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TRINITY COLLEGE
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from molecules to mind



Candidate genes in child psychiatry: What do we know and where to from here? Examples from ADHD

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Overview

- **Symptoms and Etiology of ADHD**
- **Candidate gene approach to ADHD**
- **Rationale behind the endophenotype approach**
- **Genotype/Phenotype studies of ADHD**
 - **Spatial Attention**
 - **Sustained Attention/Response Inhibition**

Symptoms of ADHD

- **ADHD is a behavioural disorder of childhood**
 - Age inappropriate levels of inattention, hyperactivity and impulsivity
- **Onset is early (before 7 years of age), 3-6% of school-aged children affected.**
- **30-60% carry psychopathology into adulthood**
- **70% respond well to stimulant medications**
 - Methylphenidate

Etiology of ADHD

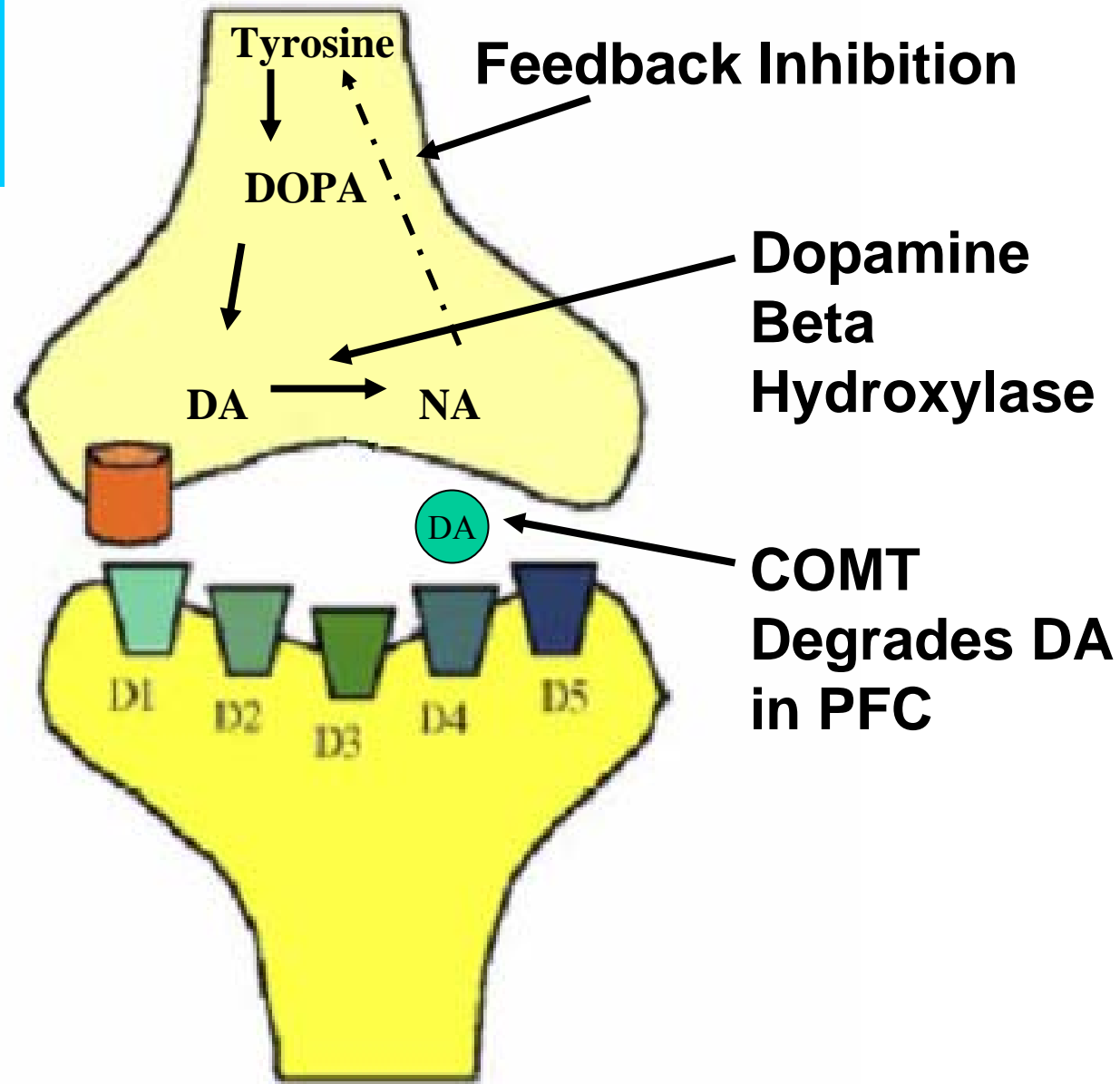
- **Exact etiology is uncertain**
- **Family, twin and adoption studies suggest strong genetic component**
 - E.g., concordance rates in MZ twins of 68-81%
- **Imaging studies consistently implicate dysfunction to frontal and sub-cortical regions, particularly within the right-hemisphere**
- **Neuropsychology shows deficit in sustained attention, spatial working memory and inhibition- all frontally mediated functions**

Candidate Gene Approach

- **Dysfunction to catecholamine (e.g., DA and NA) systems seems likely, since stimulants act on these systems**
- **Candidate gene approach seeks to determine whether genetic variants are associated with ADHD at a greater than chance frequency**
- **Candidate genes for ADHD include those coding for receptors, enzymes or transporters, amongst others, involved in catecholamine function**

Potential sites of expression for genetic effects

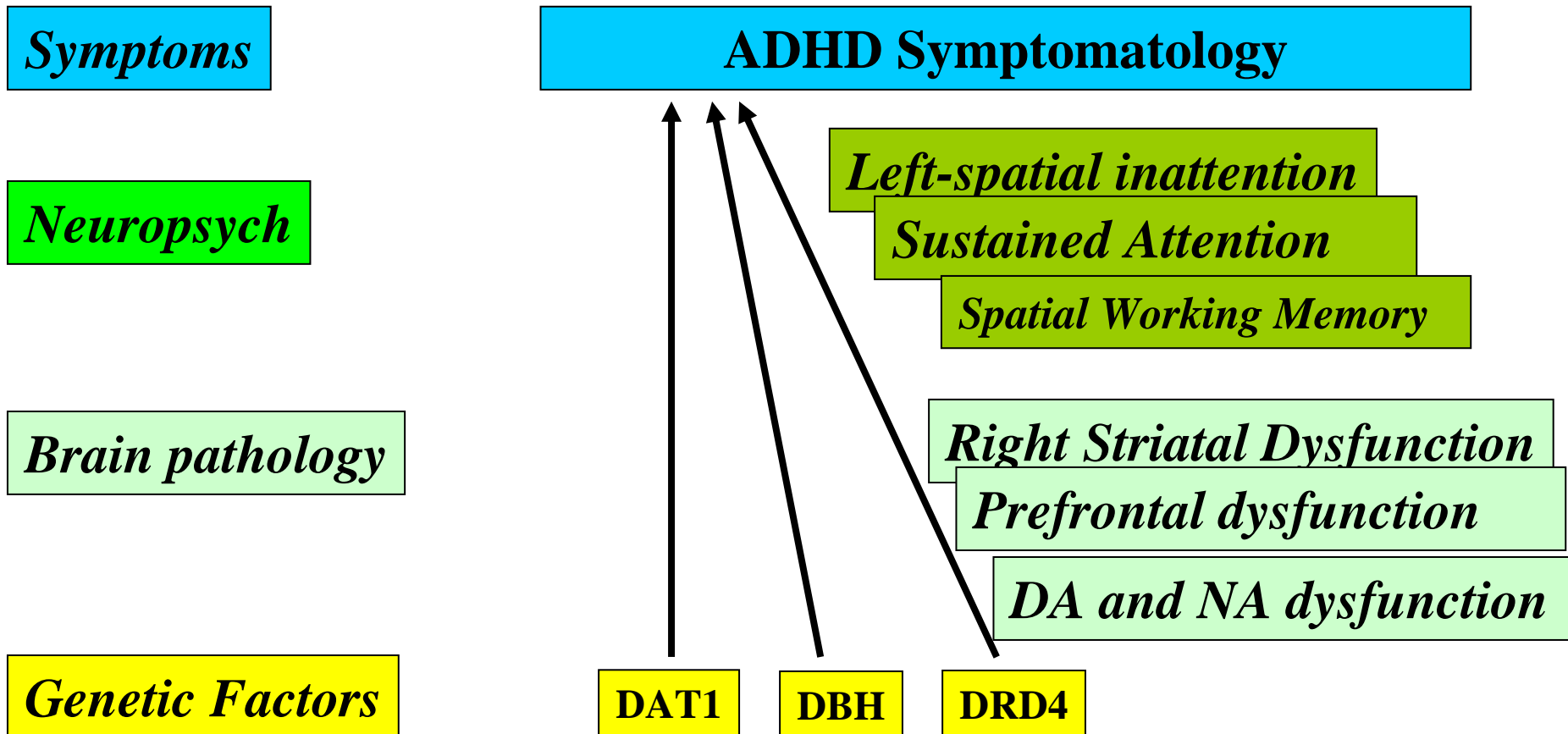
Transporter Blocked by MPH, particularly in striatum



