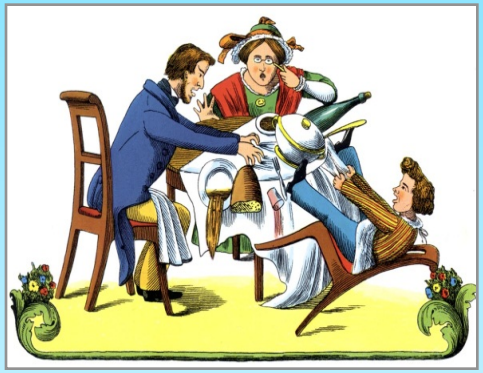
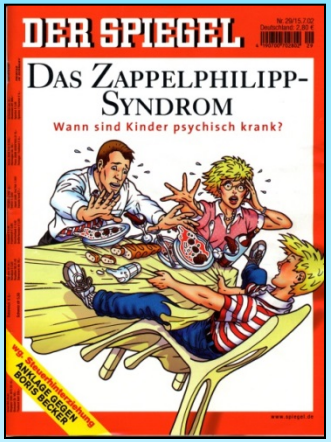
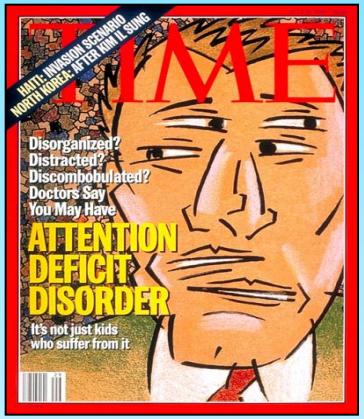
15th International ESCAP Congress 2013
6-10 July 2013, Dublin, Ireland

Attention Deficit/Hyperactivity Disorder







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Disclosure of potential conflicts of interest

- Dr. Banaschewski served in an advisory or consultancy role for Hexal Pharma, Lilly, Medice, Novartis, PCM scientific, Shire, Vivor Pharma
- Dr. Banaschewski received conference attendance support or was paid for public speaking by Lilly, Janssen McNeil, Medice, Novartis
- Dr. Banaschewski received research funding from EU, German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF)

Overview

- ADHD - DSM 5
- Risk factors
  - Genetical risks
  - Environmental risks
- Neurobiological correlates
  - Brain structure
  - Neurotransmitter systems
  - Brain function (imaging studies)
  - Neuropsychology
- Treatment
  - Medication effects
  - Nonpharmacological treatment options

ADHD (DSM-V)

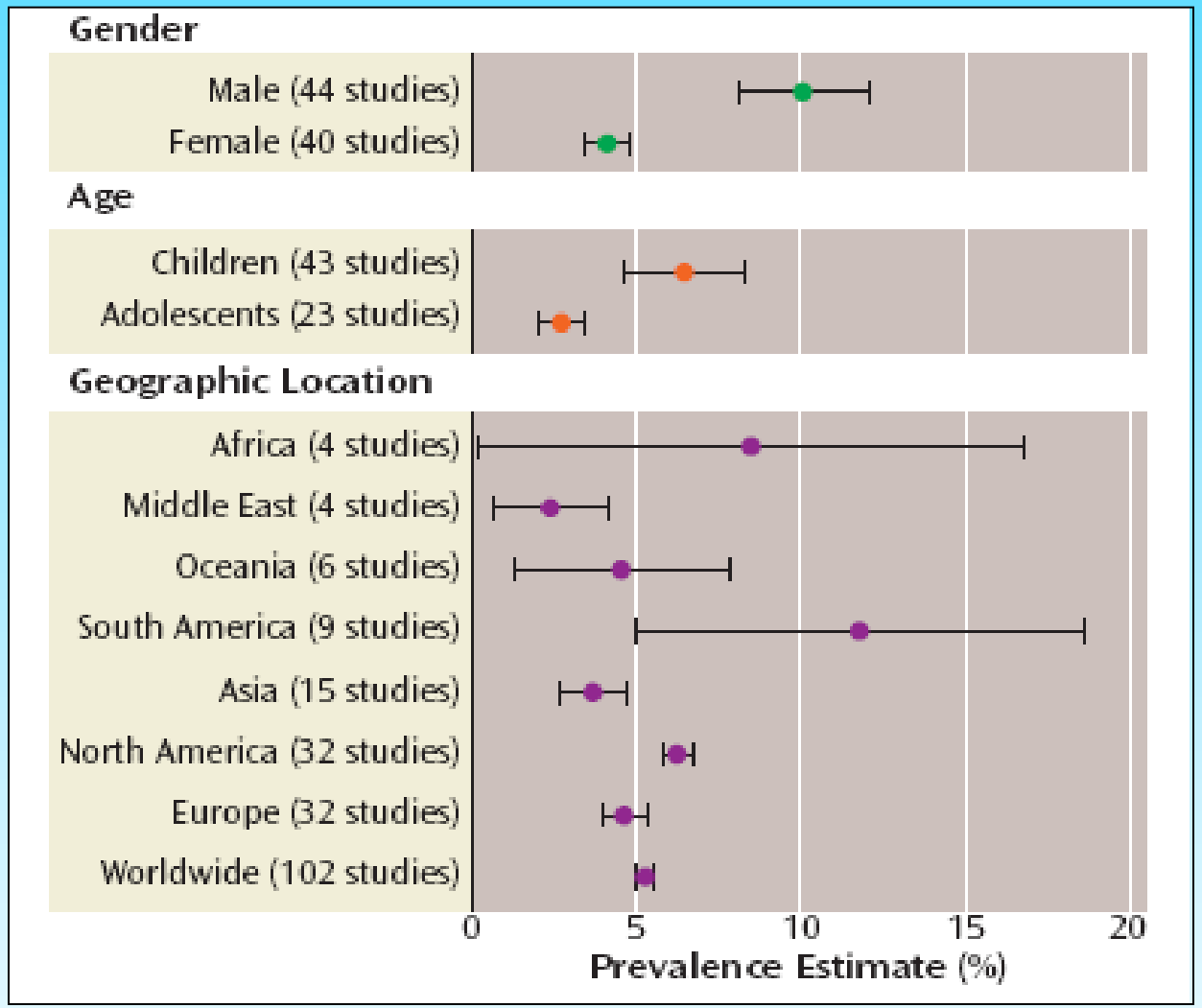
Persistent pattern of inattention and/or hyperactivity-impulsivity interfering with functioning/development

- Age of onset
  - Several symptoms present prior to age 12 y
- Duration
  - At least 6 month
- Significant degree of impairment
  - Interference with social, academic or occupational functioning
- Situational pervasiveness
  - Several symptoms present in two or more settings (e.g., at home, school, or work; with friends or relatives; in other activities)
- Symptoms must not be solely attributable to other mental disorders

Changes made in DSM-5

- Symptom threshold change for adults and older adolescents to 5 instead of 6 symptoms
- Comorbid diagnosis with ASD is now allowed
- Onset criterion changed to “several symptoms present prior to age 12”
- Cross-situational requirement strengthened to “several” symptoms in each setting
- Examples added to facilitate application across life span
- Subtypes replaced with presentation specifiers
- ADHD included in neurodevelopmental disorder chapter

ADHD Prevalence



Polanczyk et al., 2007

Comorbidity

Very frequent

- Oppositional defiant or conduct disorder

Frequent

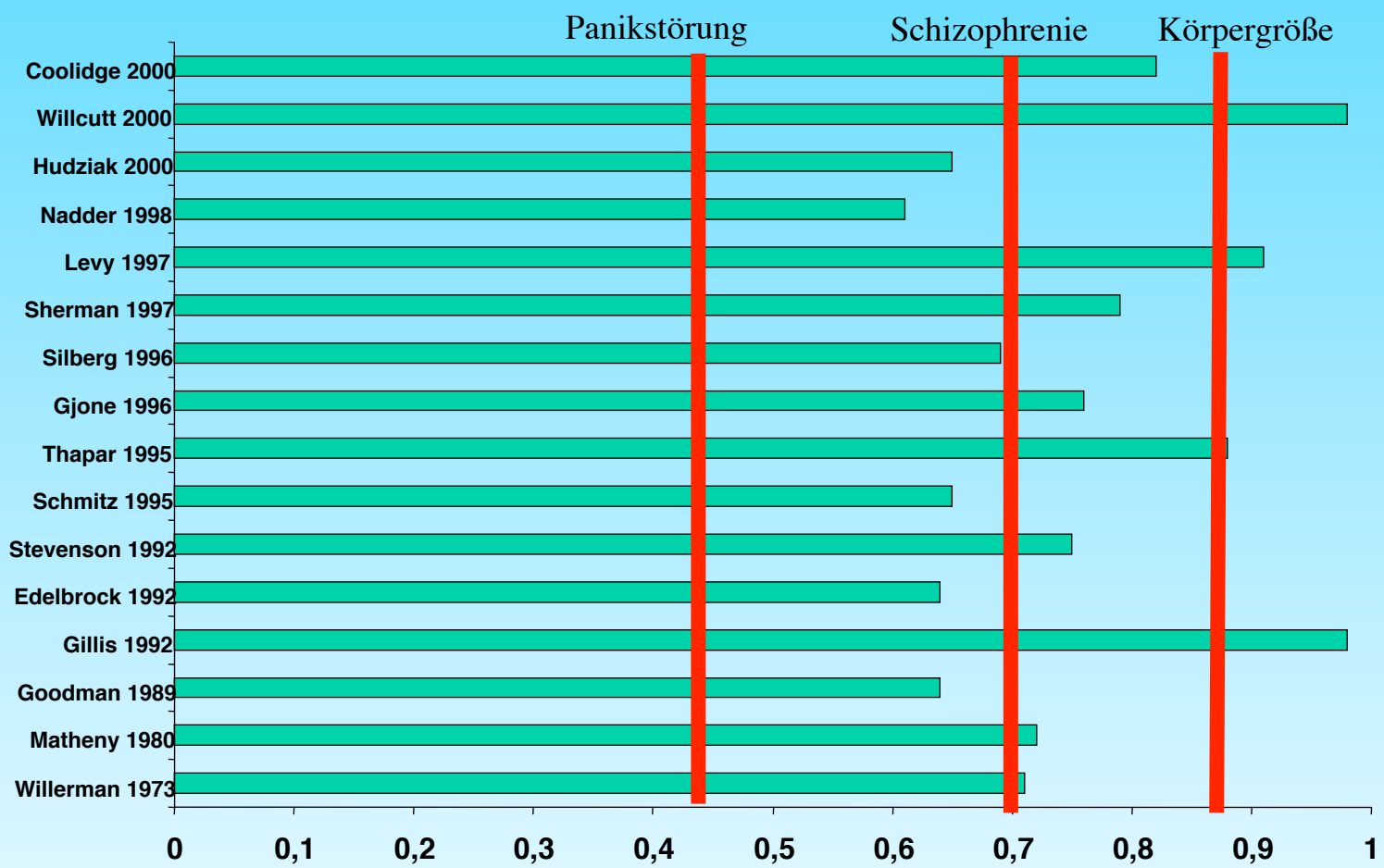
- Specific learning disorder
- Anxiety disorder
- Developmental coordination disorder
- Disruptive mood dysregulation disorder

Less frequent

- Tic disorders
- Depressive disorder
- Autistic features
- Substance abuse

Over 85% of patients have at least one comorbidity & approximately 60% of patients have at least two comorbidities

Heritability

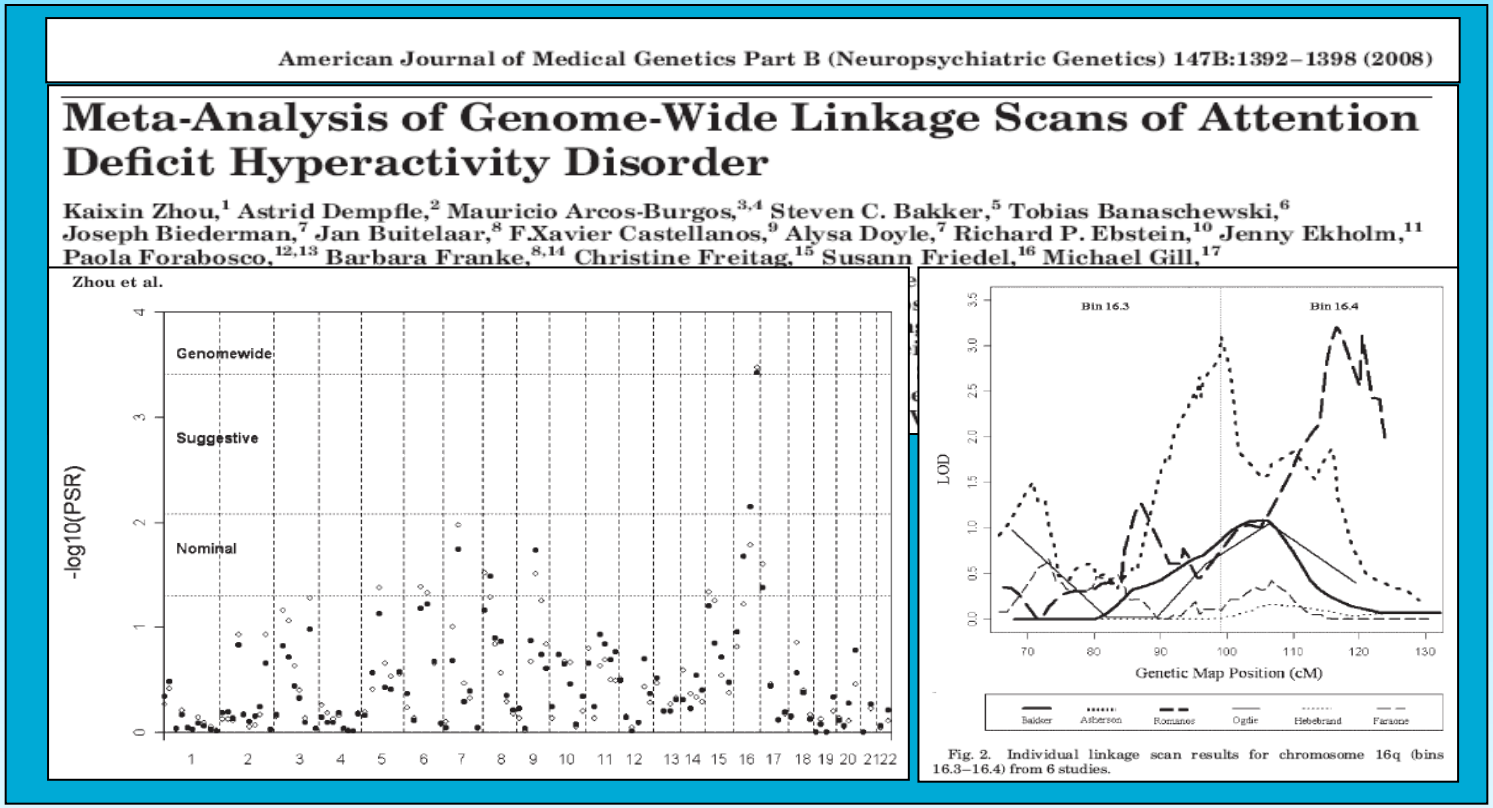


Genes are etiologically relevant

Faraone et al., 1998

Linkage studies

- Replicated linkage findings
  - e.g. 5p13, 11q22-25, 17p11
- But: no region consistently identified & most findings not replicated



American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 147B:1392–1398 (2008)

Meta-Analysis of Genome-Wide Linkage Scans of Attention Deficit Hyperactivity Disorder

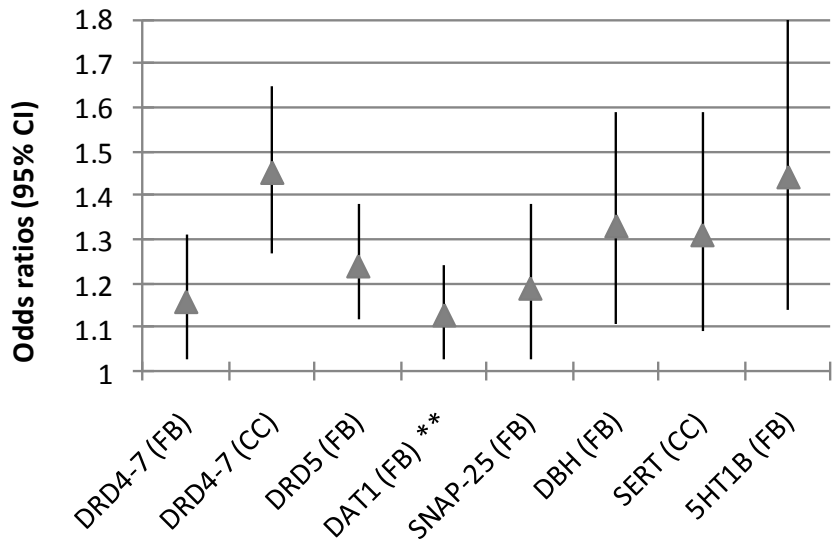
Kaixin Zhou,[1] Astrid Dempfle,[2] Mauricio Arcos-Burgos,[3,4] Steven C. Bakker,[5] Tobias Banaschewski,[6] Joseph Biederman,[7] Jan Buitelaar,[8] F.Xavier Castellanos,[9] Alysa Doyle,[7] Richard P. Ebstein,[10] Jenny Ekholm,[11] Paola Forabosco,[12,13] Barbara Franke,[8,14] Christine Freitag,[15] Susann Friedel,[16] Michael Gill,[17]

Fig. 2. Individual linkage scan results for chromosome 16q (bins 16.3–16.4) from 6 studies.

