay sensitivity) and Cognitive (EDF) pathways are each sufficient but neither are necessary for C-ADHD.

TIMING AS A POTENTIAL THIRD PATHWAY (Toplak & Tannock, 2006)

- **Multi-Second Intervals – Cortico-striatal**
  - Interval underestimation (Sonuga-Barke et al., 1998)
  - poor time reproduction (Smith et al., 2002)

Tasks rely heavily on inhibition and working memory.

- **Millisecond Intervals – Cortico-cerebellar**
  - Poor tapping synchrony (Rubia et al., 1999; Ben-Pazi et al., 2003)
  - Deficient temporal discrimination (Smith et al., 2002, Toplak et al., 2003)

STARTING TO TEST CASUAL MODELS

The search for endophenotypes

IN GENERAL

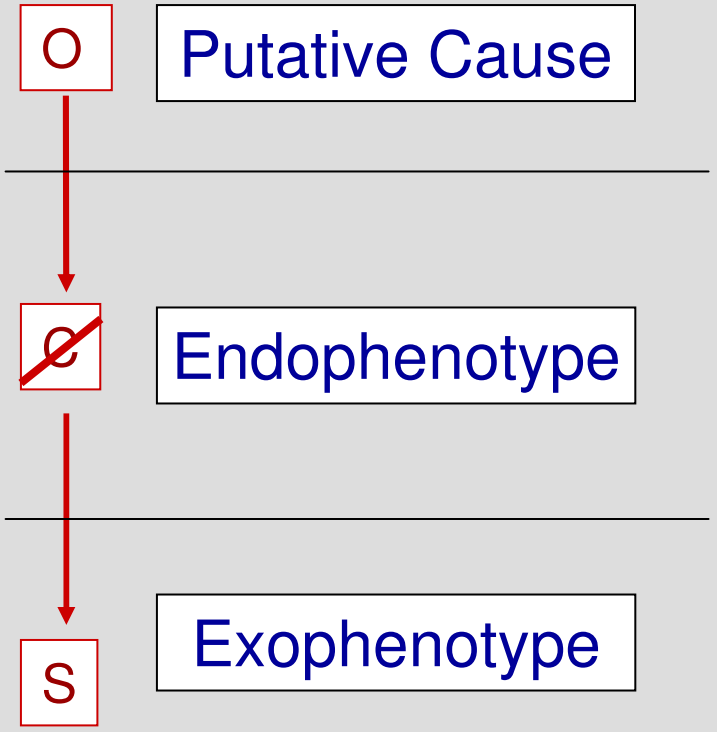
- Quantifiable trait
- 'Closer' to cause than exophenotype is
- Associated with both disorder and cause
- Carries effect of cause on disorder
- State independent

TO BE USEFUL FOR FINDING GENES IN ADHD

- Heritable
- Co-segregate with disorder within families.
- More homogeneous than exophenotype.

5)

From Gottesman & Gould, (2003)



CANDIDATE CAUSES

A continuum of neurobiological risk

- Good evidence implicating genetic factors
  - Heritable
  - Candidate genes – e.g., DRD4 and DAT1
- Environmental factors also implicated
  - Perinatal (Thapar et al. 2004; Pineda et al, 2004)
  - Prematurity (Bhutta et al., 2002)
  - Diet? (Bateman et al. 2004)
  - Institutional Care (Rutter et al., 2004)
- Genetic and environmental factors of small effect acting together to produce a spectrum of liability.

ARE NEUROPSYCHOLOGICAL ENDOPHENOTYPES FAMILIAL?

Nigg et al., (2004)

Are relatives of children with ADHD and neuropsychological deficits impaired relative to relatives of other children with ADHD + controls?