Rationale behind the endophenotype approach

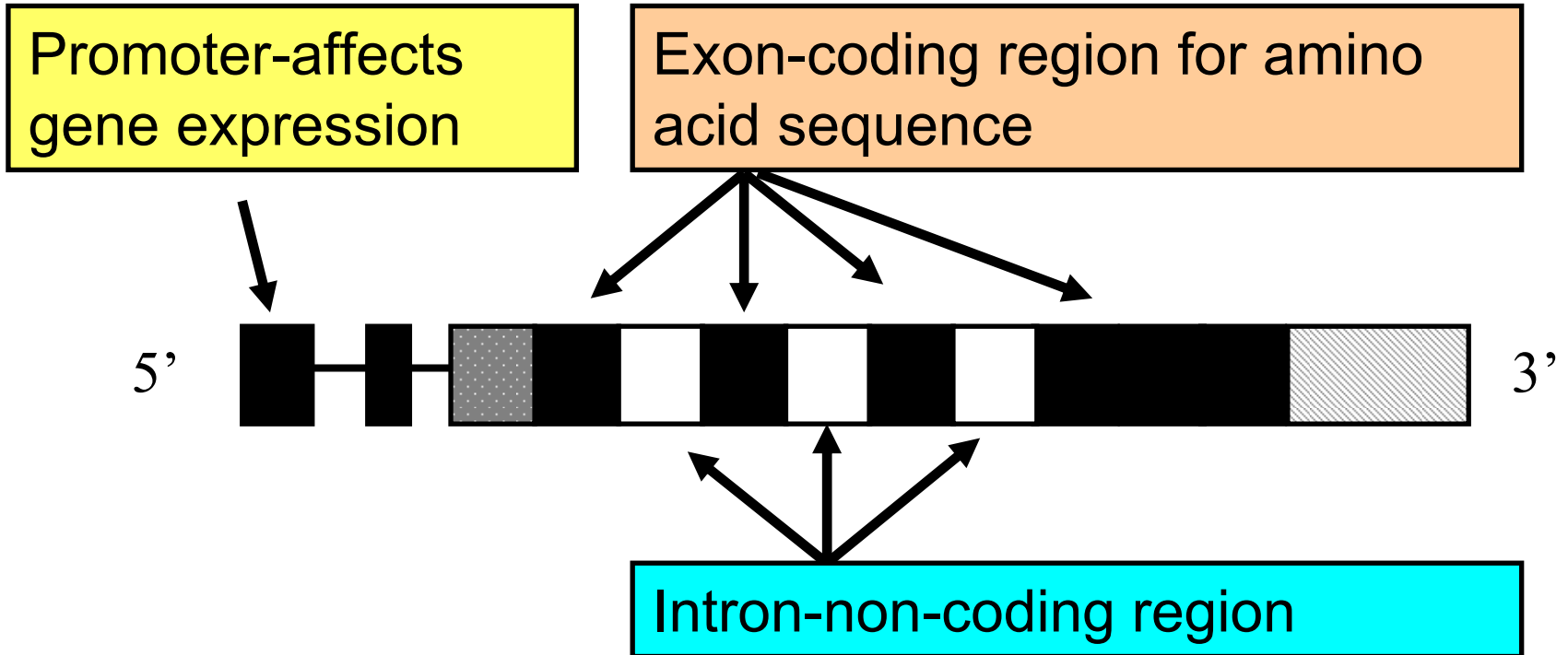
Castellanos and Tannock (2002)

Neuropsychological endophenotypes should be related to symptoms but be closer to the site of gene action



Molecular Biology

Gene Structure



DNA sequences

SNP- single nucleotide polymorphism (point mutation)
VNTR- variable number of tandem repeats

Genotype/Phenotype studies of ADHD

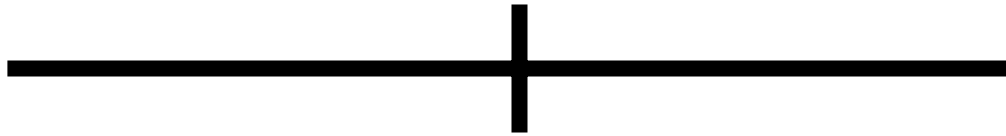
DAT1 and left-spatial inattention

- **Dopamine Transporter (DAT1)**
 - **10-repeat allele of a VNTR of the DAT1 gene associated with ADHD in a number of studies (Cook et al, 1995; Gill et al, 1997; Daly et al, 1999)**
 - **10-repeat allele associated with an enhanced therapeutic response to MPH (Kirley et al, 2003)**
 - **The 10-repeat allele affects expression levels of the transporter**
 - ***DAT1 Hypothesis*: greater density of transporter or activity associated with the 10-repeat DAT1 allele leads to a reduction of available dopamine in the striatum. MPH normalises this.**

Genotype/Phenotype studies of ADHD DAT1 and left-spatial inattention

- **Voeller and Heilman (1988) first proposed that ADHD could be a “neglect syndrome”**
 - ADHD children made more left-sided errors resembling patients with right-hemisphere lesions
- **Supporting evidence has been inconsistent.**
- **Evidence that attentional asymmetries may be normalised with MPH** (Sheppard et al, 1999; Nigg et al, 1997)
- **Neglect is also consequent upon lesions to striatum and DA pathways**
 - *Hypothesis:* Left-spatial inattention in ADHD would relate to DAT1 genotype

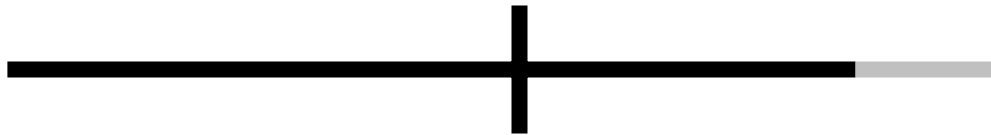
The Landmark Task



Subject is presented with a pre-bisected line
Which end is the shortest?

Left-spatial Inattention in ADHD

The Landmark Task

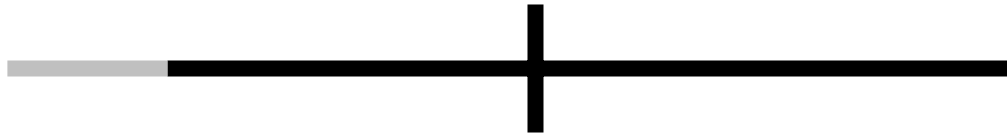


Healthy subjects show a leftward bias and relative inattention to the rightward extent

“The right end of the line is the shortest!”