Involvement of genes with large effects is unlikely

Association studies

Gene	OR	95% CI		Allele frequency	QTL	Number of families to replicate with 80% power	Power in sample of 200 cases and 200 controls
DRD4	1.16	1.03	1.31	0.12	0.001	3196	0.115
DRD5	1.24	1.12	1.65	0.35	0.004	728	0.341
DAT1	1.13	1.03	1.24	0.73	0.001	2748	0.125
DBH	1.33	1.11	1.59	0.5	0.007	391	0.561
SNAP-25 (T1065G)	1.19	1.03	1.38	0.5	0.003	1043	0.253
SERT (HTTLPR)	1.31	1.09	1.59	0.6	0.006	466	0.490
HTR1B	1.44	1.14	1.83	0.71	0.010	315	0.652



Statistical significant, but small effect sizes

Ca. 5% of the heritability explained by replicated candidate genes

Kuntsi et al. Behav Brain Funct. 2006;2:27
Faraone et al. Biol Psychiatry 2005;57(11):1313-23

Meta-Analysis of Genome-Wide Association Studies of Attention-Deficit/Hyperactivity Disorder

Benjamin M. Neale, Ph.D., Sarah E. Medland, Ph.D., Stephan Ripke, M.D., Philip Asherson, M.R.C.Psych., Ph.D., Barbara Franke, Ph.D., Klaus-Peter Lesch, M.D., Stephen V. Faraone, Ph.D., Thuy Trang Nguyen, Dipl. Math. oec., Helmut Schäfer, Ph.D., Peter Holmans, Ph.D., Mark Daly, Ph.D., Hans-Christoph Steinhausen, M.D., Ph.D., D.M.Sc., Christine Fre… Andreas Reif, M.D., Tobias J. Renner, M.D., Marcel Rom… Jasmin Romanos, M.D., Susanne Walitza, M.D., Andreas Wa… Jobst Meyer, Ph.D., Haukur Palmason, Ph.D., Jan Buitel… Alejandro Arias Vasquez, Ph.D., Nanda Lambregts-Rom… Michael Gill, Mb B.Ch. B.A.O., M.D., M.R.C.Psych., F.T.C.D., Richard J.… Kate Langely, Ph.D., Michael O'Donovan, F.R.C.Psych., Ph.D., Nige… Michael Owen, Ph.D., F.R.C.Psych., Anita Thapar, M.D., Lindsey … Joseph Sergeant, Ph.D., Herbert Roeyers, M.D., Ph.D., Eric … Joseph Biederman, M.D., Alysa Doyle, Ph.D., Susan Sm… Sandra Loo, Ph.D., Hakon Hakonarson, M.D., Ph.D., Josephi… Alexandre Todorov, Ph.D., Ana Miranda, M.D., Fernando M… Richard P. Ebstein, Ph.D., Aribert Rothenberger, M.D… Tobias Banaschewski, M.D., Ph.D., Robert D. Oades… Edmund Sonuga-Barke, Ph.D., James McGough, M.D., Laura N… Frank Middleton, Ph.D., Xiaolan Hu, Ph.D., Stan Nelson, M.D., f…
GWAS Consortium: ADHD Subgroup

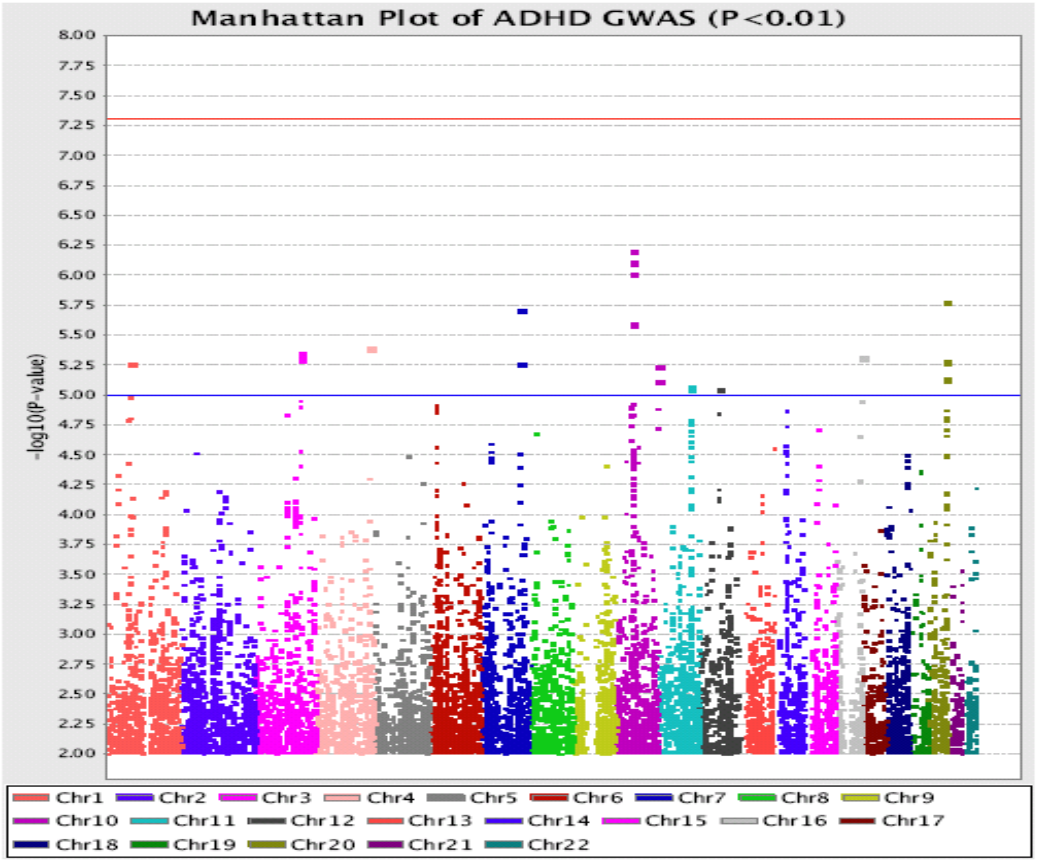
Sample	Cases	Controls	Trios	SNPs
CHOP	—	—	423	469,283
IMAGE	—	—	909	438,784
IMAGE II	896	2,455	—	294,811
PUWMa	—	—	732	645,995
Total	896	2,455	2,064	1,206,462[a]

Note: CHOP = Children's Hospital of Philadelphia; IMAGE = International Multicenter ADHD Genetics Project; PUWMa = Pfizer-funded study from the University of California, Los Angeles, Washington University, and Massachusetts General Hospital; SNP = single-nucleotide polymorphism.

[a]*Imputes SNPs using Beagle 3.0.6.*

Case-Control Genome-Wide Association Study of Attention-Deficit/Hyperactivity Disorder

Benjamin M. Neale, Ph.D., Sarah Medland, Ph.D., Stephan Ripke, M.D., Richard J.L. Anney, Ph.D., Philip Asherson, M.R.C.Psych., Ph.D., Jan Buitelaar, M.D., Barbara Franke, Ph.D., Michael Gill, M.B., Bch, BAO, M.D., MRCPsych, F.T.C.D., Lindsey Kent, M.D., Ph.D., Peter Holmans, Ph.D., Frank Middleton, Ph.D., Anita Thapar, M.D., Klaus-Peter Lesch, M.D., Stephen V. Faraone, Ph.D.



➢ No genome-wide significant associations

Finding the missing heritability of complex diseases

Teri A. Manolio[1], Francis S. Collins[2], Nancy J. Cox[3], David B. Goldstein[4], Lucia A. Hindorff[5], David J. Hunter[6], Mark I. McCarthy[7], Erin M. Ramos[5], Lon R. Cardon[8], Aravinda Chakravarti[9], Judy H. Cho[10], Alan E. Guttmacher[1], Augustine Kong[11], Leonid Kruglyak[12], Elaine Mardis[13], Charles N. Rotimi[14], Montgomery Slatkin[15], David Valle[9], Alice S. Whittemore[16], Michael Boehnke[17], Andrew G. Clark[18], Evan E. Eichler[19], Greg Gibson[20], Jonathan L. Haines[21], Trudy F. C. Mackay[22], Steven A. McCarroll[23] & Peter M. Visscher[24]

Disease	Number of loci	Proportion of heritability explained	Heritability measure
Age-related macular degeneration[72]	5	50%	Sibling recurrence risk
Crohn's disease[21]	32	20%	Genetic risk (liability)
Systemic lupus erythematosus[73]	6	15%	Sibling recurrence risk
Type 2 diabetes[74]	18	6%	Sibling recurrence risk
HDL cholesterol[75]	7	5.2%	Residual* phenotypic variance
Height[15]	40	5%	Phenotypic variance
Early onset myocardial infarction[76]	9	2.8%	Phenotypic variance
Fasting glucose[77]	4	1.5%	Phenotypic variance

* Residual is after adjustment for age, gender, diabetes.

Genetic Heterogeneity

American Journal of Medical Genetics Part B (Neuropsychiatric Genetics) 147B:1481–1487 (2008)

Genetic Heterogeneity in ADHD:
DAT1 Gene Only Affects Probands Without CD

Kaixin Zhou,[1] Wai Chen,[1] Jan Buitelaar,[2] Tobias Banaschewski,[3,4] Robert D. Oades,[5] Barbara Franke,[2,6] Edmund Sonuga-Barke,[7] Richard Ebstein,[8] Jacques Eisenberg,[9] Michael Gill,[10] Iris Manor,[8] Ana Miranda,[11] Fernando Mulas,[11] Herbert Roeyers,[12] Aribert Rothenberger,[3] Joseph Sergeant,[13] Hans-Christoph Steinhausen,[14] Jessica Lasky-Su,[15,16,17] Eric Taylor,[1] Keeley J. Brookes,[1] Xiaohui Xu,[1] Benjamin M. Neale,[1,18,19] Fruhling Rijsdijk,[1] Margaret Thompson,[7] Philip Asherson,[1] and Stephen V. Faraone[15,16,17]*

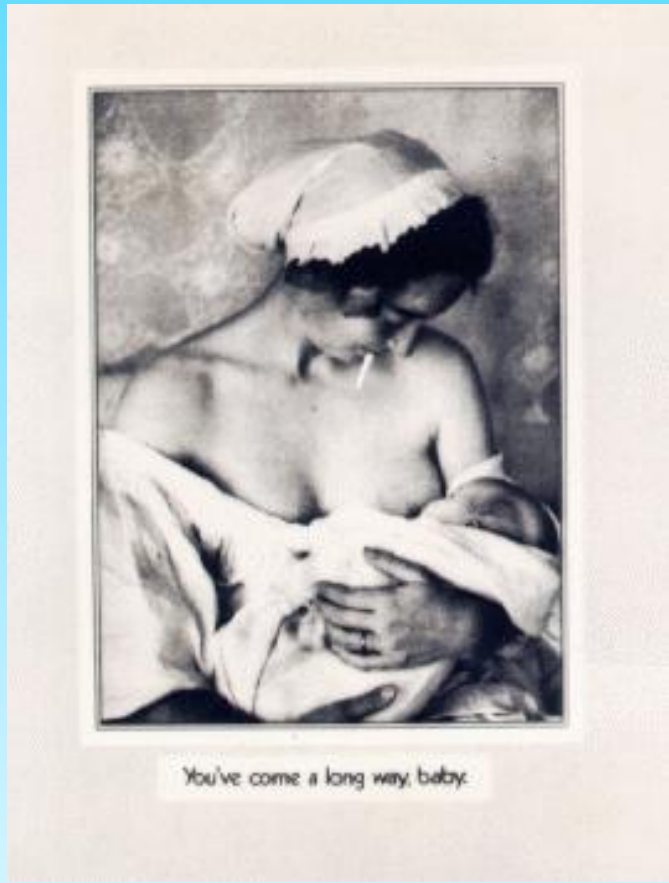
ADHD + conduct disorder

genetically diferent from

ADHD - conduct disorder ?

Environmental Risk Factors

- Pregnancy & birth complications
  - premature birth or very low birth weight
- Infections & brain traumata
- Toxins
  - intrauterine exposure to alcohol or nicotine
  - exposure to low levels of lead
- Abnormal psychosocial circumstances
  - e.g., severe early deprivation



Gene – environmental interactions
Psychosocial Risks & DAT

Interacting Effects of the Dopamine Transporter Gene and Psychosocial Adversity on Attention-Deficit/ Hyperactivity Disorder Symptoms Among 15-Year-Olds From a High-Risk Community Sample

Manfred Laucht, PhD; Markus H. Skowronek, PhD; Katja Becker, MD; Martin H. Schmidt, MD, PhD; Günter Esser, PhD; Thomas G. Schulze, MD; Marcella Rietschel, MD

Context: Recent evidence suggests that gene × environment interactions could explain the inconsistent findings of association studies relating the dopamine transporter (*DAT1*) gene with attention-deficit/hyperactivity disorder (ADHD).

Objective: To examine whether psychosocial adversity moderated the effect of genetic variation in *DAT1* on ADHD symptoms in adolescents from a high-risk community sample.

Design: Prospective cohort study.

Setting: Data were taken from the Mannheim Study of Children at Risk, an ongoing longitudinal study of the long-term outcomes of early risk factors followed up from birth on.

Participants: Three hundred five adolescents (146 boys, 159 girls) participated in a follow-up assessment at age 15 years.

Main Outcome Measures: Measures of ADHD symptoms according to *DSM-IV* were obtained using standardized structural interviews with adolescents and their parents. Psychosocial adversity was determined according to an "enriched" family adversity index as proposed by Rutter and Quinton. DNA was genotyped for the common *DAT1* 40–base pair (bp) variable number of tandem repeats (VNTR) polymorphism in the 3′ untranslated region; 3 previously described single nucleotide polymorphisms in exon 15, intron 9, and exon 9; and a novel 30-bp VNTR polymorphism in intron 8.

Results: Adolescents homozygous for the 10-repeat allele of the 40-bp VNTR polymorphism who grew up in greater psychosocial adversity exhibited significantly more inattention and hyperactivity-impulsivity than adolescents with other genotypes or who lived in less adverse family conditions (significant interaction, $P = .013$-$.017$). This gene × environment interaction was also observed in individuals homozygous for the 6-repeat allele of the 30-bp VNTR polymorphism and the haplotype comprising both markers.

Conclusions: These findings provide initial evidence that environmental risks as described by the Rutter Family Adversity Index moderate the impact of the *DAT1* gene on ADHD symptoms, suggesting a *DAT1* effect only in those individuals exposed to psychosocial adversity.

Arch Gen Psychiatry. 2007;64:585-590

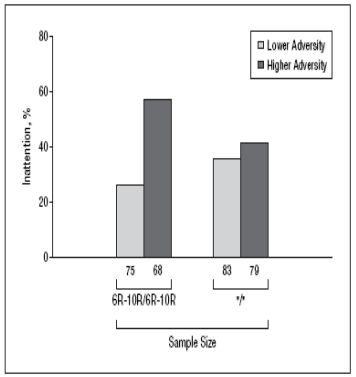


Figure 1. Percentage of inattention in adolescents grouped by the presence or absence of the *DAT1* 6-repeat allele–10-repeat allele (6R-10R) haplotype and exposure to psychosocial adversity. The 6R-10R/6R-10R haplotype exposed to higher adversity is significantly different from all other groups. */* indicates all other genotypes/haplotypes.

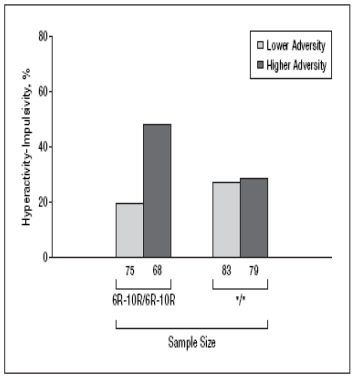
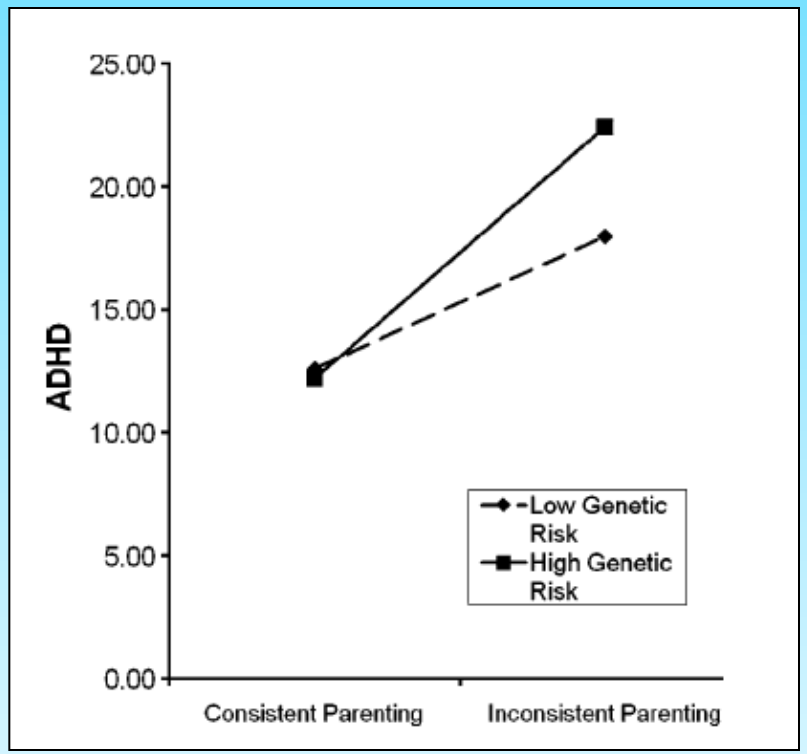


Figure 2. Percentage of hyperactivity-impulsivity in adolescents grouped by the presence or absence of the *DAT1* 6-repeat allele–10-repeat allele (6R-10R) haplotype and exposure to psychosocial adversity. The 6R-10R/6R-10R haplotype exposed to higher adversity is significantly different from all other groups. */* indicates all other genotypes/haplotypes.