- 176 children (62 ADHD-C, 35 ADHD-PI, 79 CONS)
- 307 parents
- NIMHD Interview - DSM-IV checklist
- Behavioural inhibition- Set shifting - Planning-WM - Interference - Response Variability - Response and naming speed.
  - a) parents of controls
  - b) parents of ADHD children - non-impaired
  - c) parents of ADHD children - impaired

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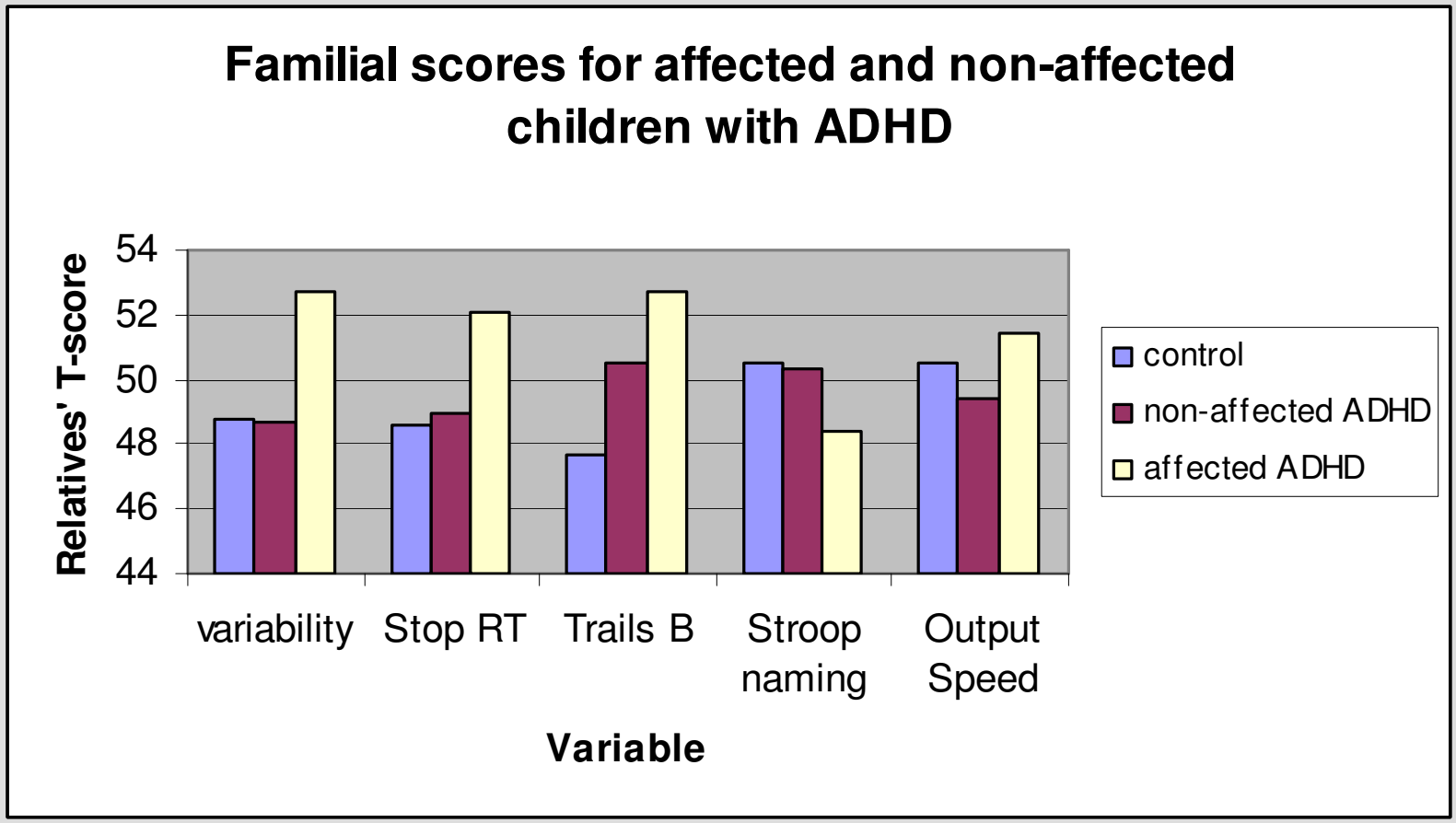


CONCEPTUALISING AND PARTITIONING HETEROGENEITY IN ADHD

The heterogeneity suggested by the moderate strength of association with EDf leads us to postulate that ADHD, is not a single pathophysiologic entity but rather a heterogeneous condition consisting of multiple more or less discrete groupings each with distinctive elements to its neuropsychological profile: EDf, DA and TD may be important markers for some groupings.