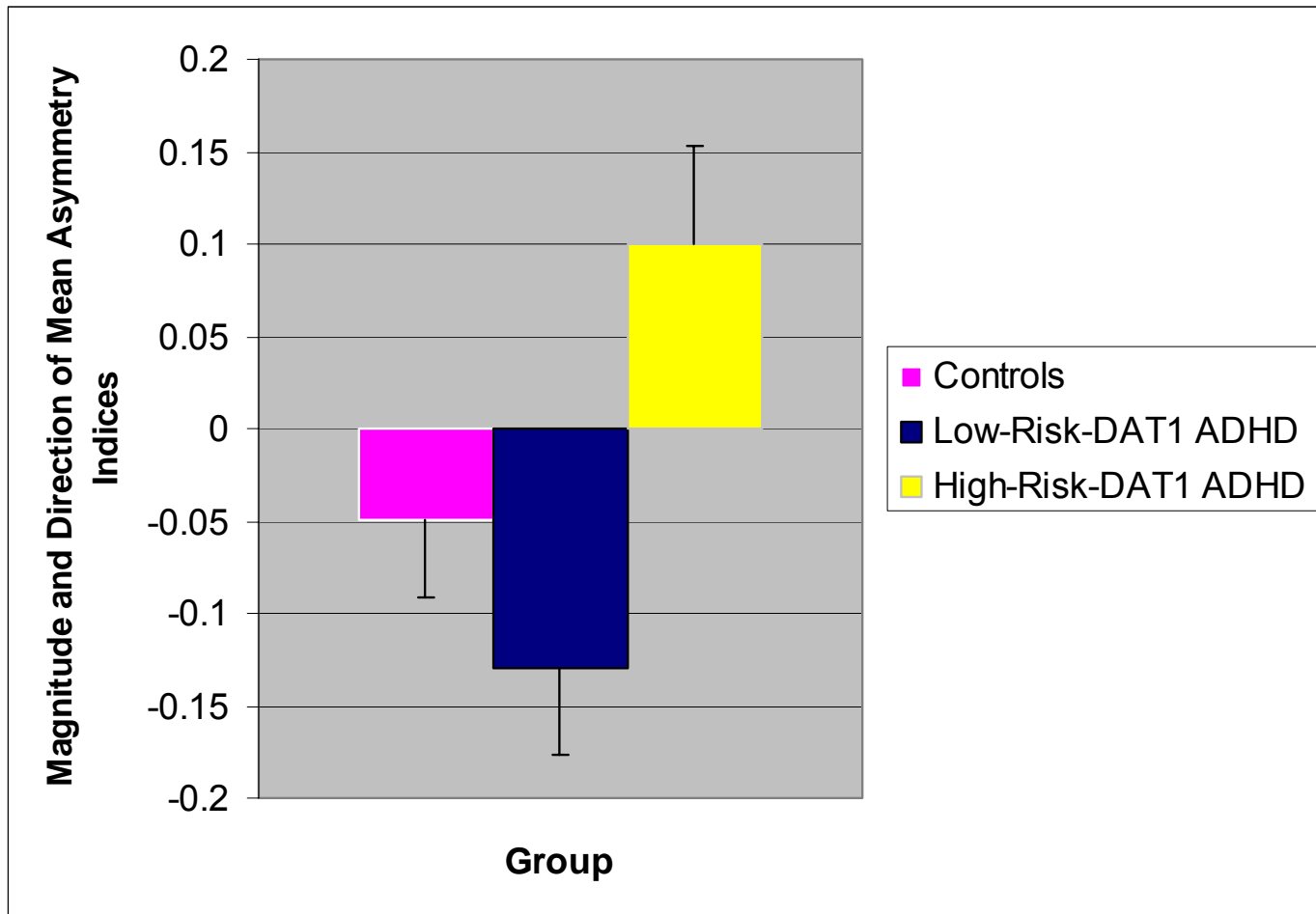
Left-spatial Inattention in ADHD

The Landmark Task



In left-neglect subjects show a rightward bias and relative inattention to the leftward extent

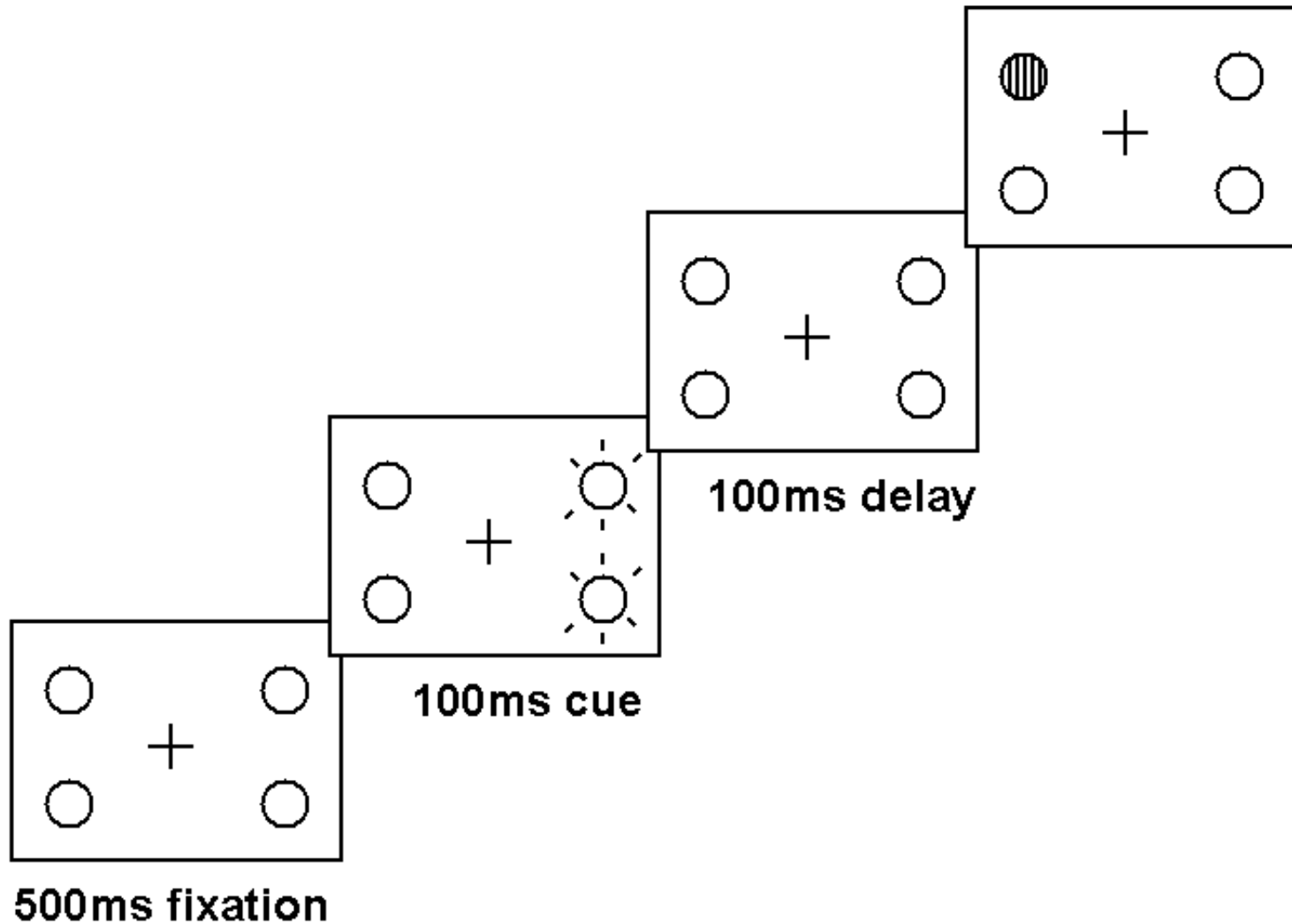
“The left end of the line is the shortest!”