The Dopamine Receptor D4 Gene (*DRD4*) Moderates Family Environmental Effects on ADHD

Michelle M. Martel · Molly Nikolas · Katherine Jernigan · Karen Friderici · Irwin Waldman · Joel T. Nigg

J Abnorm Child Psychol (2011) 39:1–10



DRD4 risk status (promoter 120-bp tandem repeat insertion allele)
=> more ADHD symptoms in presence of inconsistent parenting

Brief Report

Confirmation That a Specific Haplotype of the Dopamine Transporter Gene Is Associated With Combined-Type ADHD

Philip Asherson, M.R.C.Psych., Ph.D.
Keeley Brookes, B.Sc.
Barbara Franke, Ph.D.
Wai Chen, M.R.C.Psych.
Michael Gill, M.R.C.Psych., Ph.D.
Richard P. Ebstein, Ph.D.
Jan Buitelaar, M.D., Ph.D.
Tobias Banaschewski, M.D., Ph.D.
Edmund Sonuga-Barke, Ph.D.
Jacques Eisenberg, M.D.
Iris Manor, M.D.
Ana Miranda, M.D.
Robert D. Oades, Ph.D.
Herbert Roeyers, M.D., Ph.D.
Aribert Rothenberger, M.D., Ph.D.
Joseph Sergeant, Ph.D.
Hans-Christoph Steinhausen, M.D., Ph.D.
Stephen V. Faraone, M.D., Ph.D.

Objective: The primary purpose of this study was to confirm the association of a specific haplotype of the dopamine transporter gene and attention deficit hyperactivity disorder (ADHD), which could be one source of the heterogeneity seen across published studies.

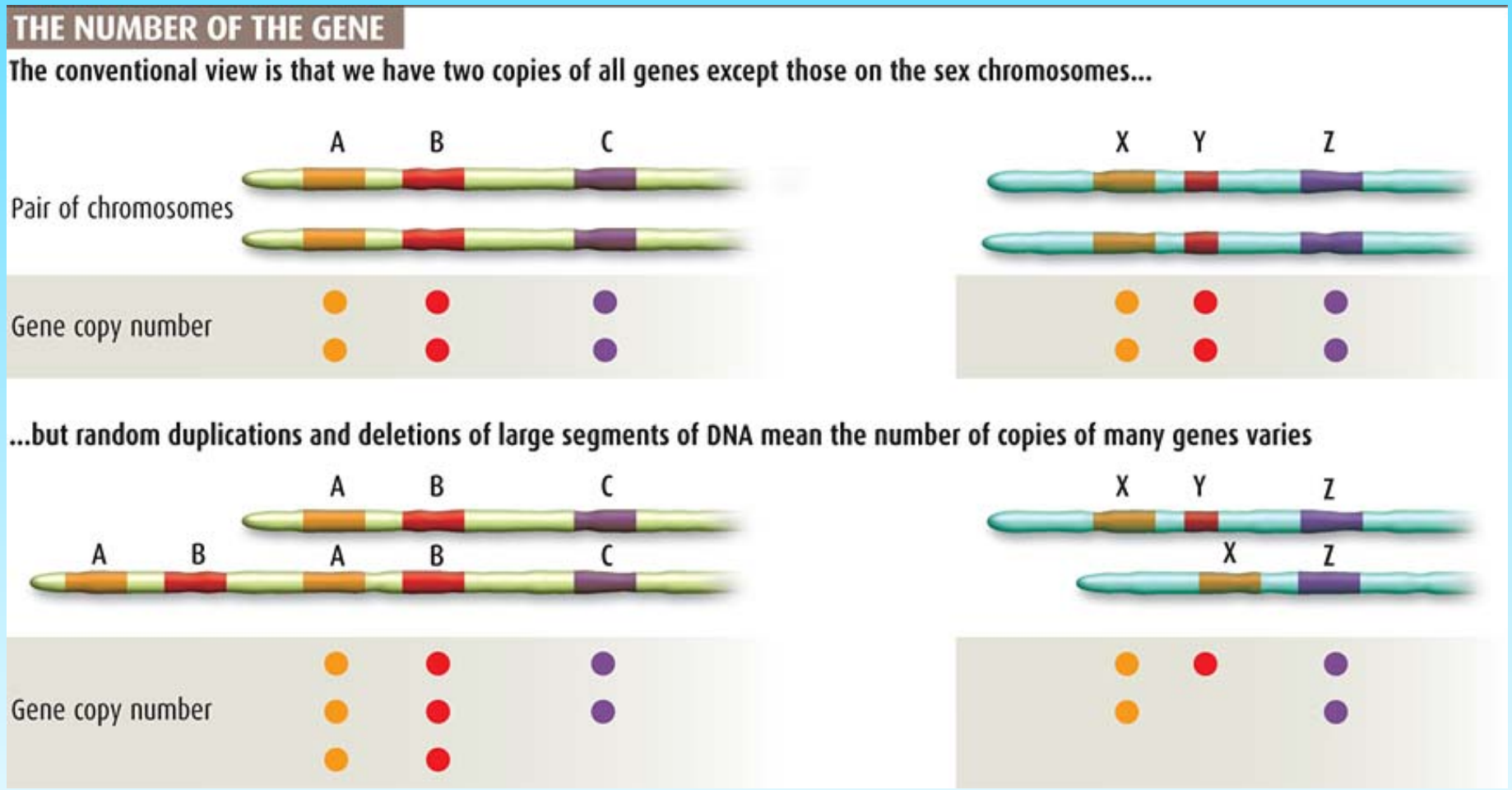
Method: The authors previously reported the association of ADHD with a subgroup of chromosomes containing specific alleles of two variable-number tandem repeat polymorphisms within the 3′ untranslated region and intron 8 of the dopamine transporter gene. They now report on this association in a sample of ADHD combined-type probands.

Results: The original observations were confirmed, with an overall odds ratio of 1.4 across samples.

Conclusions: These data challenge results of meta-analyses suggesting that dopamine transporter variation does not have an effect on the risk for ADHD, and they indicate that further investigation of functional variation in the gene is required.

(Am J Psychiatry 2007; 164:674–677)

Copy Number Variations



Rare structural variants found in attention-deficit hyperactivity disorder are preferentially associated with neurodevelopmental genes

Molecular Psychiatry (2009), 1–10

J Elia[1,2,12], X Gai[3,12], HM Xie[3], JC Perin[3], E Geiger[4], JT Glessner[5], M D'arcy[3], R deBerardinis[1], E Frackelton[5], C Kim[5], F Lantieri[4], BM Muganga[3], L Wang[3], T Takeda[1], EF Rappaport[6], SFA Grant[4,5,7], W Berrettini[2], M Devoto[4,7,8,9], TH Shaikh[4,7], H Hakonarson[5,7,10] and PS White[3,7,11]

- No excess CNVs in the ADHD cohort
- BUT: Enrichment of ADHD CNV genes in candidate genes for autism, schizophrenia and Tourette syndrome

Gene	*Disorder(s)*[a]
A2BP1	Schizophrenia; autism; mental retardation
APOL4	Schizophrenia
ATM	Ataxia-telangiectasia; neurodegeneration
AUTS2	Mental retardation and autism
BLMH	Alzheimer's disease
CHL1	Schizophrenia
CHN2	Schizophrenia
CNTNAP2	Schizophrenia; autism; Tourette syndrome
CPLX2	Schizophrenia
CTNND2	Mental retardation in cri du chat syndrome
DPP6	Schizophrenia
GRM5	Schizophrenia; Fragile X syndrome
GRM7	Schizophrenia
IMMP2L	Autism; Tourette syndrome
NKAIN2	Schizophrenia
PARK2	Schizophrenia
PDCD10	Cerebral cavernous malformations
PTPRD	Restless legs syndrome
RTN4	Schizophrenia
SEPP1	Schizophrenia
SERPINI1	Schizophrenia
TACR3	Schizophrenia

AJP in Advance. Published February 15, 2011 (doi: 10.1176/appi.ajp.2010.10070948)

Do the GWAS results point to common signaling pathways?

Integrated Genome-Wide Association Study Findings: Identification of a Neurodevelopmental Network for Attention Deficit Hyperactivity Disorder

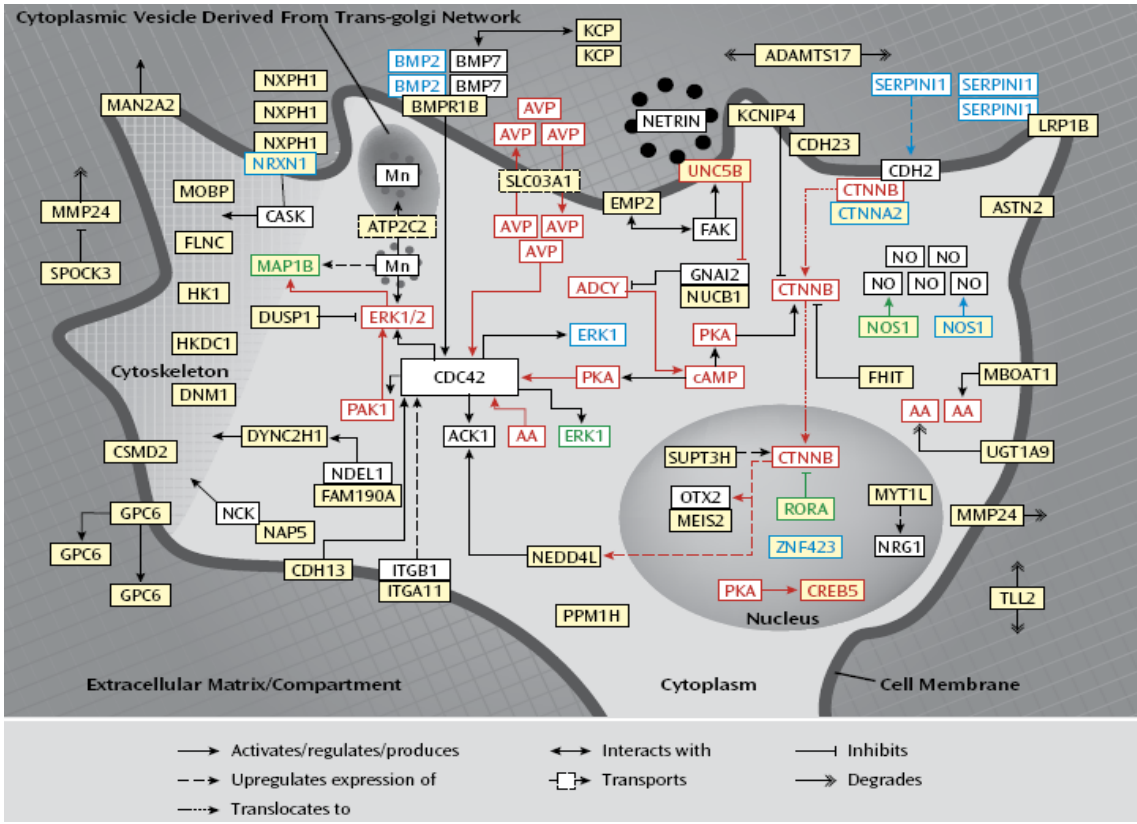
Geert Poelmans, M.D.

David L. Pauls, Ph.D.

Jan K. Buitelaar, M.D., Ph.D.

Barbara Franke, Ph.D.

5 GWAS => 85 genes selected
(p < 10 E-05)



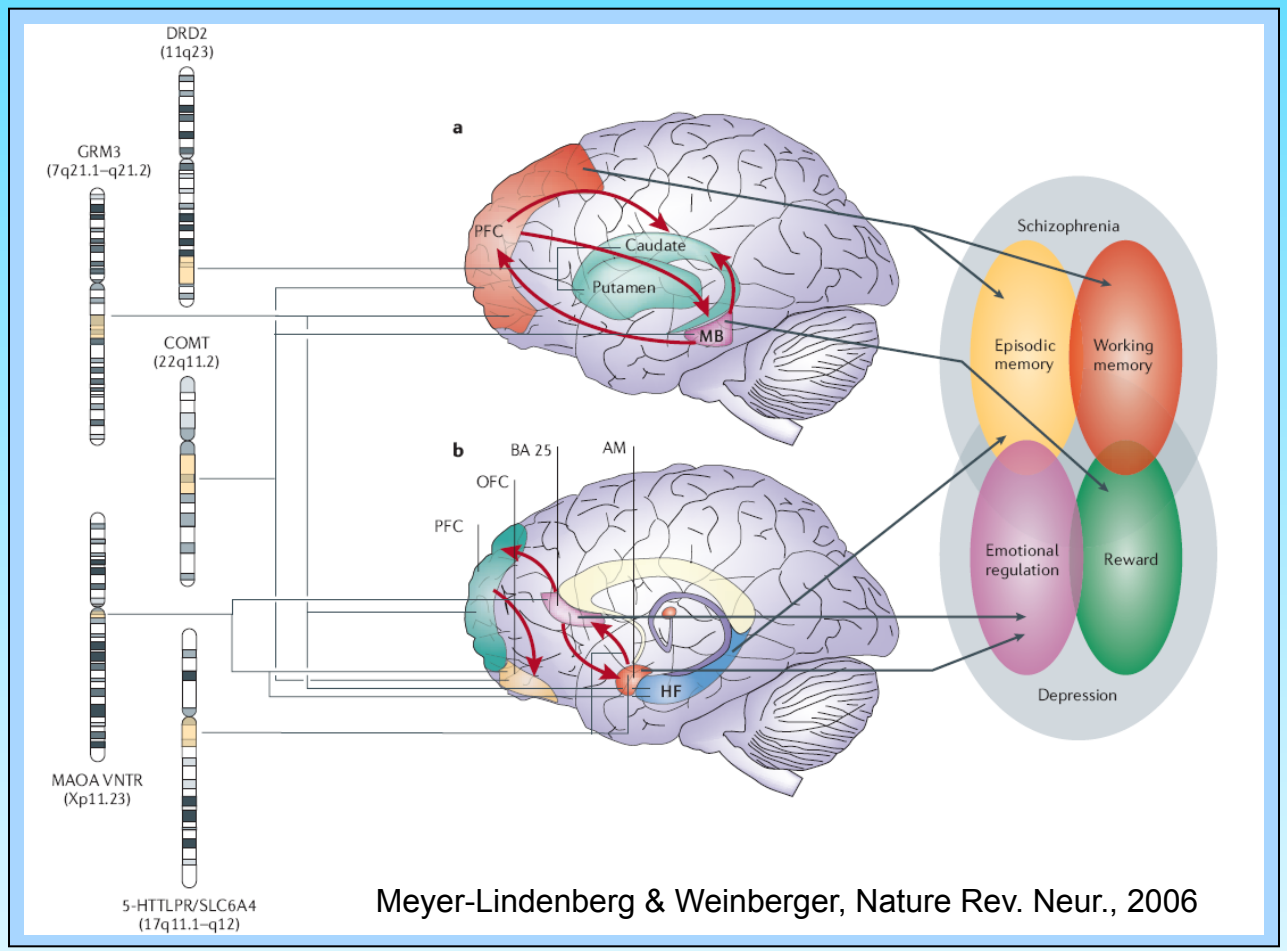
GWAS-, CNV-, Knockout- findings converge:

45/85 top GWAS genes involved in neurite outgrowth

Genetics - Summary

- Genetical factors are important
  - BUT: ca. 5% of the heritability explained by replicated candidate genes
- ADHD is likely a dimensional trait & genetically heterogeneous
- Multiple gene effects (of small effect size)
  - BUT: small effects do not necessarily imply lacking clinical relevance
- Risk stems mainly from normal variants of genes
  - BUT: rare mutations and copy number variations might be relevant & risk alleles are not specific for ADHD
- Environmental risks factors, gene-environmental & gene-gene interactions & developmental effects need to be considered
- Risk alleles are associated with altered brain development, structure & function