SCIENCE TO PRACTICE

- **SHOULD THERE BE NEUROPSYCHOLOGICAL SUBTYPES?**
- EDF & DEL as epiphenomenon
- EDF & DEL as complication & comorbidity
- EDF & DEL as subtypes of disorder

IMPLICATIONS OF SUBTYPES

- Assessment & Diagnosis
  - From phenomenological to theoretical approaches
  - Biological/psychological markers
  - The role of context
- Treatment
  - targeting subtypes with specific treatments/agents
  - novel and more effective psychosocial treatment

THE CHANGING ROLE OF PRACTICAL NEUROPSYCHOLOGY

Old paradigm neuropsychology – *limited diagnostic role*

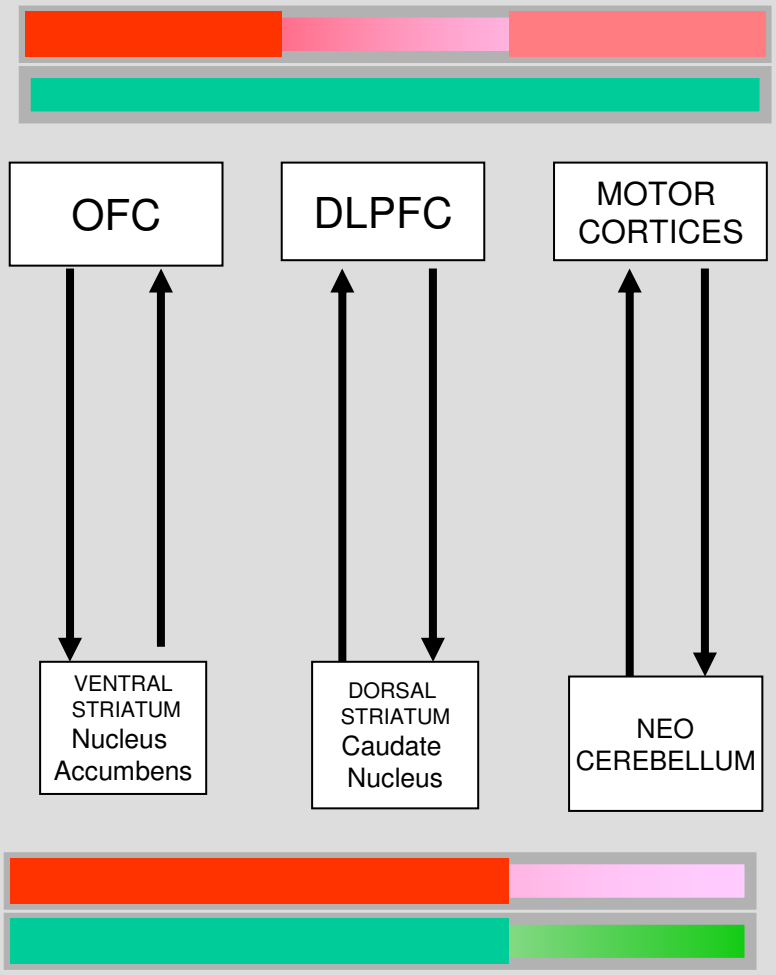
- EF tests show good +ve predictive power but poor -ve predictive power.
- Similar patterns for children and adults-where data exist.
- Little known about value in differential diagnosis.