High-Risk DAT1 ADHD group display left spatial inattention

Bellgrove et al (2005), *Neuropsychopharmacology*

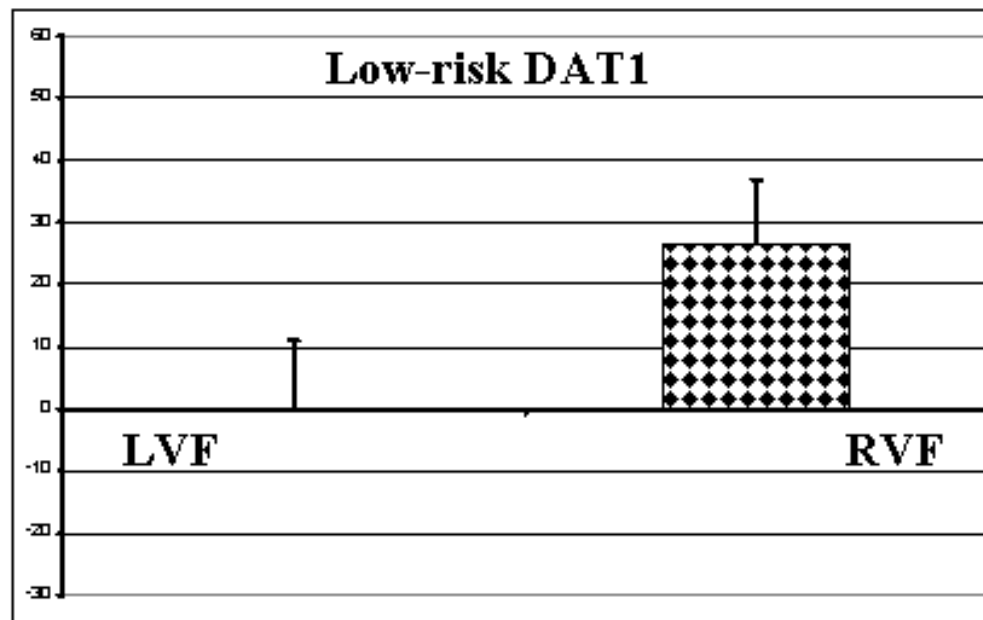
Exogenous Orienting Task



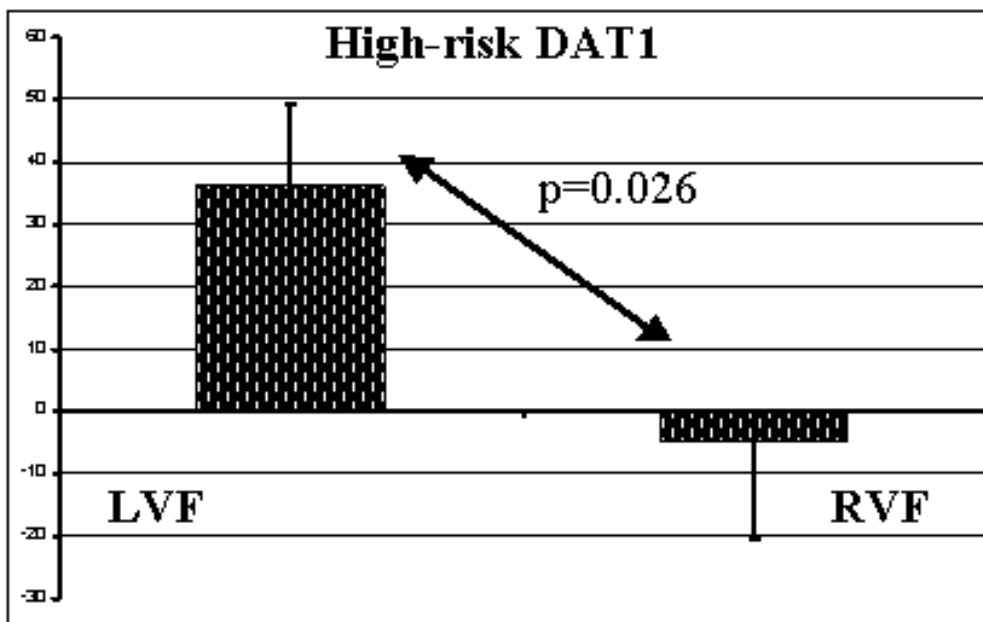
Exogenous Orienting Task

- **If the observed relationship between DAT1 and left-sided inattention reflects dysfunction to spatial attentional systems then:**
 - **Would predict a reorienting deficit for LVF targets (invalidly cued to the RVF) in DAT1 10-repeat homozygotes**