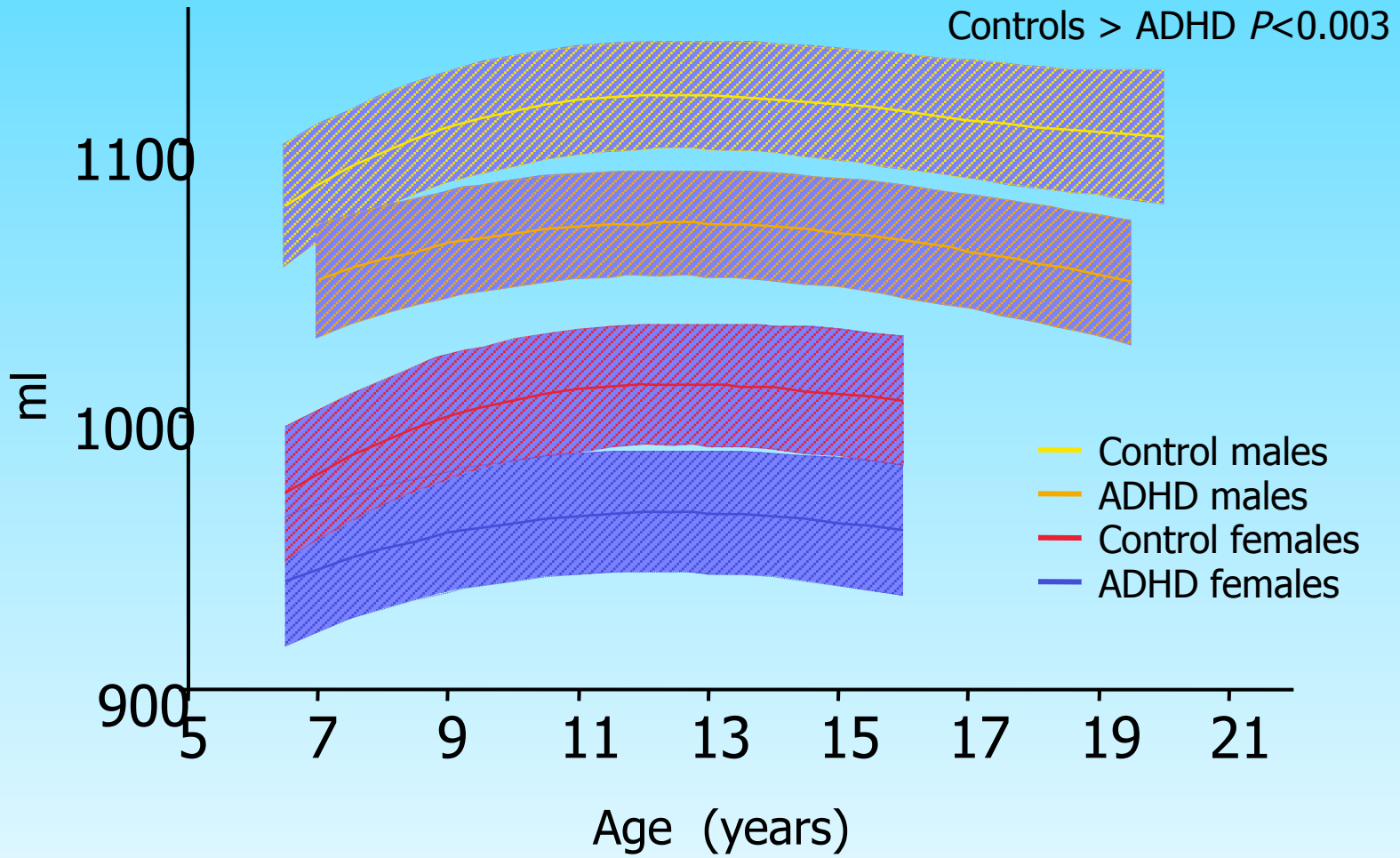
Neural mechanisms mediating between genes and behavior?



Meyer-Lindenberg & Weinberger, Nature Rev. Neur., 2006

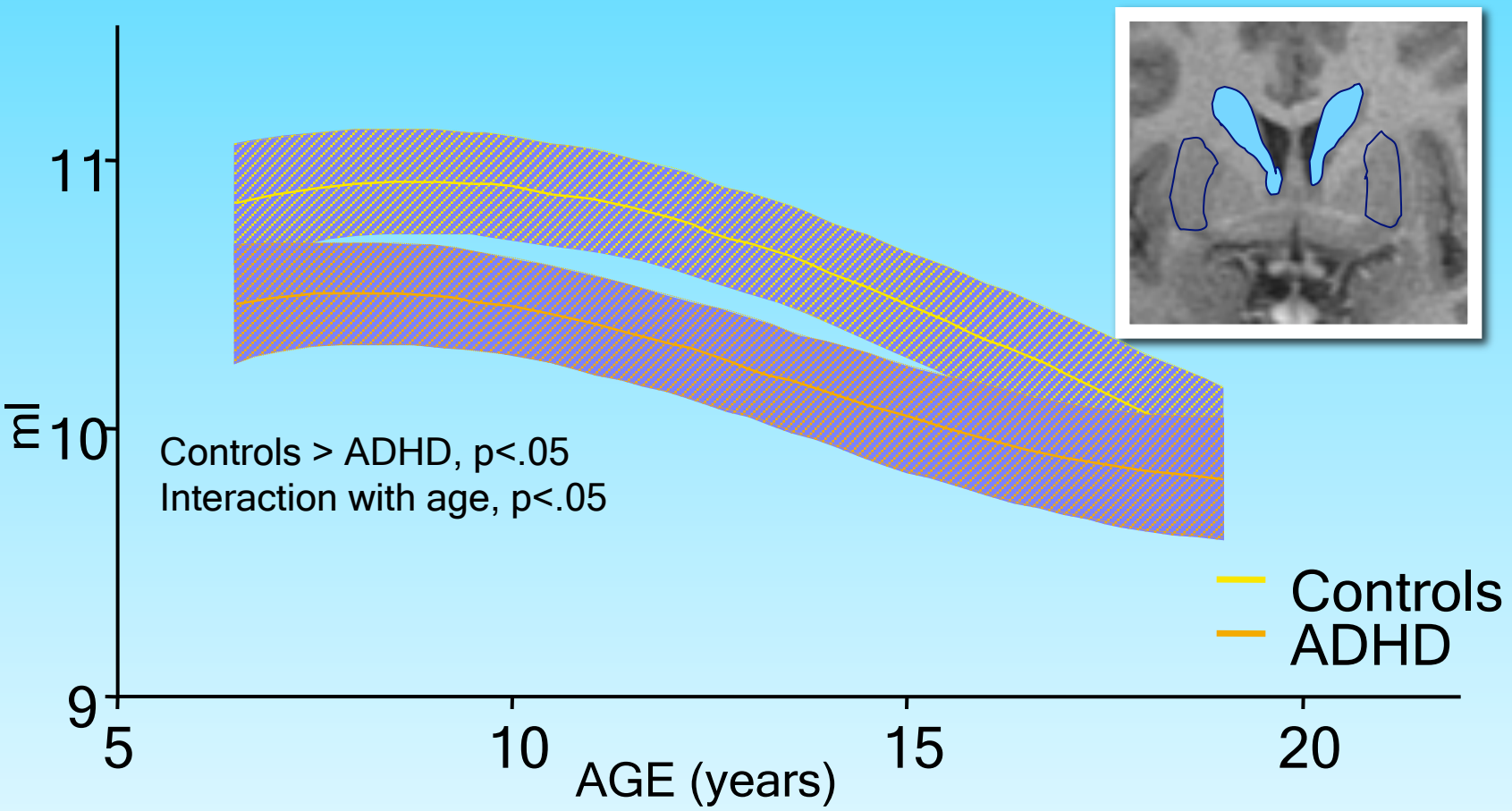
Neuroanatomy

Neuroanatomy – total brain volume



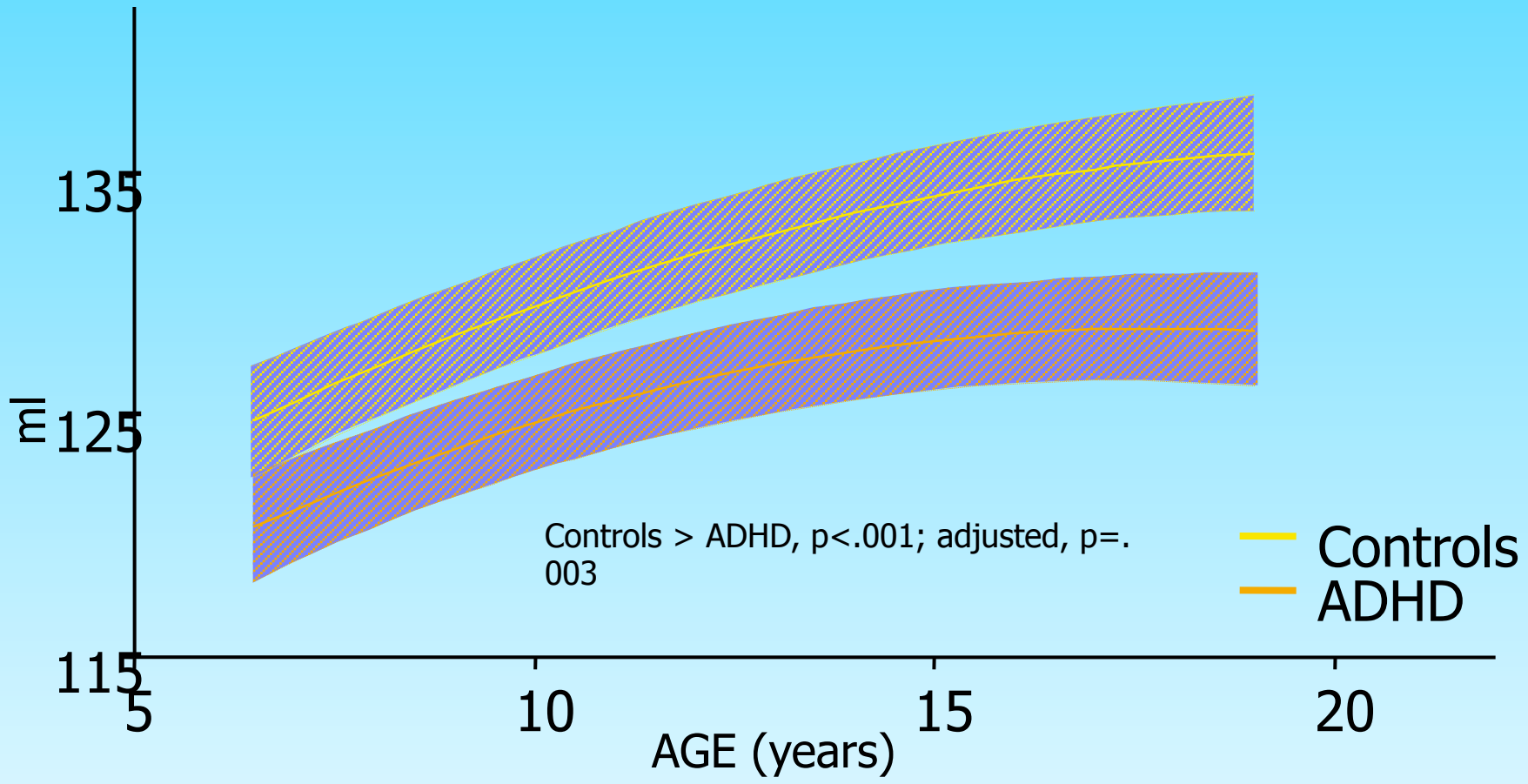
Castellanos *et al* 2002

Neuroanatomy – caudate volume



Castellanos *et al* 2002

Neuroanatomy – cerebellar volume



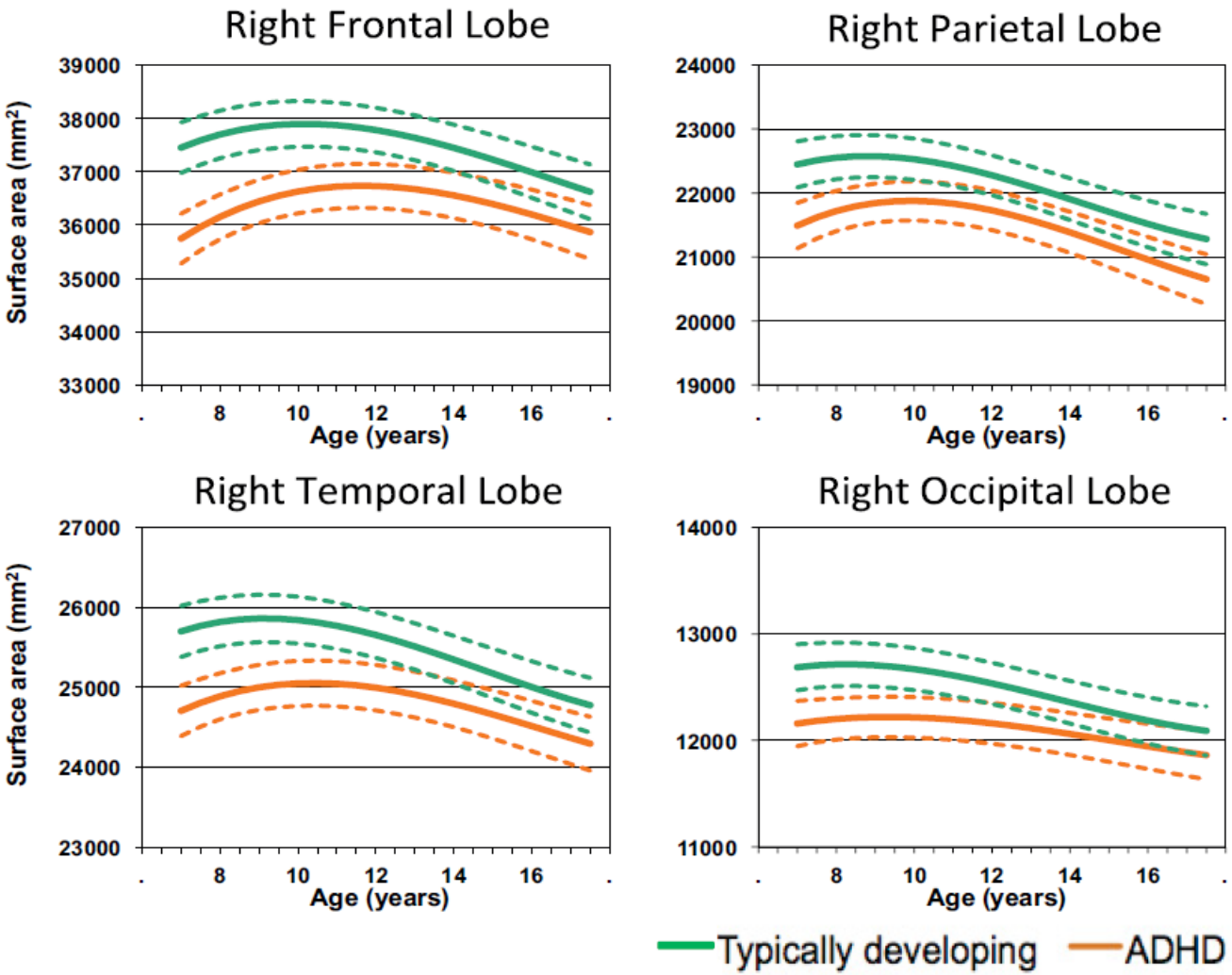
Castellanos *et al* 2002

Development of Cortical Surface Area and Gyrification in Attention-Deficit/Hyperactivity Disorder

Philip Shaw, Meaghan Malek, Bethany Watson, Wendy Sharp, Alan Evans, and Deanna Greenstein

BIOL PSYCHIATRY 2012;72:191–197

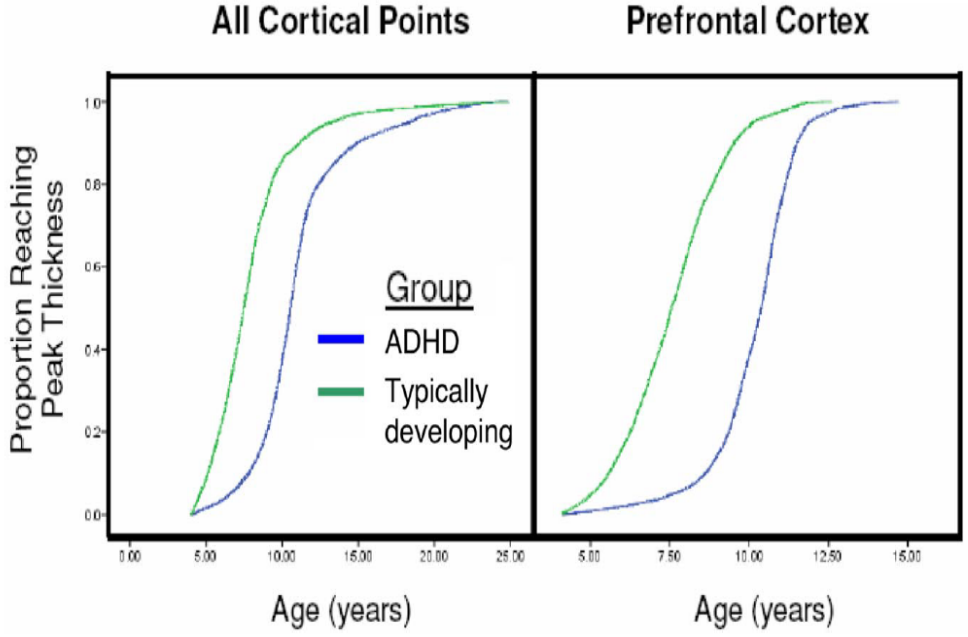
Developmental trajectories of right hemispheric lobar surface areas