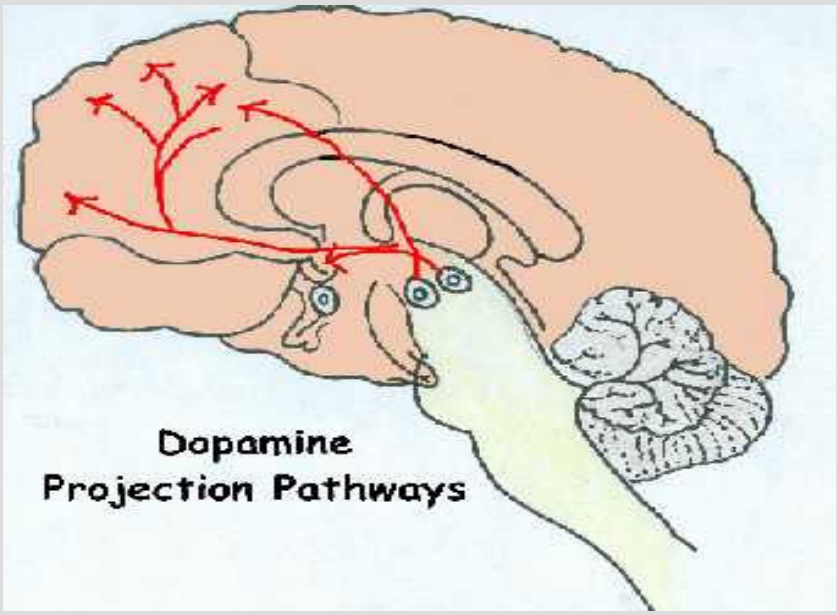
Refs. - Barkley & Grodzinsky 1994, 1999; Berlin et al., 2004; Cahn et al. 1996 Doyle et al. 2000; Lovejoy et al., 1999. Sharma et al, 1995; Mayes et al., 2001; But see Rielly et al (1999) for opposite finding.

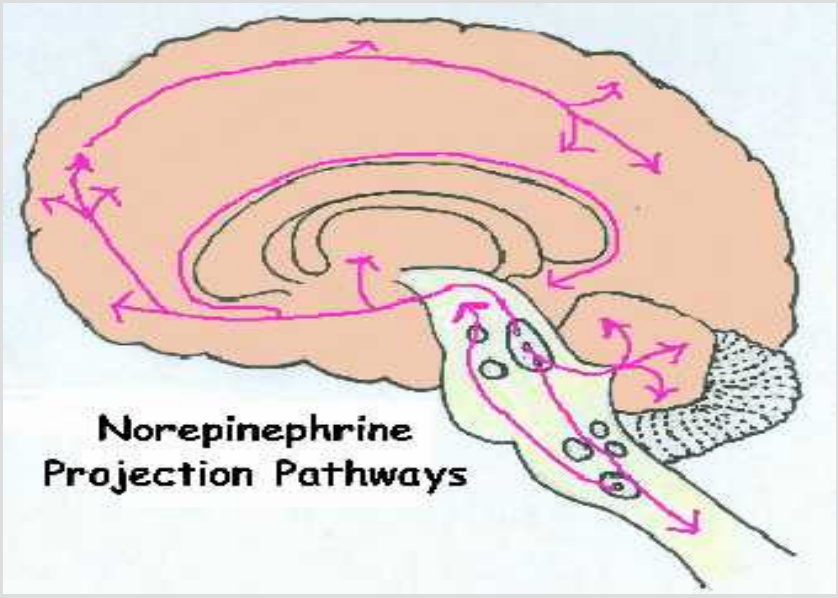
New paradigm neuropsychology - *enhanced role in assessment/diagnosis*

- profiling areas of particular deficits in individual cases
- neuropsychological subtyping
- setting treatment targets/measuring outcomes

MAJOR DOPAMINE & NOREPINEPHRINE BRANCHES







CONCLUSIONS

ADHD

- is a pathophysiologically heterogeneous disorder
- is probably underpinned by multiple distinct pathways
- caused by multiple genetic and environmental risks acting together

Future research should focus on

- delineating pathways and their overlap and interactions
- testing their links to specific causal factors
- Identifying moderators of progression (GxE interactions)
- explore their significance for diagnosis and treatment