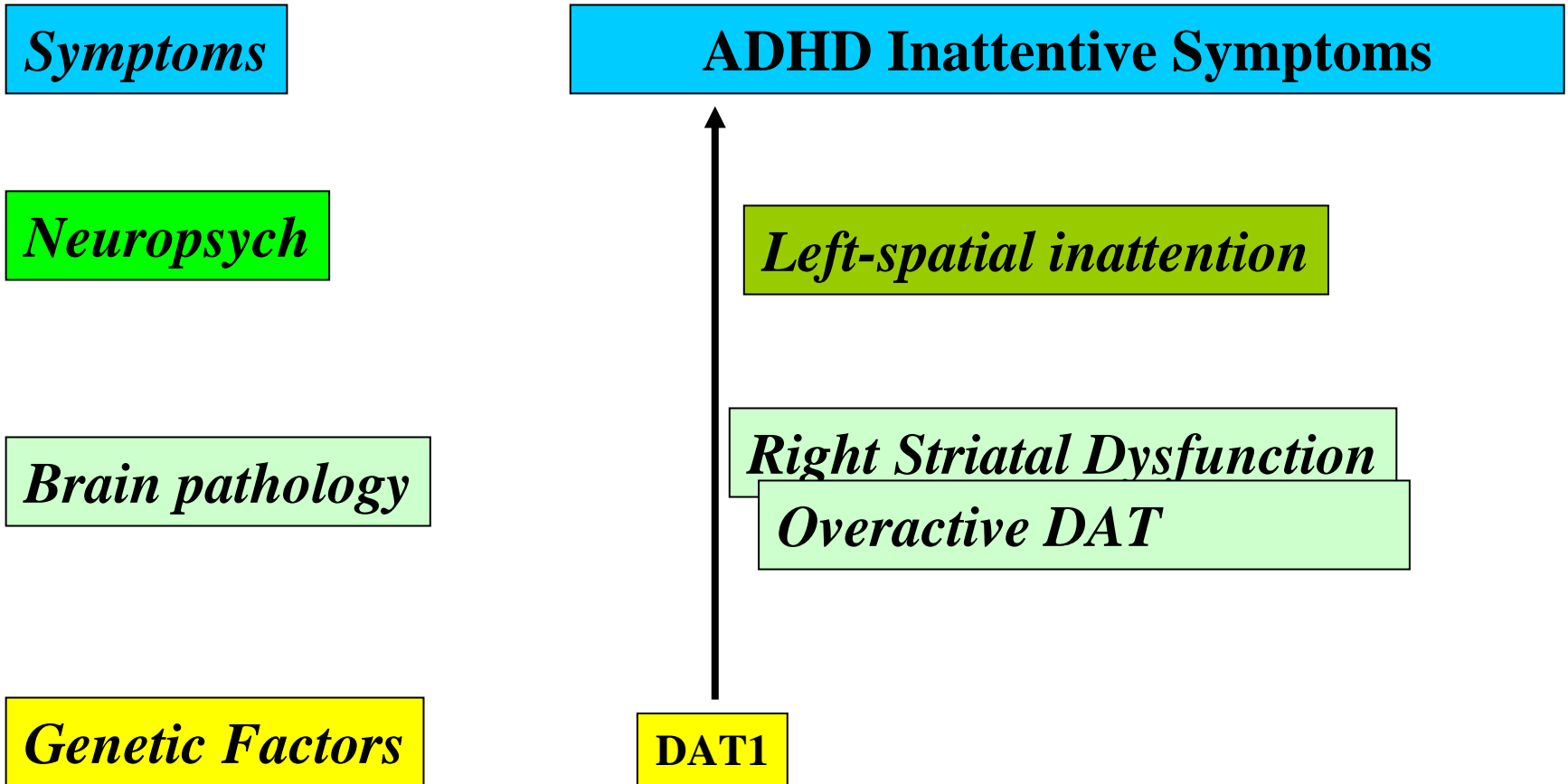
Invalidity effect



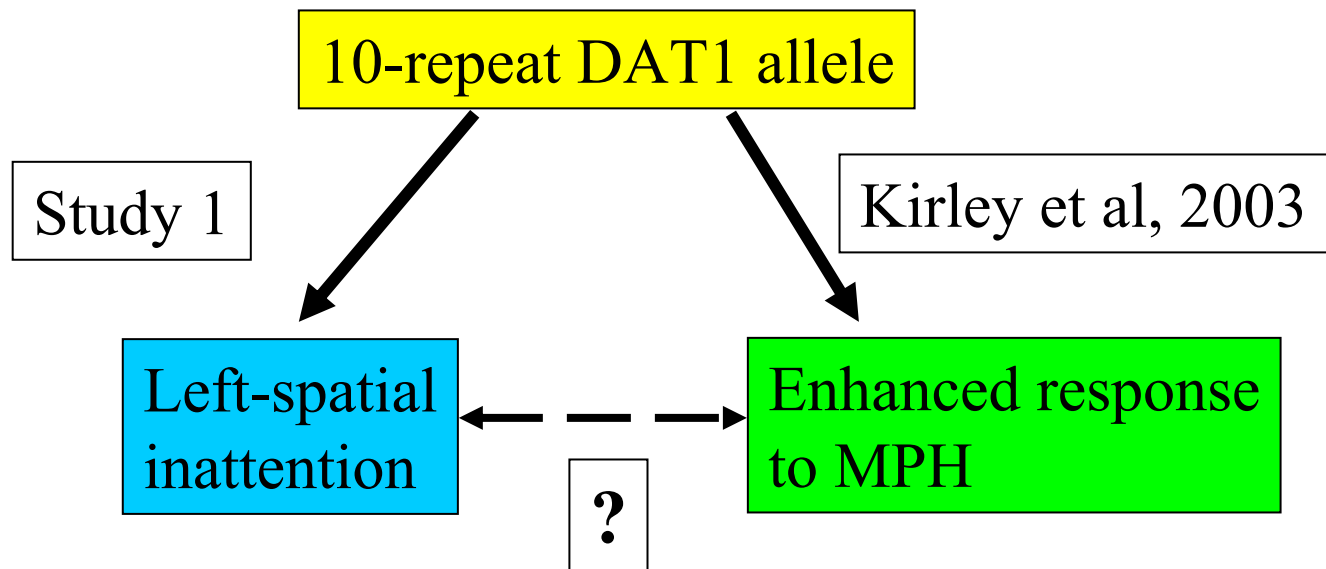
Invalidity effect



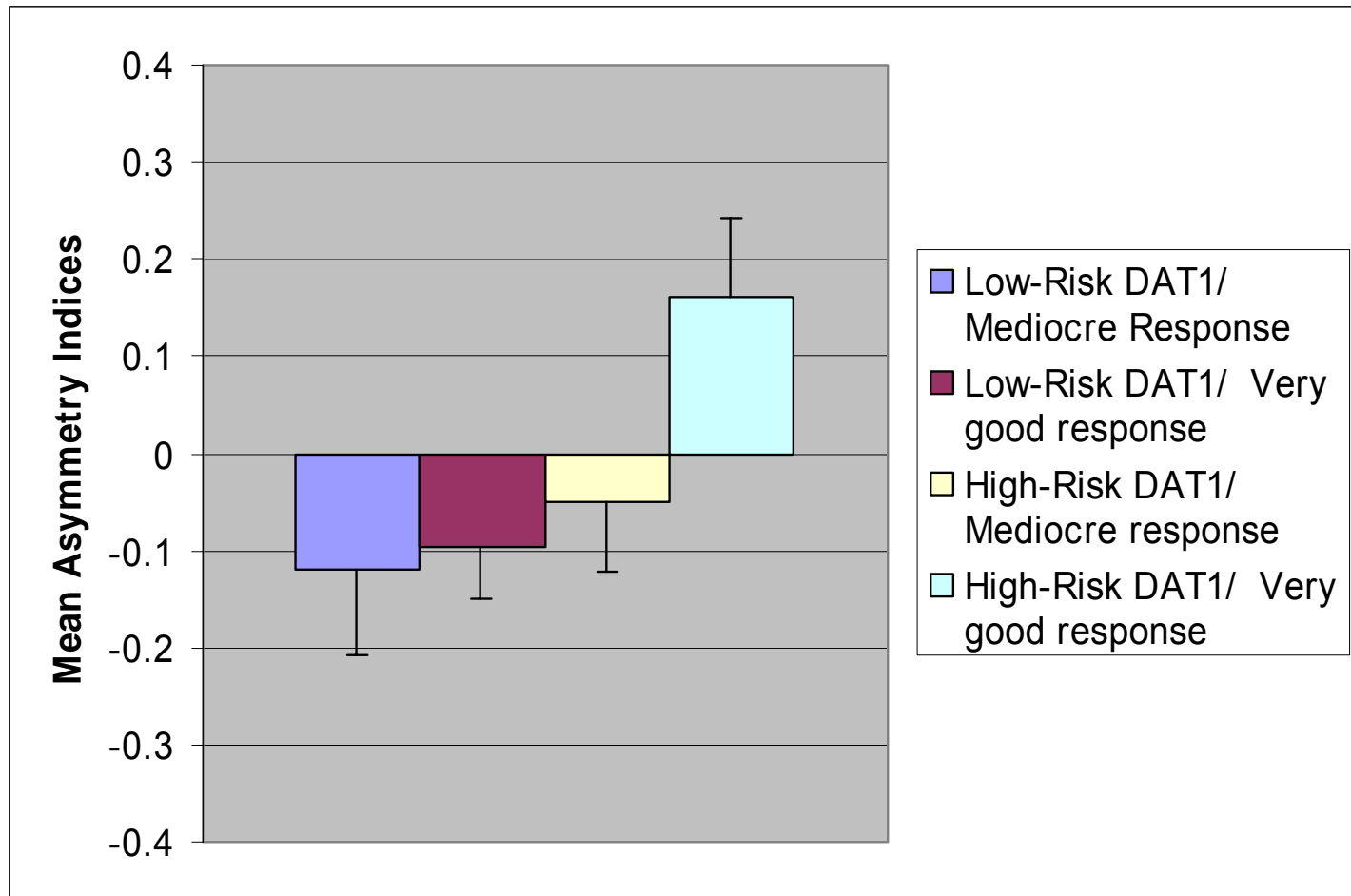
Left-spatial inattention is related to Inattentive symptoms but closer to the site of gene action (DAT1)



Pharmacogenetics: Left-spatial inattention as predictor of therapeutic response to MPH



Hypothesis: Performance on the Landmark Task will predict an enhanced therapeutic response to MPH



10-repeat DAT1 homozygotes who achieved a Very Good Response to MPH, displayed left-spatial inattention

Bellgrove et al (2005), *Neuropsychopharmacology*

Summary

- **Results support the existence of a subgroup of ADHD that is associated with the 10-repeat DAT1 allele and is defined**
 - 1) in neuropsychological terms, by left-spatial inattention.
 - 2) in symptomatological terms, by inattentive symptomatology
 - 3) in pharmacogenomic terms, by an enhanced therapeutic response to MPH.
- **Left spatial inattention might predict therapeutic response to MPH because it acts as a *proxy* for DAT1 genotype and so transporters that are overactive, perhaps within the right striatum.**
- **MPH might be most efficacious for those children presenting with left-spatial inattention, because it indexes a *hypodopaminergic state***

DBH and DRD4 and Sustained Attention and Response Inhibition

- **Children with ADHD experience problems with sustained attention and response inhibition**
- **Response inhibition deficits show familial risk profiles**
- **Response inhibition deficits are ameliorated by MPH**
 - **DBH- A2 allele of Taq I polymorphism associated with ADHD**
 - **DRD4- 7-repeat allele of a VNTR associated with ADHD**
 - **-521 SNP A allele shows trend towards association**
 - **A-, relative to G-allele, reduces transcription levels of the DRD4 gene by up to 40%**

The Sustained Attention to Response Test (SART)