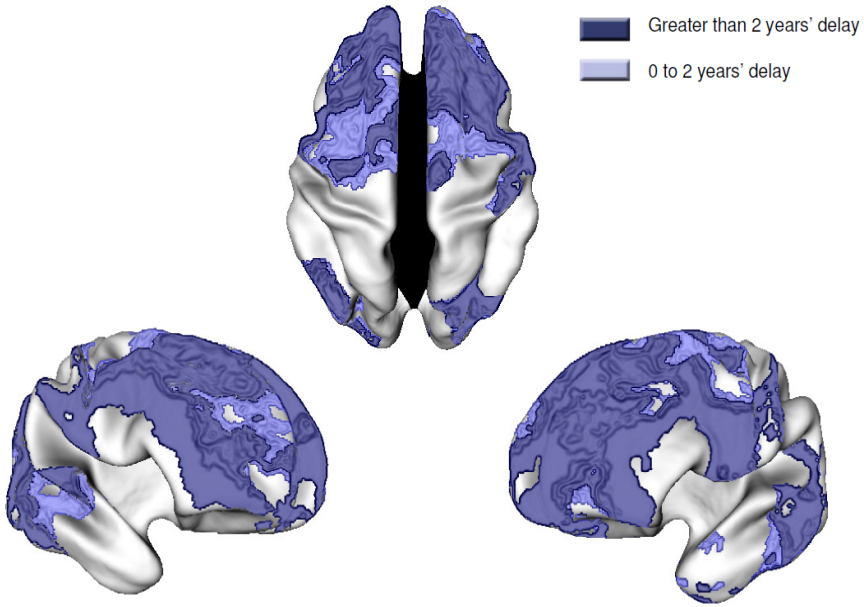


Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation

P. Shaw[†‡], K. Eckstrand[†], W. Sharp[†], J. Blumenthal[†], J. P. Lerch[§], D. Greenstein[†], L. Clasen[†], A. Evans[§], J. Giedd[†], and J. L. Rapoport[†]

PNAS | December 4, 2007 | vol. 104 | no. 49 | 19649–19654

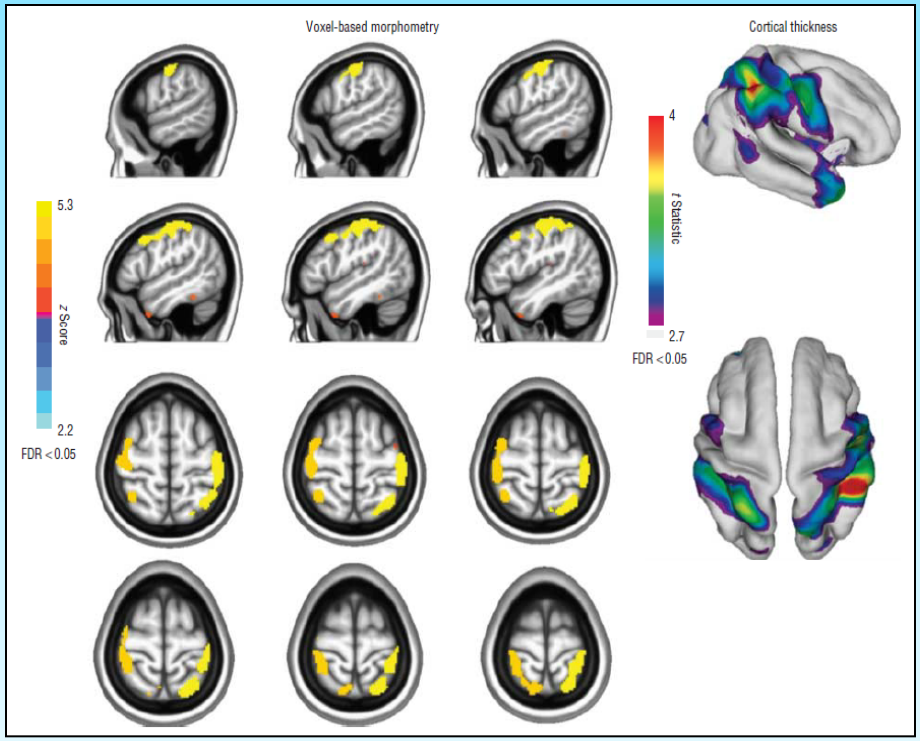


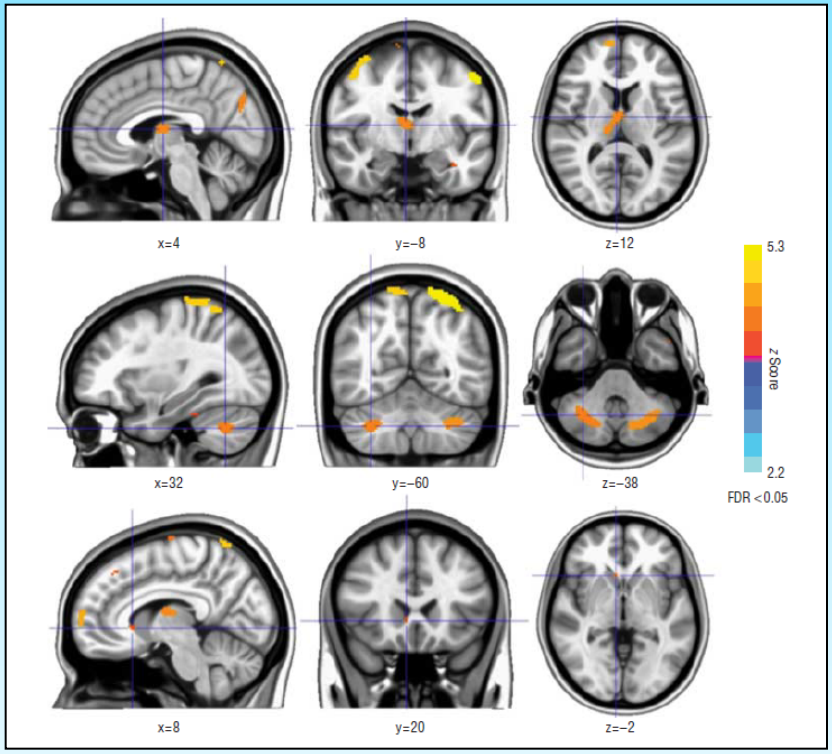


Regions where the ADHD group had delayed cortical maturation

Long-term brain development

- Long-term study 33 years; (n = 207; m; 8;3 => 41;2 age)
- Reduced volumina of posterior attentional network
- Reduced volumina of basal ganglia, thalamus, cerebellum





Proal et al., 2011

Anterior Cingulate Cortex and Symptom Severity in Attention-Deficit/Hyperactivity Disorder

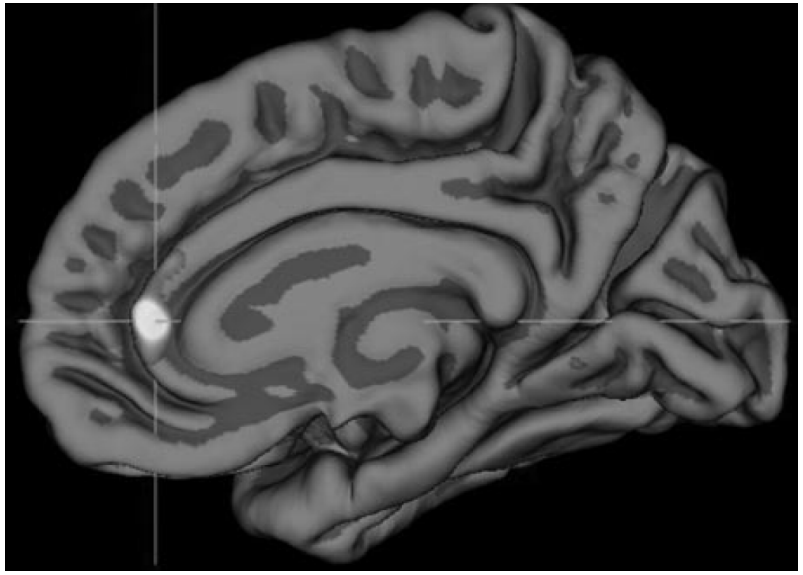
Jesse C. Bledsoe
Seattle Children's Hospital, Seattle, Washington

Margaret Semrud-Clikeman
University of Minnesota Medical School

Steven R. Pliszka
University of Texas Health Science Center of San Antonio

Journal of Abnormal Psychology
2013, Vol. 122, No. 2, 558–565

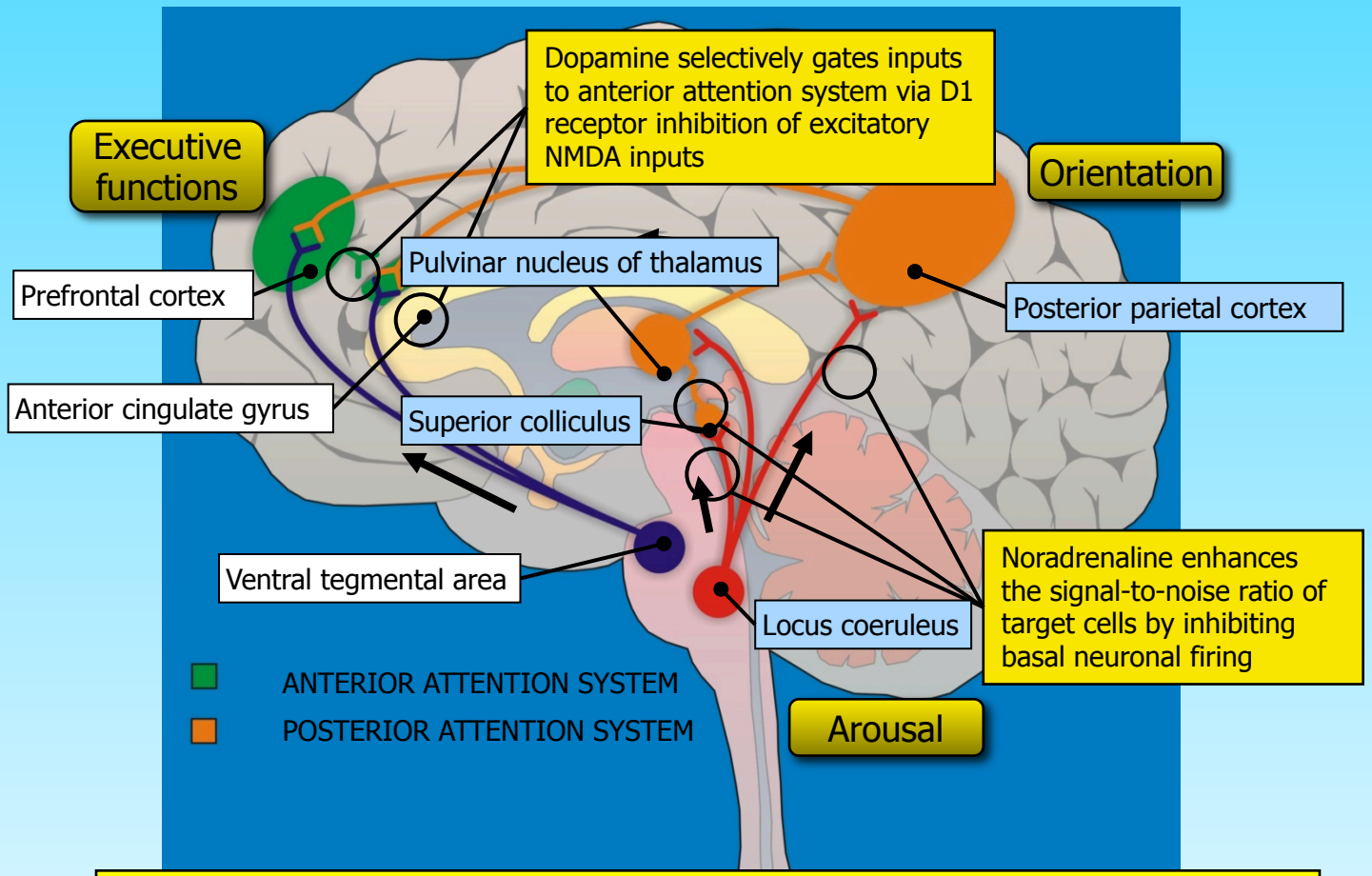
Right rostral anterior cingulate cortex:
Sign. differences between ADHD vs. controls



- ADHD associated with significant cortical thinning in the right rostral ACC (anterior attention network)
- CT predicted significant amount of the variance in parent- & teacher-reported symptoms
- CT not related to stimulant medication history

Neurochemistry

Neurotransmitter & attentional systems



DA / NA => optimal signal-to-noise ratio
(in interaction with other neurotransmitter systems)

Adapted from Himelstein *et al* 2001

Reviews and Ov (Am J Psychiatry 2012; 169:264–272)

Mechanisms of Psychiatric Illness

Striatal Dopamine Transporter Alterations in ADHD: Pathophysiology or Adaptation to Psychostimulants? A Meta-Analysis

Paolo Fusar-Poli, Ph.D.

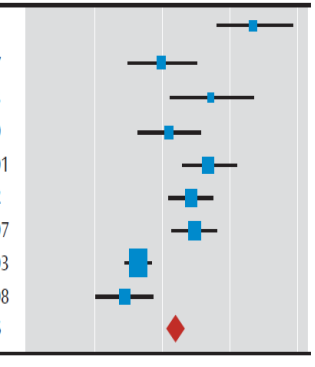
Katya Rubia, Ph.D.

Giorgio Rossi, M.D.

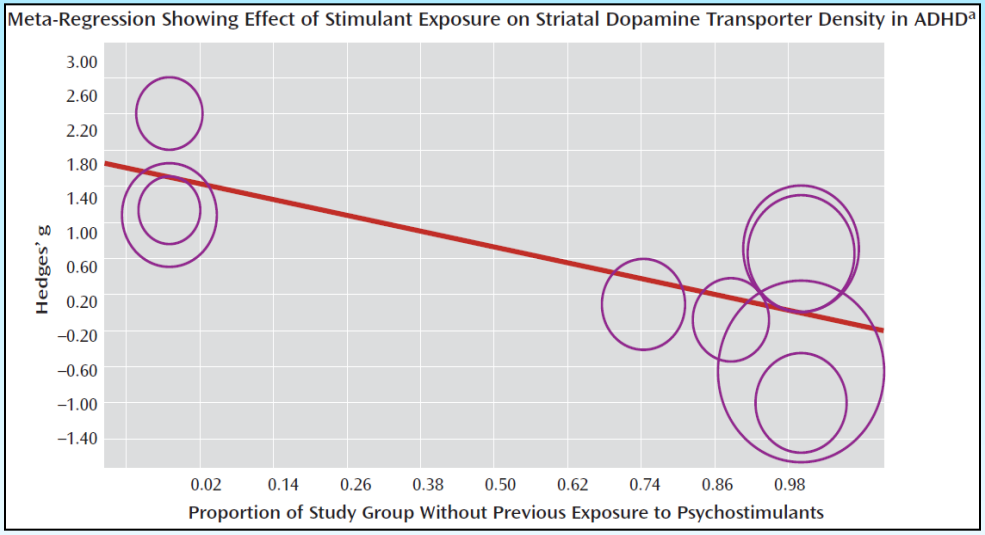
Giuseppe Sartori, Ph.D.

Umberto Balottin, M.D., Ph.D.