SART

```
graph LR; SART[SART] --> Fixed[Fixed Sequence Version]; SART --> Random[Random Sequence Version]; Fixed --- FixedTask[Sustained Attention]; Random --- RandomTask[Sustained Attention + Response Inhibition];
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Fixed Sequence Version

1,2,3,4,5,6,7,8,9,1,2,3

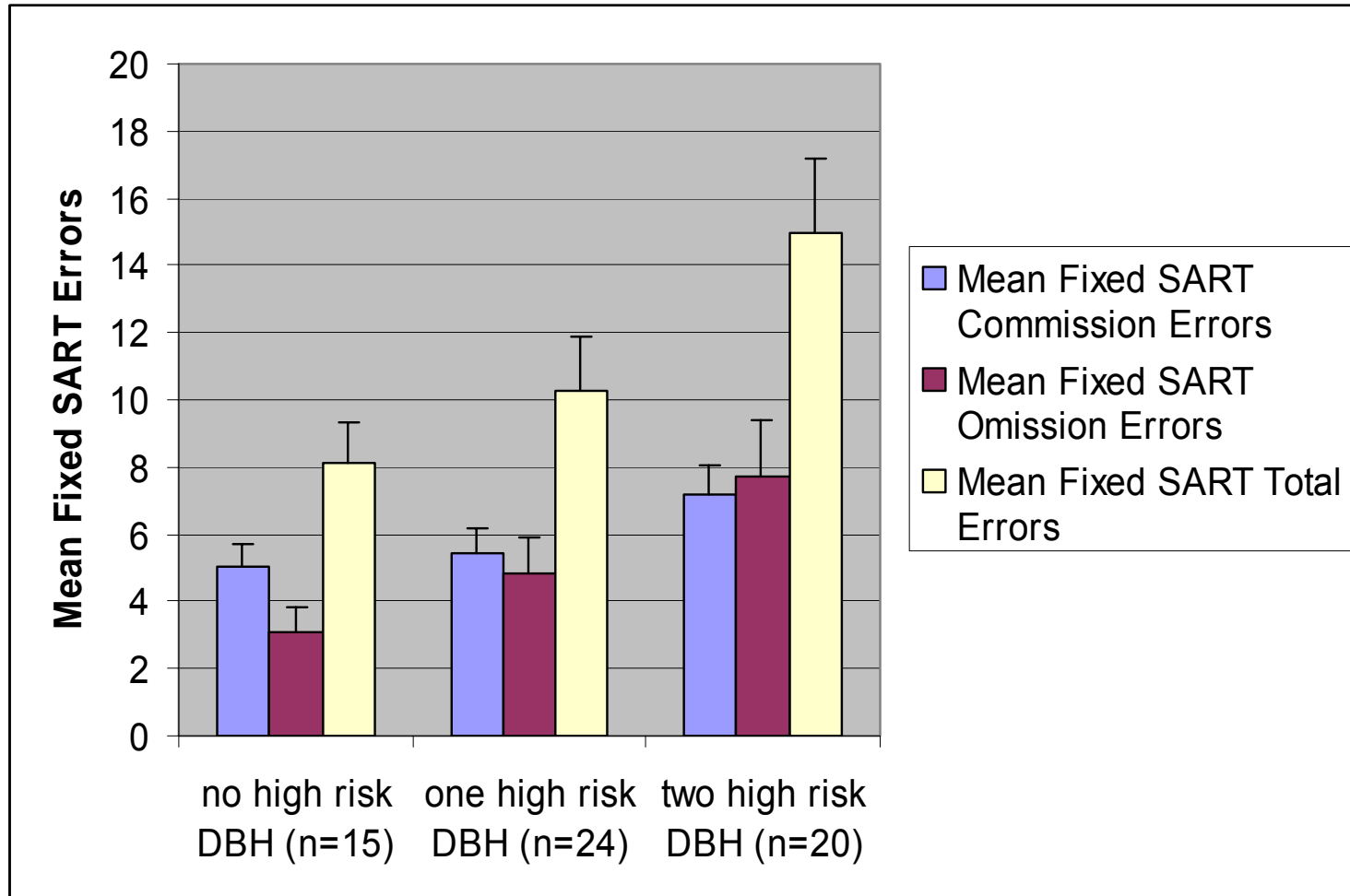
Sustained
Attention

Random Sequence Version

2,8,9,4,3,5,7,9,3,2,8,5

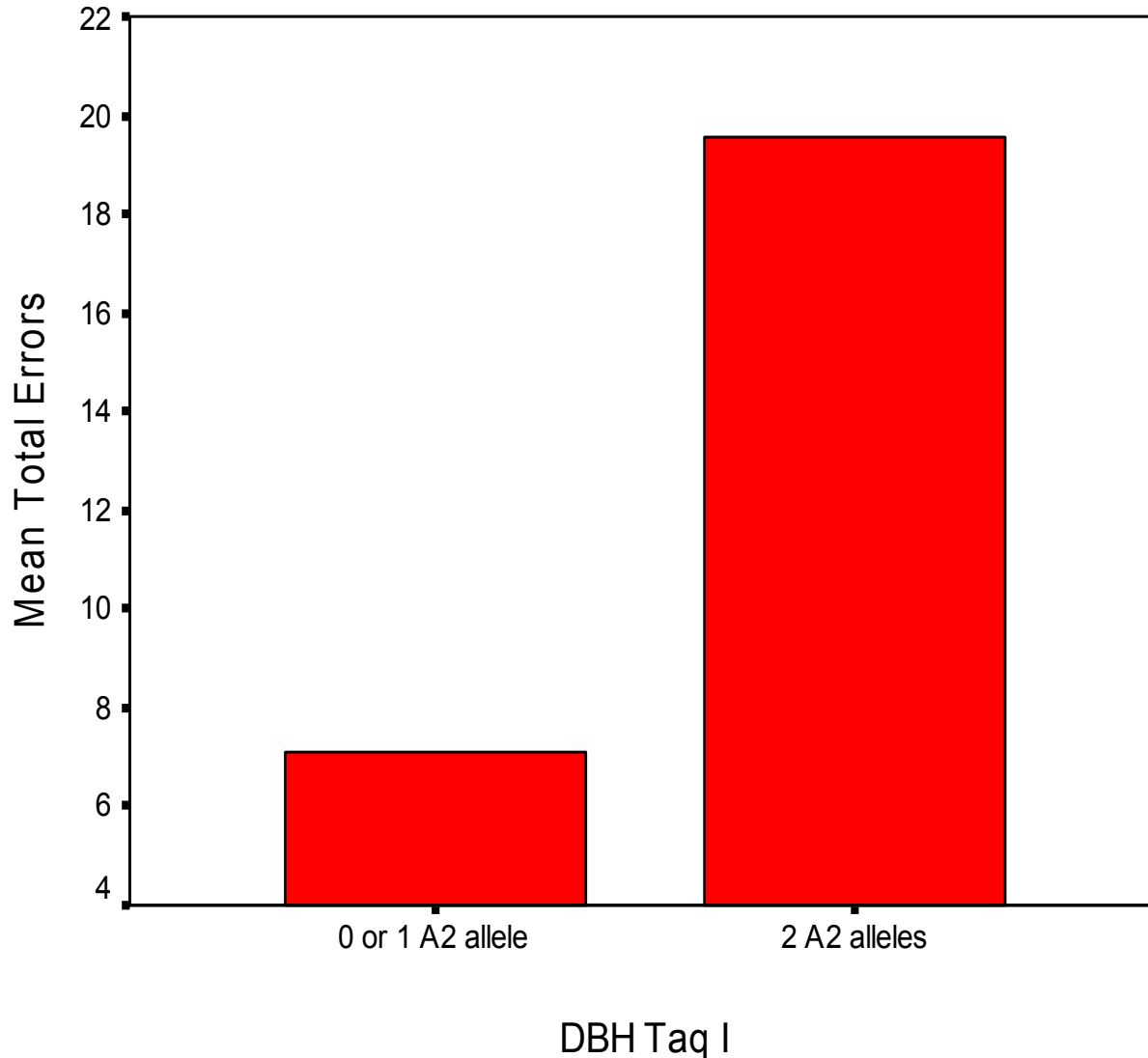
Sustained
Attention +
Response
Inhibition

Fixed SART and Taq 1 DBH



Two high-risk DBH Group had sustained attention deficits on the Fixed SART

Fixed SART and Taq 1 DBH: Healthy Undergraduates

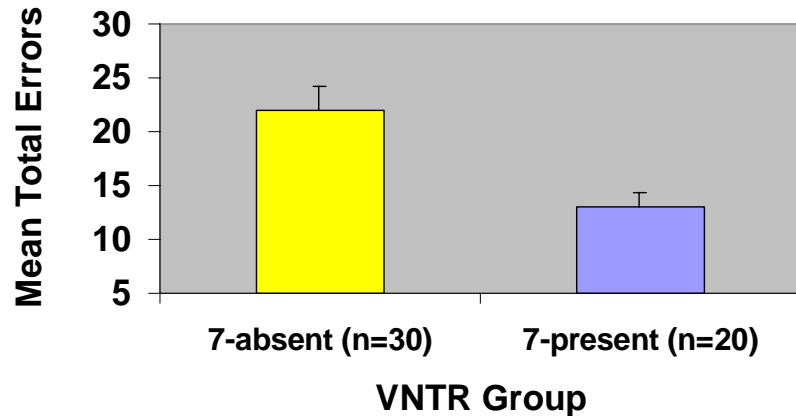


-DBH Taq I

- As in ADHD, the A2 allele impairs sustained attention

Random SART and DRD4 Genotype

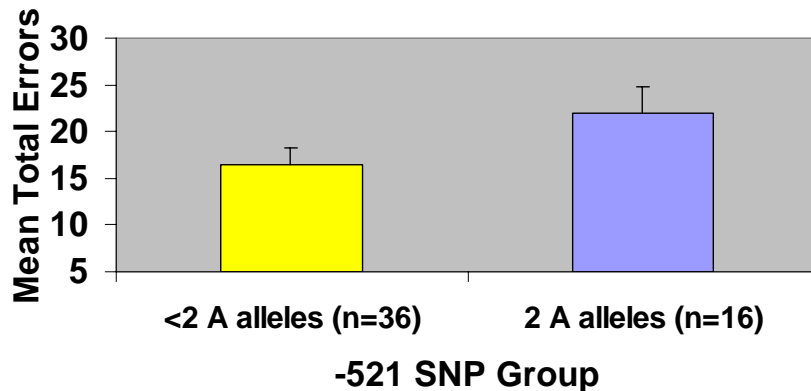
DRD 4 VNTR and Random SART



VNTR

- 7-present group outperformed 7-absent group in terms of Total errors and Variability only on the Random SART
- No effects on the Fixed SART

DRD4 -521 SNP and Random SART