Study	Hedges' g	SE	Variance	Lower Limit	Upper Limit	z	p
Dougherty et al., 1999 (16)	2.37	0.52	0.27	1.35	3.39	4.57	<0.01
van Dyck et al., 2002 (17)	−0.02	0.45	0.20	−0.90	0.86	−0.05	0.97
Cheon et al., 2004 (32)	1.26	0.55	0.30	0.19	2.33	2.30	0.03
Jucaite et al., 2005 (33)	0.16	0.41	0.17	−0.65	0.97	0.39	0.70
la Fougere et al., 2006 (34)	1.19	0.36	0.13	0.48	1.91	3.29	0.001
Larisch et al., 2006 (35)	0.75	0.32	0.10	0.12	1.38	2.34	0.02
Spencer et al., 2007 (36)	0.81	0.30	0.09	0.22	1.40	2.70	0.007
Volkow et al., 2009 (10)	−0.62	0.21	0.04	−1.02	−0.21	−2.98	0.003
Hesse et al., 2009 (37)	−0.99	0.37	0.14	−1.72	−0.26	−2.64	0.008
Overall	0.23	0.11	0.01	0.01	0.46	2.03	<0.05



- Striatal DAT density 14% higher in ADHD group
- DAT density higher in patients with previous medication exposure & lower in medication-naive patients
- => Striatal DAT depends on previous stimulant exposure



Neuropsychology

Impaired top-down control

Nigg, 2005: effect sizes on neuropsychological tasks:

Table 2. Selected Meta-analytic Findings in Neuropsychology of ADHD Versus Non-ADHD Children

Measure	Effect Size (*d*)
Spatial Working Memory (Spatial Span)	.75[a] to .85[b] to 1.14[b]
Response Suppression (Stop Task SSRT/SSRT Slope)	.61[a] to .64[c] to .94[d]
Signal Detection (CPT d-prime) Arousal	.72[e]
Stroop Naming Speed	.69[f]
Full Scale IQ	.61[g]
Set Shifting (Trails B Time)	.55[a] to .59[a] to 0.75[d]
Planning (Tower of London/Hanoi)	.51[a] to .69[a]
Mazes	.58[a]
Verbal Working Memory	.51[a] to .41[b]
Decision Speed on Go-Task	.49[c]
WCST Perseverations	.35[g]/.36[a] to .53[h]
Fluency	.27[d]
Stroop Interference	.25[f]
Covert Visual Spatial Orienting	.20[i]

Scientific American, 1998

1. Cognitive control deficits (working memory & response inhibition etc), are relevant but
2. they are not specific to ADHD &
3. only 50% of cases show pronounced executive dysfunctions

ORIGINAL ARTICLE

Separation of Cognitive Impairments in Attention-Deficit/Hyperactivity Disorder Into 2 Familial Factors

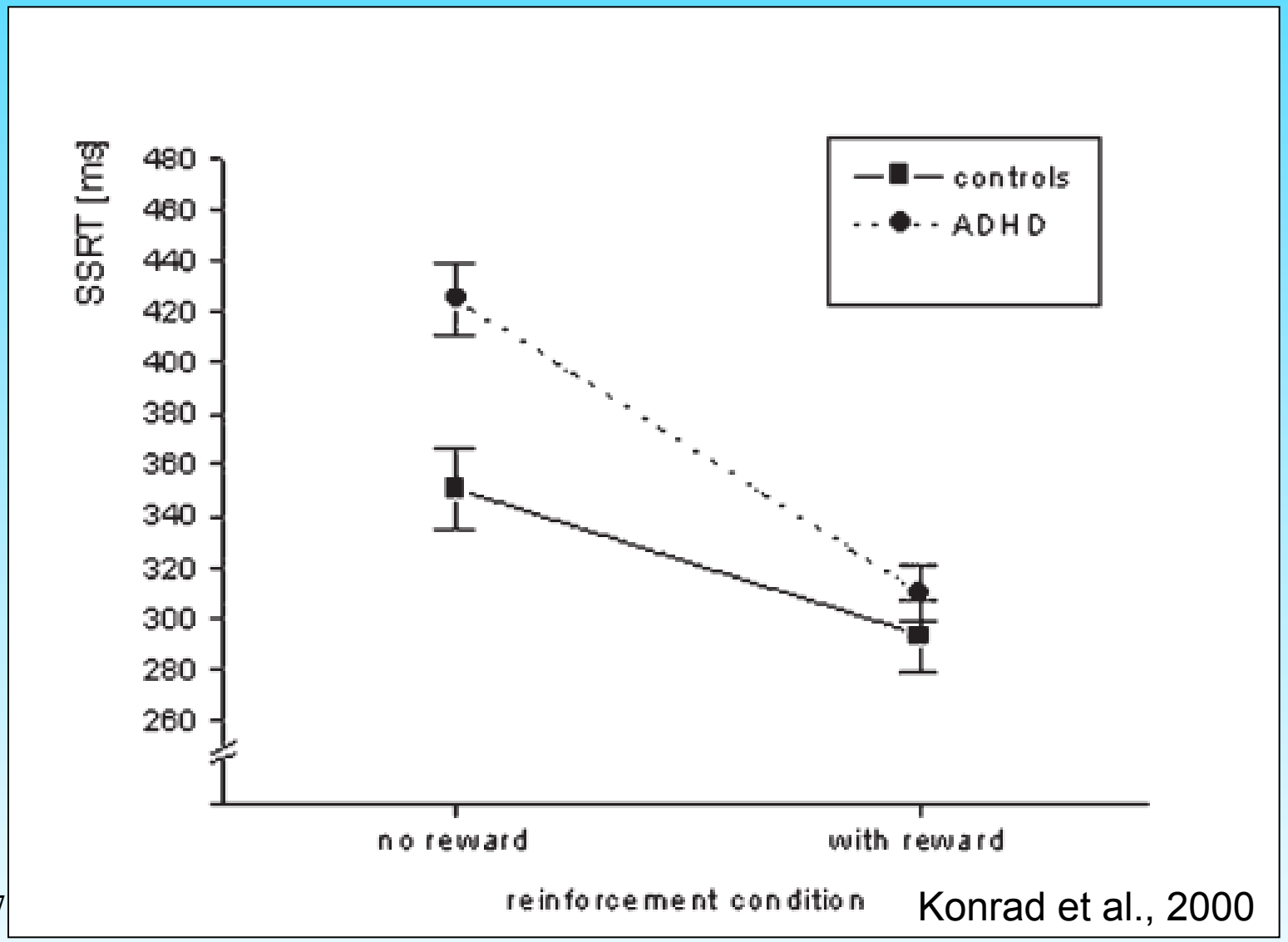
Arch Gen Psychiatry. 2010;67(11):1159-1167

Jonna Kuntsi, PhD; Alexis C. Wood, PhD; Frühling Rijsdijk, PhD; Katherine A. Johnson, PhD; Penelope Andreou, PhD; Björn Albrecht, PhD; Alejandro Arias-Vasquez, PhD; Jan K. Buitelaar, MD, PhD; Gráinne McLoughlin, PhD; Nanda N. J. Rommelse, PhD; Joseph A. Sergeant, PhD; Edmund J. Sonuga-Barke, PhD; Henrik Uebel, MD; Jaap J. van der Meere, PhD; Tobias Banaschewski, MD, PhD; Michael Gill, MRCPsych, PhD; Iris Manor, MD; Ana Miranda, MD; Fernando Mulas, MD; Robert D. Oades, PhD; Herbert Roeyers, PhD; Aribert Rothenberger, MD; Hans-Christoph Steinhausen, MD, PhD, DMSc; Stephen V. Faraone, PhD; Philip Asherson, MRCPsych, PhD

Two familial factors are underlying the multiple apparent cognitive impairments in ADHD

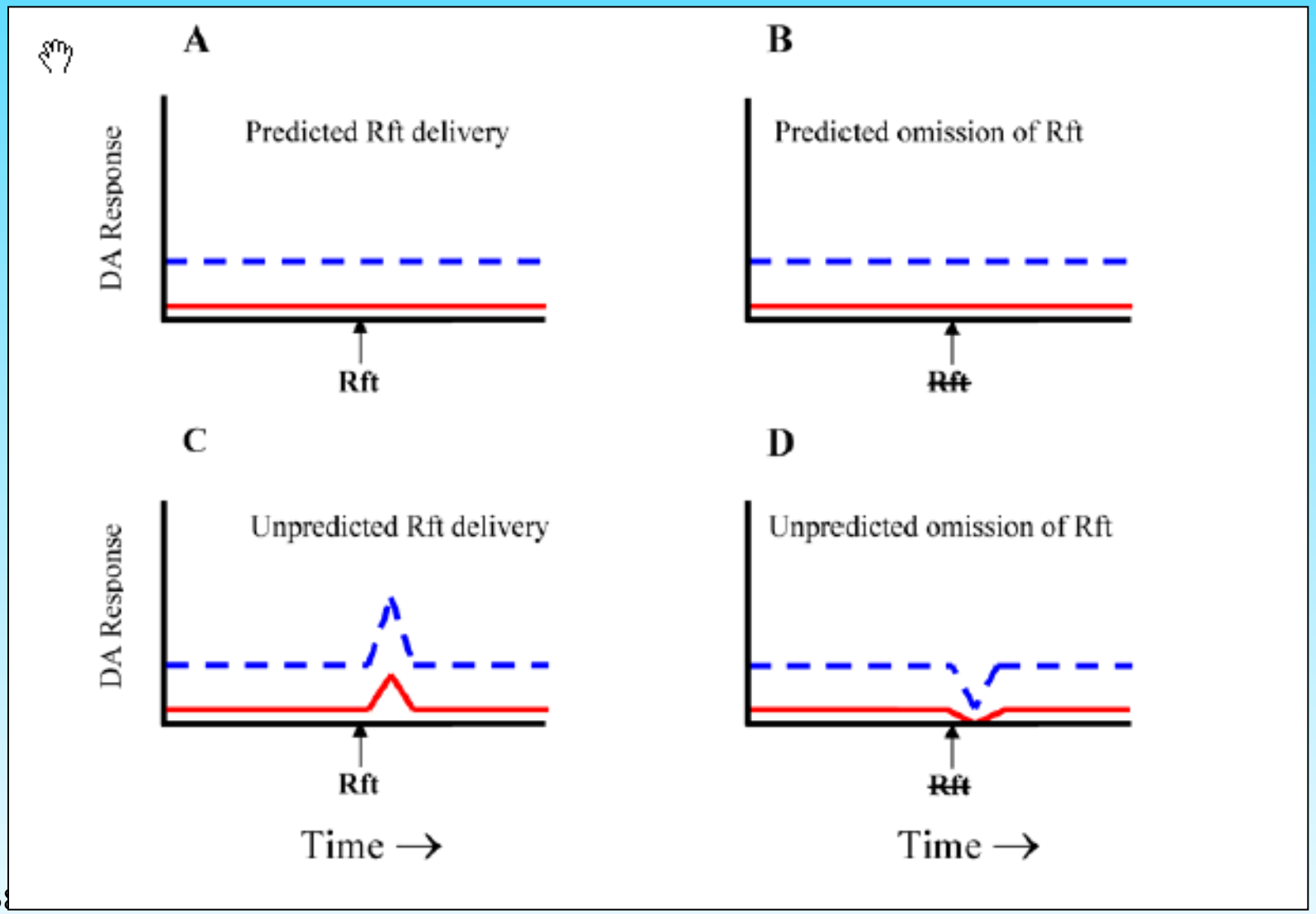
- Arousal-regulation deficit (RTV)
- Executive control dysfunction (commission and omission errors)

Motivational modulation of inhibitory control performance



Konrad et al., 2000

ADHD – altered learning mechanisms ?

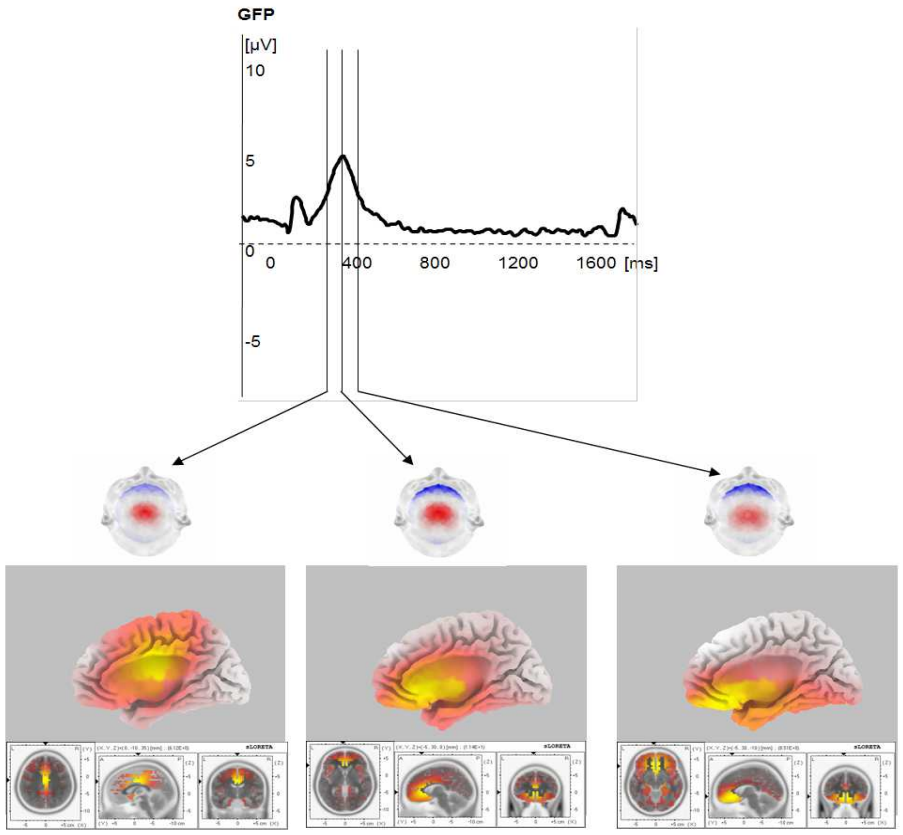


Sagvolden et al., 2005

Functional Imaging

ERP Brainmapping

Measurement of Covert Attention and Inhibition

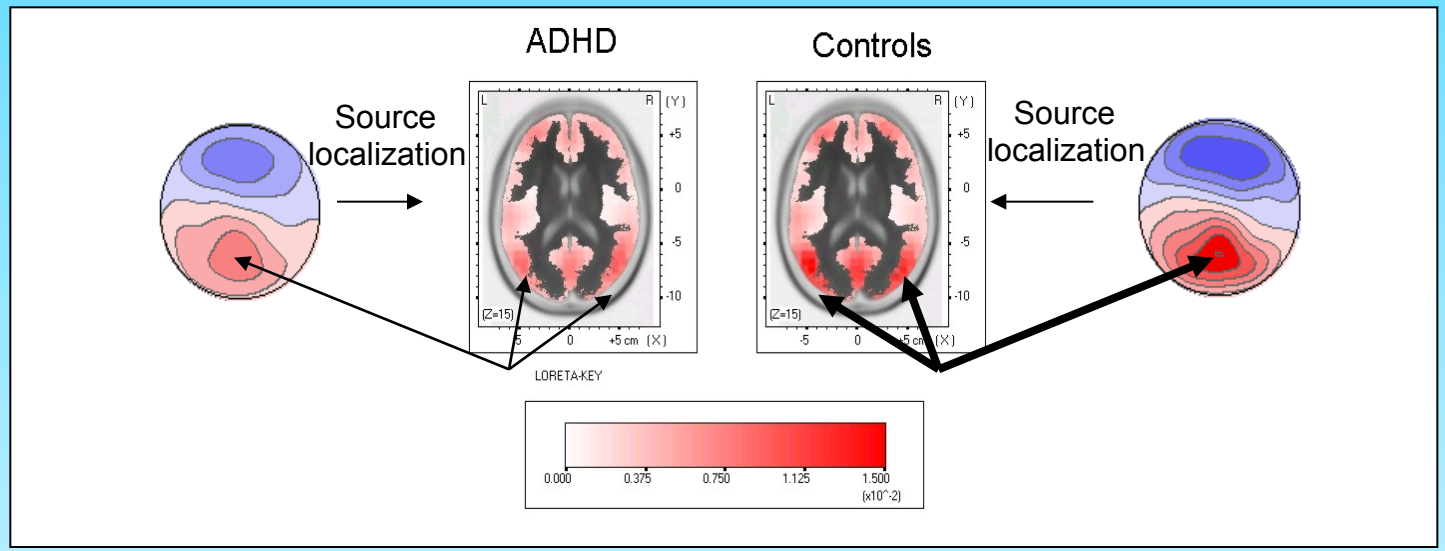


Successful Inhibition in Adults,
cued NoGo trials

➢ High temporal resolution needed to disentangle covert processing stages

Impaired Covert Attention

Reduced cue P300 amplitude in CPT A-X



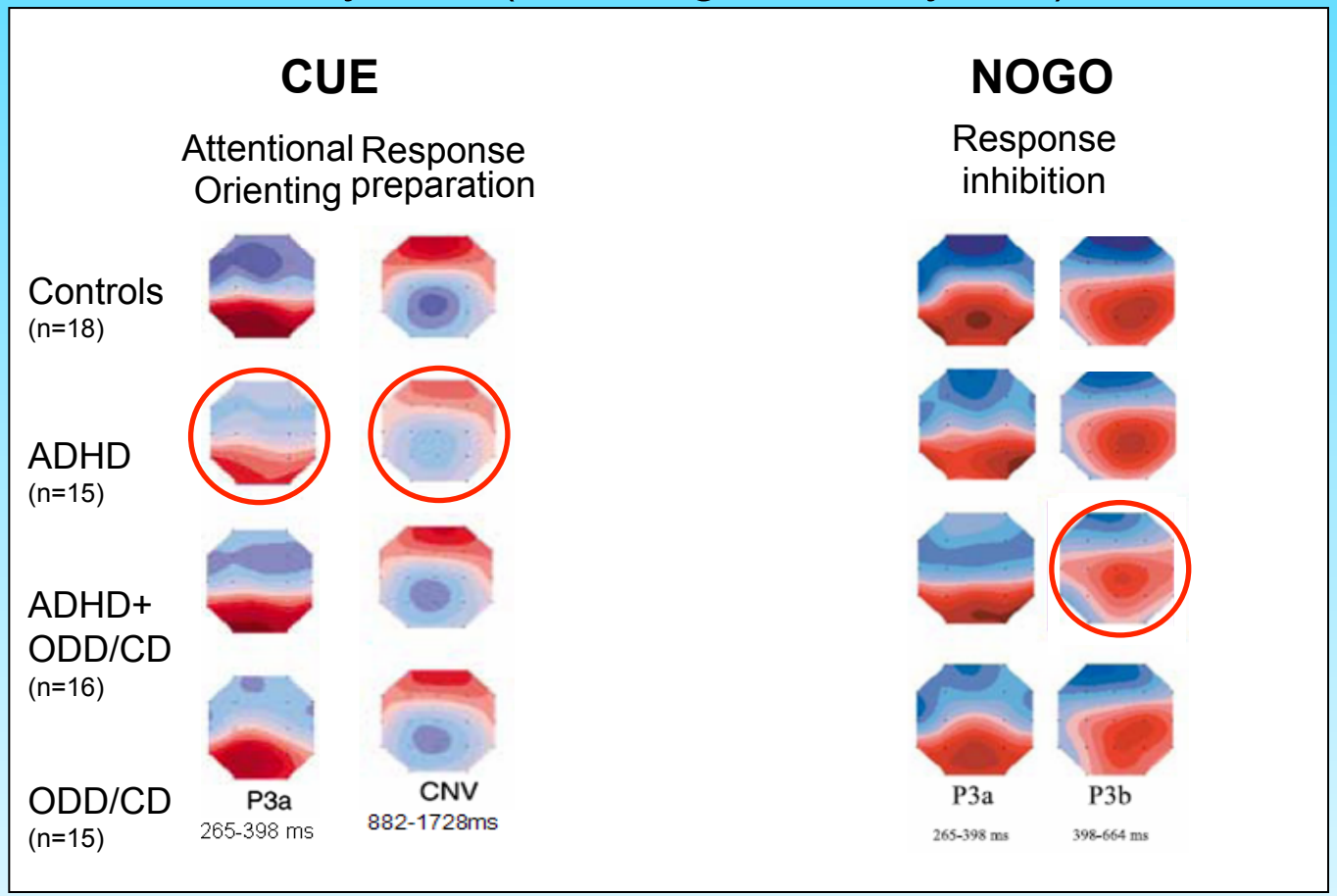
Larger cue P300 predicts better performance (1.65 s before target)

- Altered attentional orienting
- Impaired resource allocation
- Dysfunctions of posterior attentional system

van Leeuwen et al. 1998, Overtoom et al. 1998, Brandeis, et al., 2002; Banaschewski et al., 2003, 2004

Cued CPT in ADHD

Children 8-14 years, (mean age = 10.1 years)



- Attentional orienting & response preparation most impaired in pure ADHD
- Response control most impaired in comorbid children

Banaschewski et al., 2003, 2004

Action Monitoring in Boys With Attention-Deficit/ Hyperactivity Disorder, Their Nonaffected Siblings, and Normal Control Subjects: Evidence for an Endophenotype

Bjoern Albrecht, Daniel Brandeis, Henrik Uebel, Hartmut Heinrich, Ueli C. Mueller, Marcus Hasselhorn, Hans-Christoph Steinhausen, Aribert Rothenberger, and Tobias Banaschewski

Background: Attention-deficit/hyperactivity disorder (ADHD) is a very common and highly heritable child psychiatric disorder associated with dysfunctions in fronto-striatal networks that control attention and response organization. The aim of this study was to investigate whether features of action monitoring related to dopaminergic functions represent endophenotypes that are brain functions on the pathway from genes and environmental risk factors to behavior.