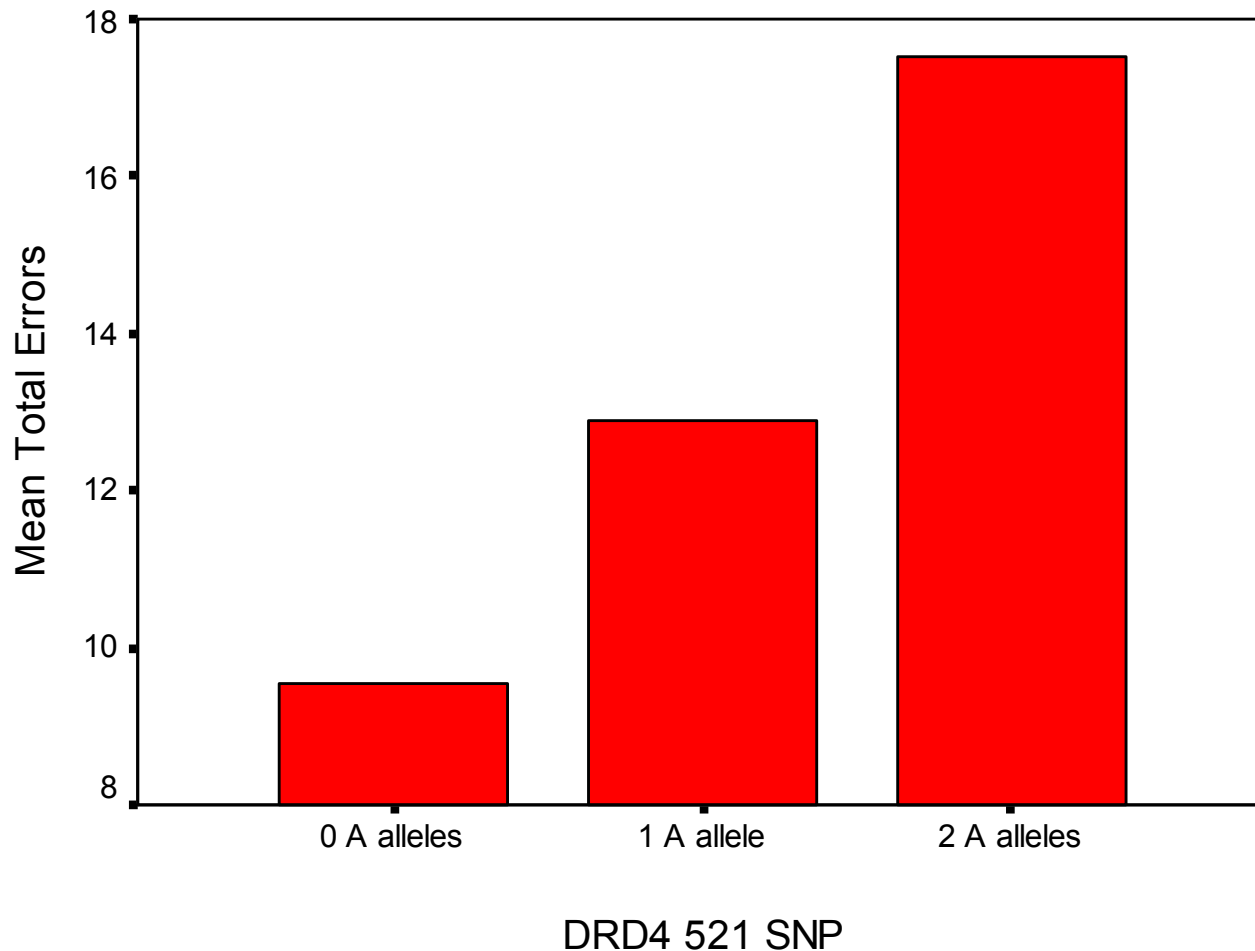


-521 SNP

- A allele homozygotes performed worse than A allele heterozygotes in terms of Total errors and Variability

Random SART and DRD4 Genotype: Healthy Undergraduates

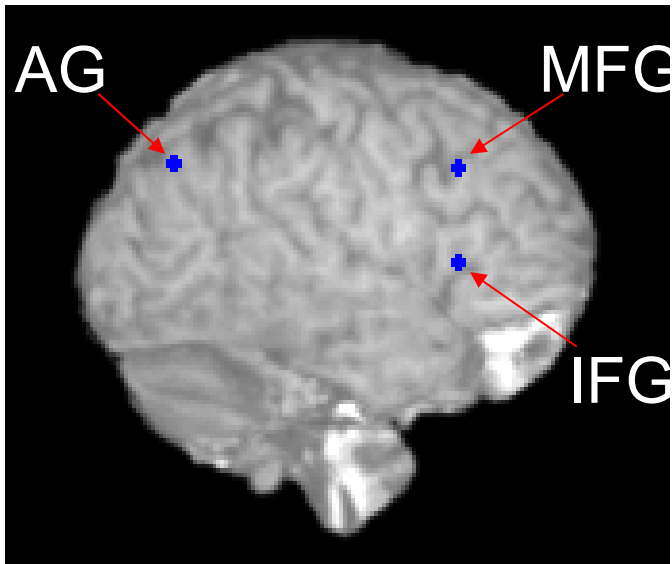
Random SART and DRD4 -521 SNP



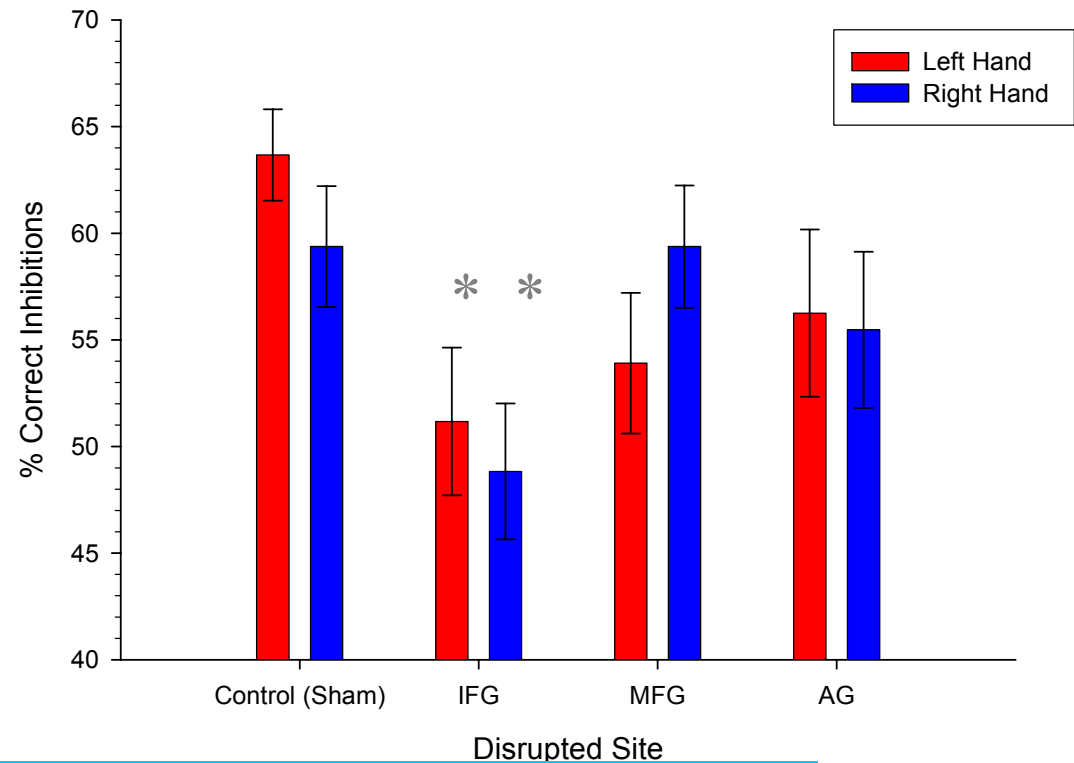
-521 SNP

- Parametric effect of the A allele on response inhibition

Response inhibition depends upon inferior frontal areas



Inhibition Performance: Block 1



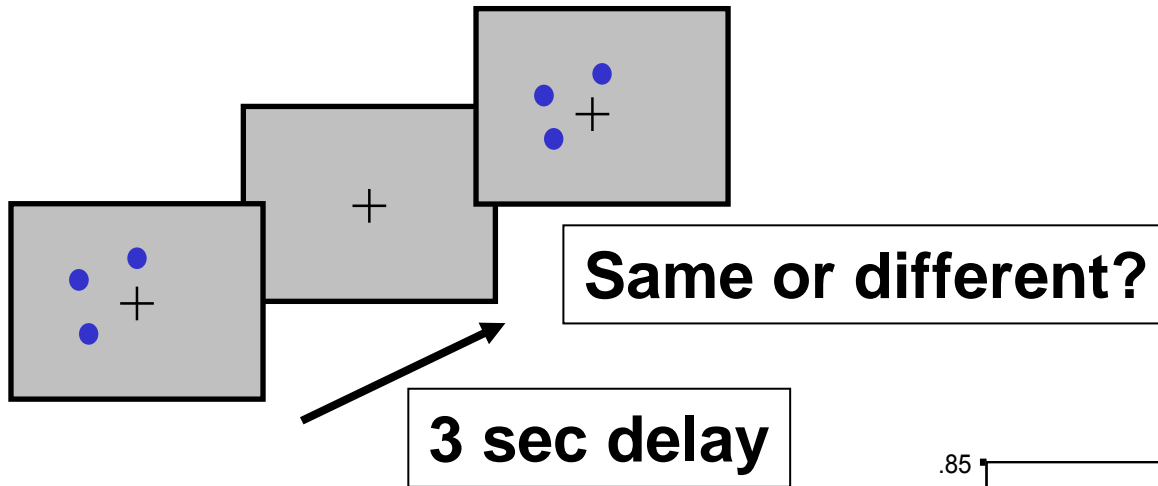
How do DRD4 variants influence activity within prefrontal regions, such as IFG?

Summary

- **Sustained attention shows genetic variation in ADHD**
 - When inhibitory demands are minimal, DBH affects the ability to endogenously maintain an alert state in ADHD
 - Response inhibition appears related to variation in the DRD4 gene.
 - DRD4 VNTR 7-repeat does not impair cognition
 - -521 SNP A allele does impair cognition
- **DBH and DRD4 may confer risk to ADHD because of their varying effects on the development of fronto-parietal networks**

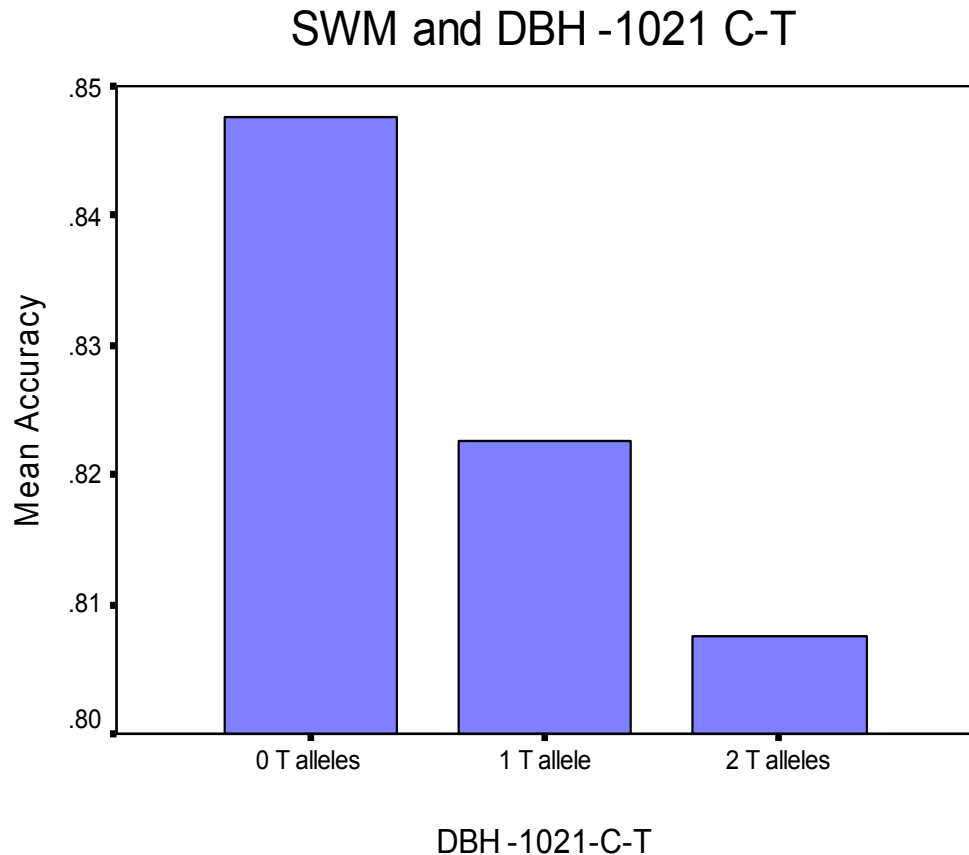
Spatial Working Memory

- **Spatial Working Memory deficits are reliably observed in ADHD**
 - **Meta-analysis shows large effect sizes (Storage $d'=0.85$; Central Executive $d'=1.06$)**
 - **Human and animal lesion studies show regions in the prefrontal and parietal cortices are critical for SWM**
 - **Dopamine and noradrenaline modulate SWM**
 - **Candidate endophenotype for ADHD?**



-DBH -1021 C-T

- Parametric effect of the T allele on SWM
- T allele is associated with lower plasma levels of $D\beta H$
- Suggests that T allele lowers expression of $D\beta H$
- Role in ADHD?



Conclusions

- **Our studies provide evidence that molecular genetics can assist in dissecting complex phenotypes such as ADHD.**
 - **Inconsistencies in the neuropsychology of ADHD may be clarified by this approach.**
- **Molecular genetics may provide a powerful new tool for studying individual differences and testing models of cognitive function.**

Acknowledgements

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