Methods: Action monitoring and error processing as indicated by behavioral and electrophysiological parameters during a flanker task were examined in boys with ADHD combined type according to DSM-IV (n = 68), their nonaffected siblings (n = 18), and healthy control subjects with no known family history of ADHD (n = 22).

Results: Boys with ADHD displayed slower and more variable reaction-times. Error negativity (Ne) was smaller in boys with ADHD compared with healthy control subjects, whereas nonaffected siblings displayed intermediate amplitudes following a linear model predicted by genetic concordance. The three groups did not differ on error positivity (Pe). The N2 amplitude enhancement due to conflict (incongruent flankers) was reduced in the ADHD group. Nonaffected siblings also displayed intermediate N2 enhancement.

Conclusions: Converging evidence from behavioral and event-related potential findings suggests that action monitoring and initial error processing, both related to dopaminergically modulated functions of anterior cingulate cortex, might be an endophenotype related to ADHD.

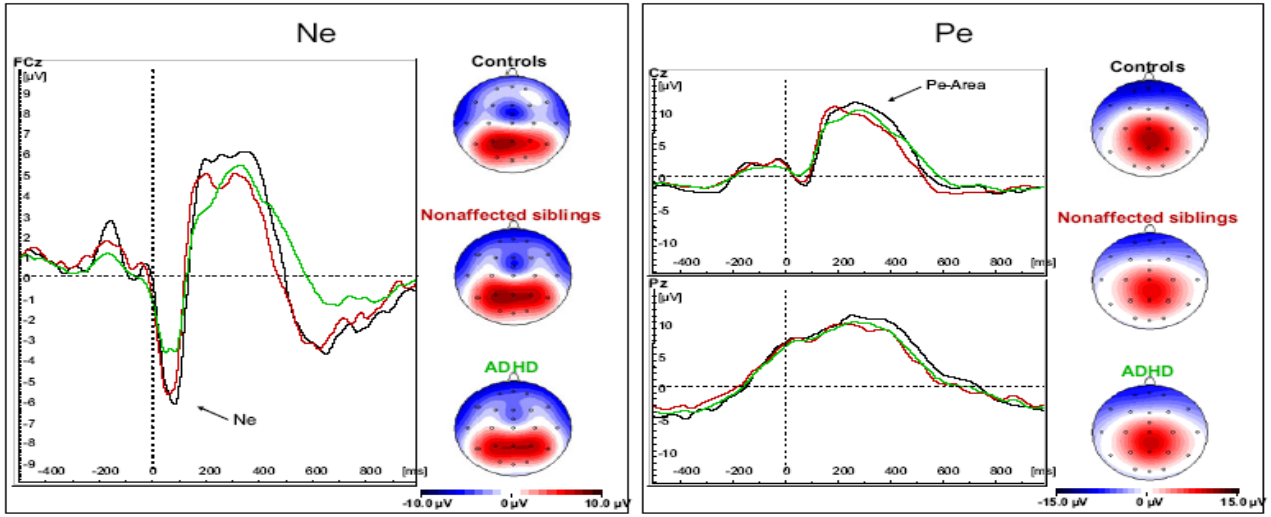


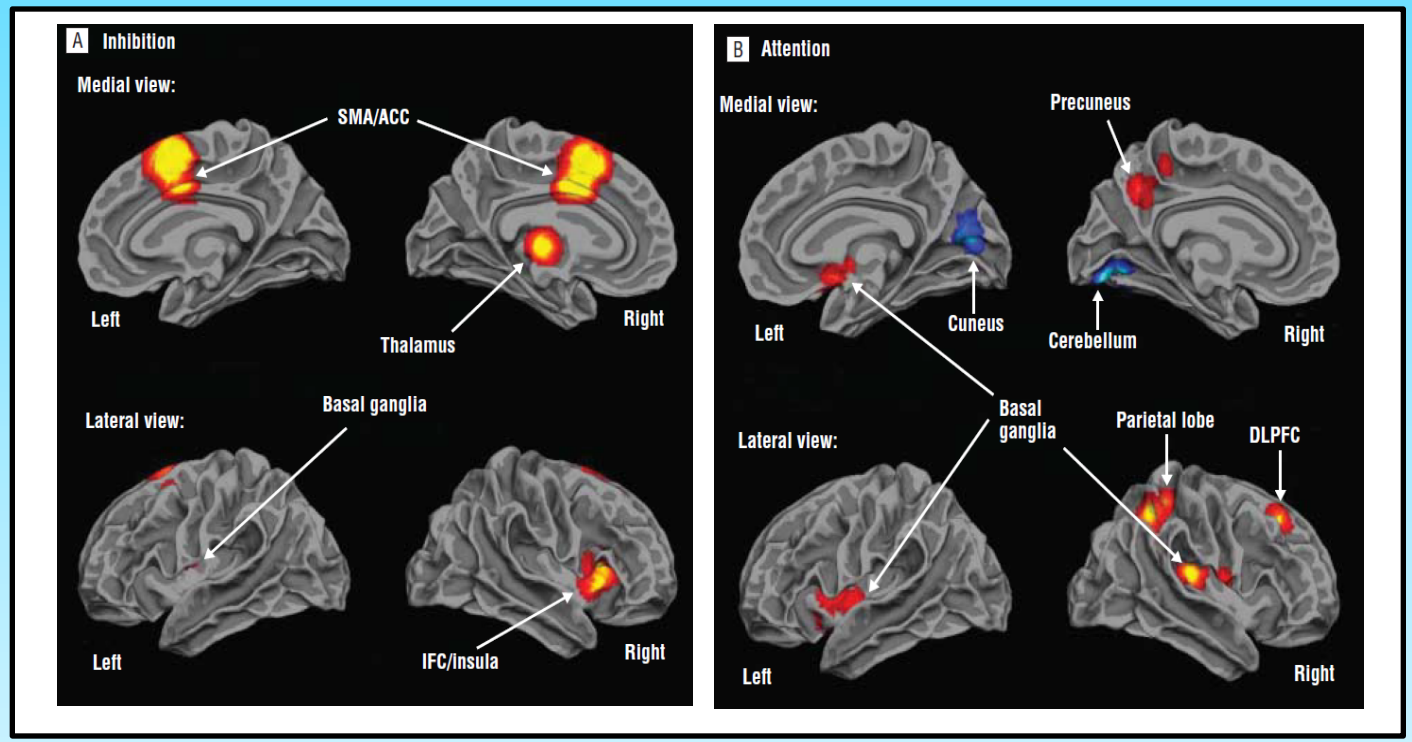
Figure 5. Response-locked error-related components. Response-locked grand average waves of control subjects (black), nonaffected siblings (red), and attention-deficit/hyperactivity disorder (ADHD) boys (green) with spline-interpolated maps of error negativity (Ne) at the respective group mean latency (left side) and error positivity (Pe) mean activity 200–500 msec after error response (right side). The response-locked Ne has its maximum at FCz (even more prominent when measured peak-to-peak), whereas Pe was maximal at centro-parietal electrodes.

Meta-analysis of Functional Magnetic Resonance Imaging Studies of Inhibition and Attention in Attention-deficit/Hyperactivity Disorder

JAMA Psychiatry. 2013;70(2):185-198.

Exploring Task-Specific, Stimulant Medication, and Age Effects

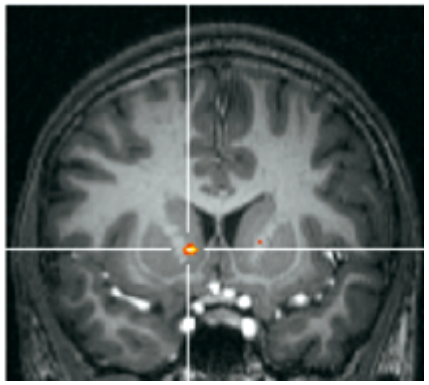
Heledd Hart, PhD; Joaquim Radua, MD; Tomohiro Nakao, MD, PhD; David Mataix-Cols, PhD; Katya Rubia, PhD



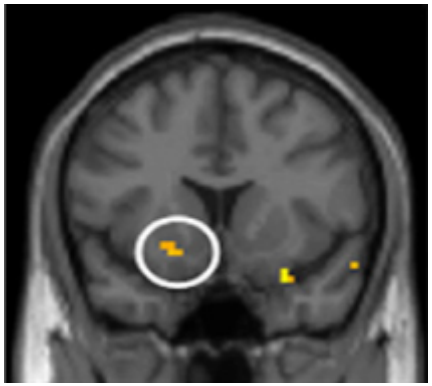
- ADHD => functional abnormalities in 2 distinct domain-dissociated right hemispheric fronto-basal ganglia networks
- IFC, SMA, and ACC for inhibition
- DLPFC, parietal, & cerebellar areas for attention

Motivational alterations

Reduced activation in ventral striatum



Scheres et al. 2007
Biological Psychiatry



Ströhle et al. 2007
Neuroimage

Plichta et al. 2008
Biological Psychiatry

Neural and Psychophysiological Markers of Delay Aversion in Attention-Deficit Hyperactivity Disorder

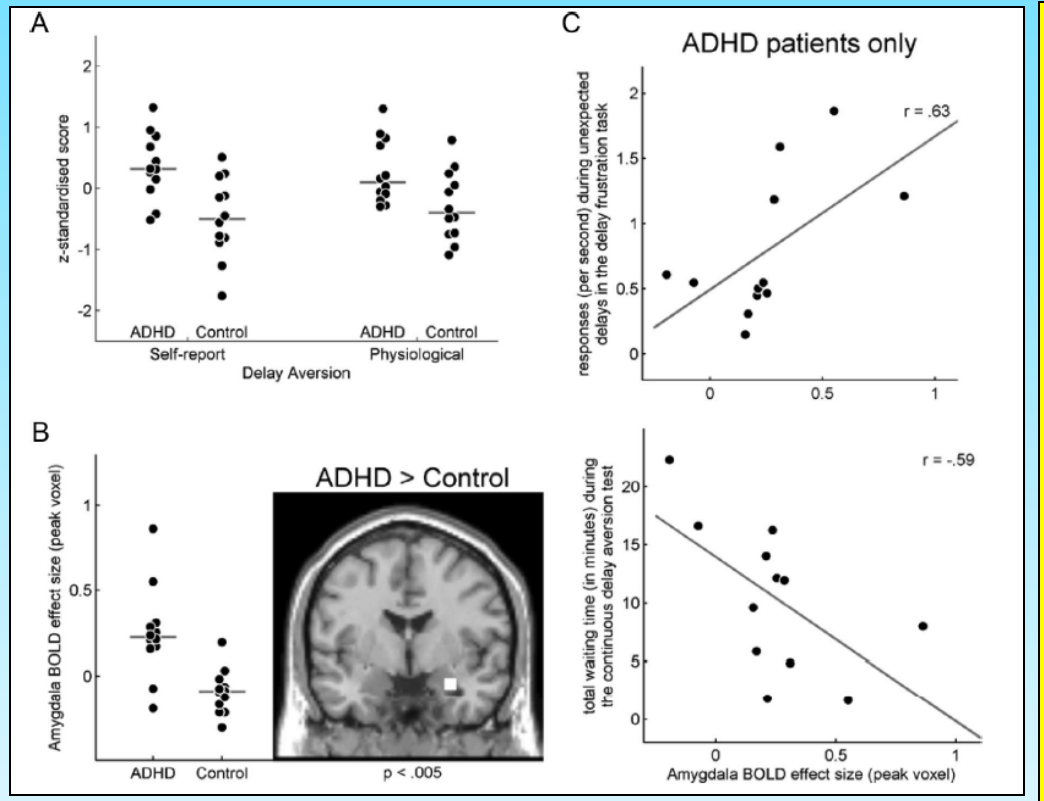
Journal of Abnormal Psychology
2013, Vol. 122, No. 2, 566–572

Gregor Wilbertz and Amalie Trueg
University of Freiburg

Edmund J. S. Sonuga-Barke
University of Southampton and Ghent University

Jens Blechert
University of Salzburg

Alexandra Philipsen and Ludger Tebartz van Elst
University of Freiburg

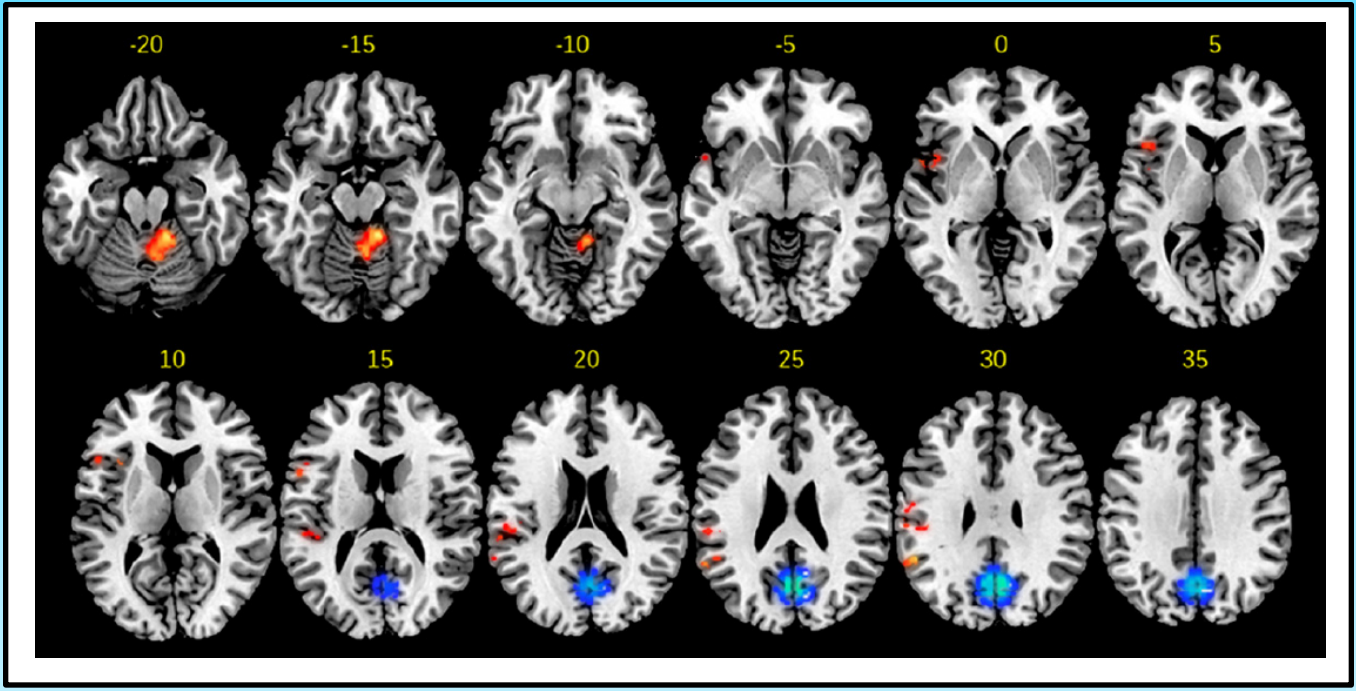


- Longer delays => decreased vs. increased right amygdala activation in controls vs. ADHD
- Amygdala increase correlated with behavioral DAv within ADHD
- => Exacerbated negative emotional state during the anticipation and processing of delay in ADHD

Meta-analysis of fMRI studies of timing in attention-deficit hyperactivity disorder (ADHD)

Neuroscience and Biobehavioral Reviews 36 (2012) 2248–2256

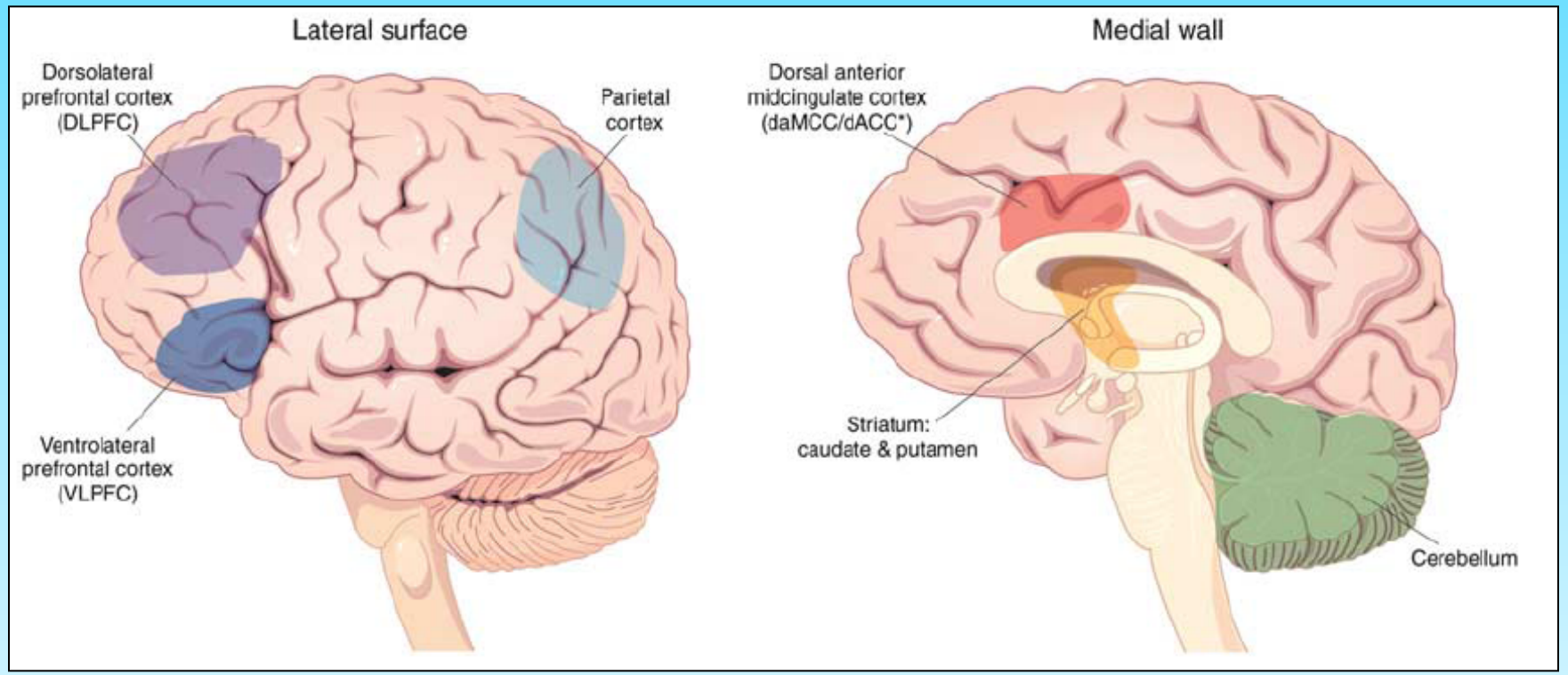
Heledd Hart[a], Joaquim Radua[b,c], David Mataix-Cols[b], Katya Rubia[a,*]



- Timing tasks
- Decreased activation in right cerebellum, left supramarginal gyrus, left IFC/insula
- Increased activation in bilateral precuneus & posterior cingulate

From Simple Causal Models to Complex Development Pathways

Brain structures implicated in ADHD



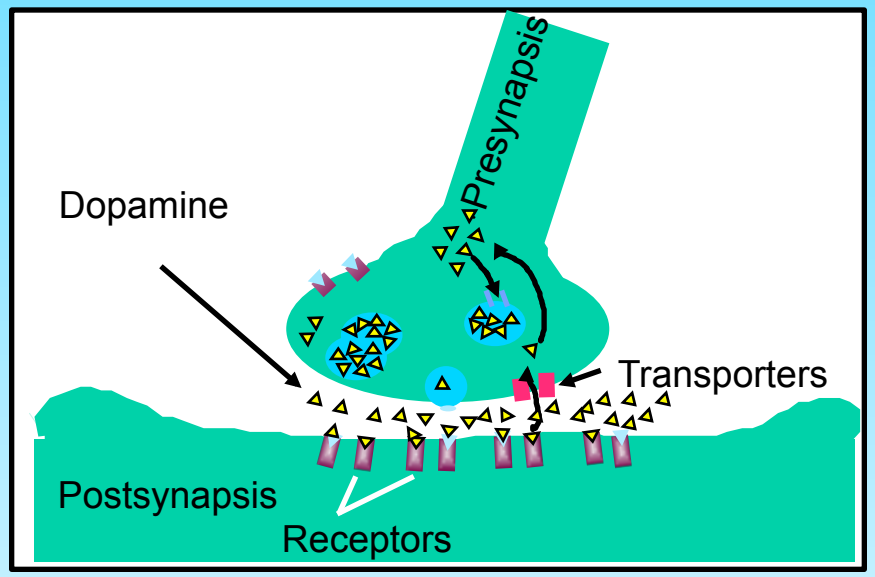
"A single abnormality of any one region alone does not cause ADHD"

Bush, 2010

Treatment

Mechanisms of action

Stimulants increase extrasynaptic DA (Volkow et al., 2003)



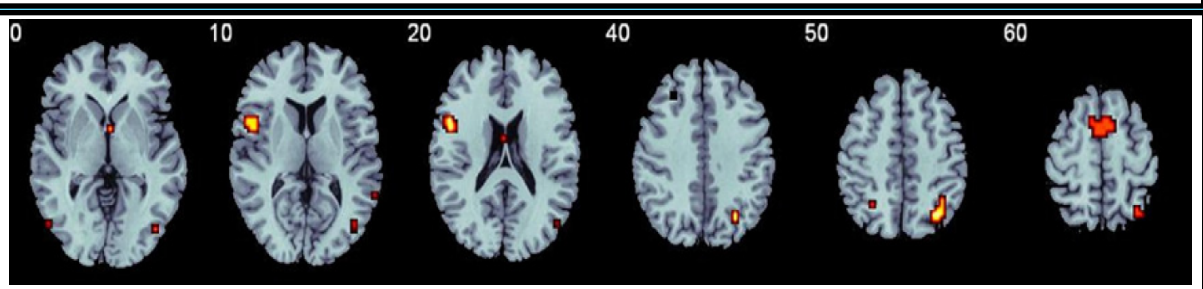
- DA-Reuptake-Inhibition (MPH, AMP)
- Increased presynaptic release (AMP)

- Stimulants are more effective than non-stimulants
- AMP may be moderately more efficacious than MPH

Methylphenidate Normalizes Frontocingulate Underactivation During Error Processing in Attention-Deficit/Hyperactivity Disorder

Katya Rubia, Rozmin Halari, Abdul-Majeed Mohammad, Eric Taylor, and Michael Brammer

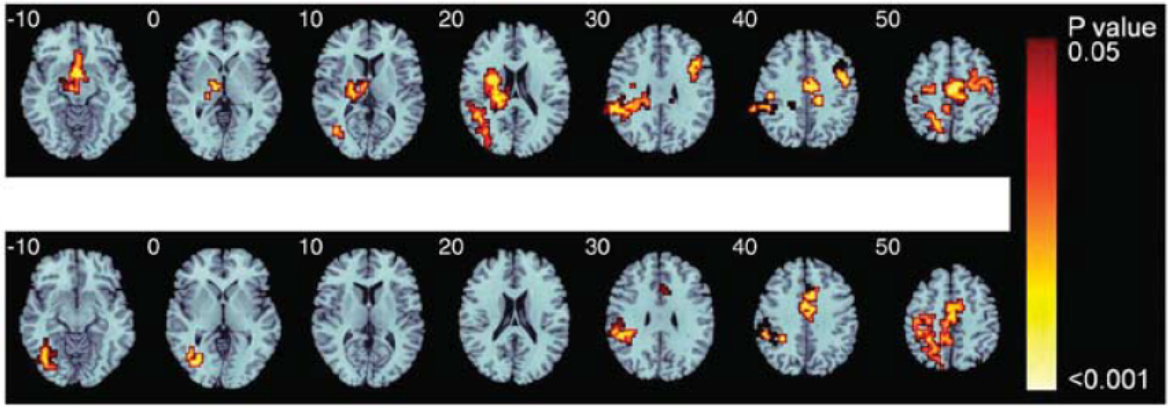
BIOL PSYCHIATRY 2011;70:255–262



Methylphenidate Normalizes Fronto-Striatal Underactivation During Interference Inhibition in Medication-Naïve Boys with Attention-Deficit Hyperactivity Disorder

Neuropsychopharmacology (2011) 36, 1575–1586

Katya Rubia*,[1], Rozmin Halari[1], Ana Cubillo[1], Anna B Smith, Abdul-Majeed Mohammad[1], Michael Brammer[2] and Eric Taylor[1]



Psychostimulant Treatment and the Developing Cortex in Attention Deficit Hyperactivity Disorder

Philip Shaw, M.D., Ph.D.

Wendy S. Sharp, M.S.W.

Meaghan Morrison, B.S.

Kristen Eckstrand, B.S.

Deanna K. Greenstein, Ph.D.

Liv S. Clasen, Ph.D.

Alan C. Evans, Ph.D.

Judith L. Rapoport, M.D.

Objective: While there has been considerable concern over possible adverse effects of psychostimulants on brain development, this issue has not been examined in a prospective study. The authors sought to determine prospectively whether psychostimulant treatment for attention deficit hyperactivity disorder (ADHD) was associated with differences in the development of the cerebral cortex during adolescence.

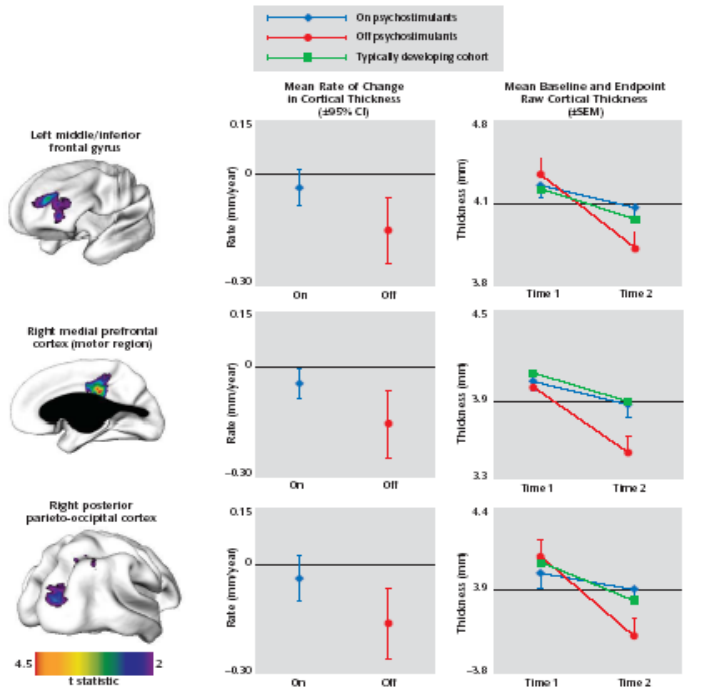
Method: Change in cortical thickness was estimated from two neuroanatomic MRI scans in 43 youths with ADHD. The mean age at the first scan was 12.5 years, and at the second scan, 16.4 years. Nine-

Results: Adolescents taking psychostimulants differed from those not taking psychostimulants in the rate of change of the cortical thickness in the right motor strip, the left middle/inferior frontal gyrus, and the right parieto-occipital region. The group difference was due to more rapid cortical thinning in the group not taking psychostimulants (mean cortical thinning of 0.16 mm/year [SD=0.17], compared with 0.03 mm/year [SD=0.11] in the group taking psychostimulants). Comparison against the typically developing cohort without ADHD showed that cortical thinning in the group not taking psychostimulants was in excess of age-appropriate rates. The treatment groups did not differ in clinical outcome, however.

Conclusions: These findings show no evidence that psychostimulants were associated with slowing of overall growth of the cortical mantle.

(Am J Psychiatry 2009; 166:58–63)

FIGURE 1. Differences in Rate of Cortical Growth in Adolescents With ADHD Taking or Not Taking Psychostimulant Medication[a]



[a] Brain templates on the left show the regions where the two groups had a significantly different rate of cortical growth. The middle column shows the rate of change in raw cortical thickness in these regions, and the right-hand column shows the baseline and endpoint raw cortical thickness for each group and the age-expected values for a typically developing adolescent.

 (Am J Psychiatry 2011; 168:1154–1163)

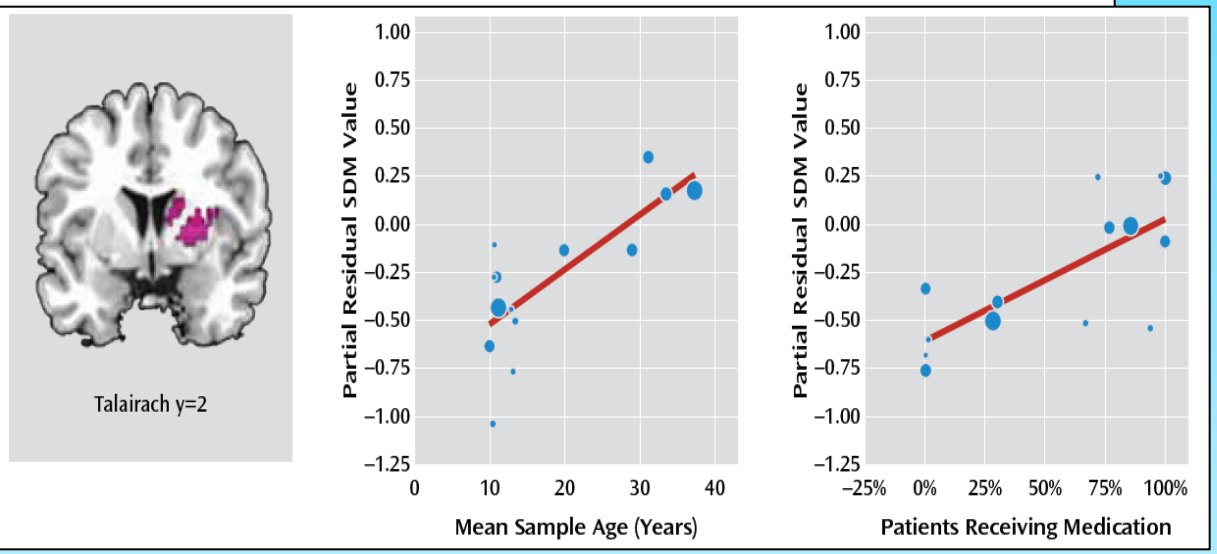
Gray Matter Volume Abnormalities in ADHD: Voxel-Based Meta-Analysis Exploring the Effects of Age and Stimulant Medication

Tomohiro Nakao, M.D., Ph.D.

Joaquim Radua, M.D.

Katya Rubia, Ph.D.

David Mataix-Cols, Ph.D.



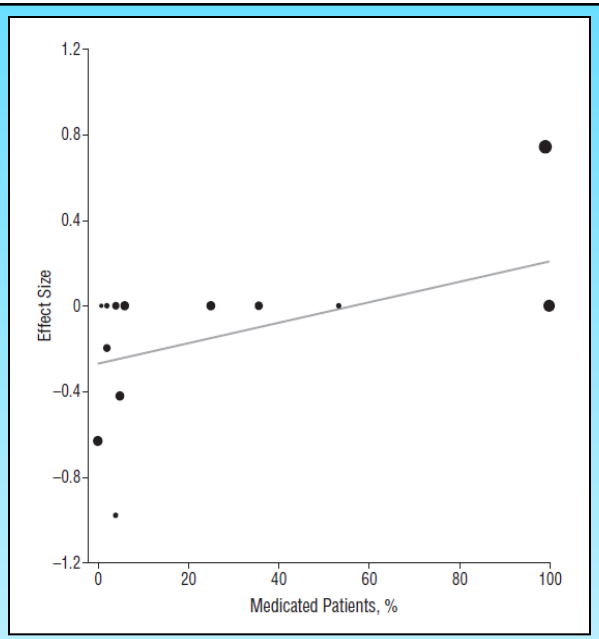
- 378 patients with ADHD & 344 healthy subjects
- Independent association of mean age & percentage of patients receiving stimulant medication with more normal gray matter volumes in the right basal ganglia

Meta-analysis of Functional Magnetic Resonance Imaging Studies of Inhibition and Attention in Attention-deficit/Hyperactivity Disorder

JAMA Psychiatry. 2013;70(2):185-198.

Exploring Task-Specific, Stimulant Medication, and Age Effects

Heledd Hart, PhD; Joaquim Radua, MD; Tomohiro Nakao, MD, PhD; David Mataix-Cols, PhD; Katya Rubia, PhD

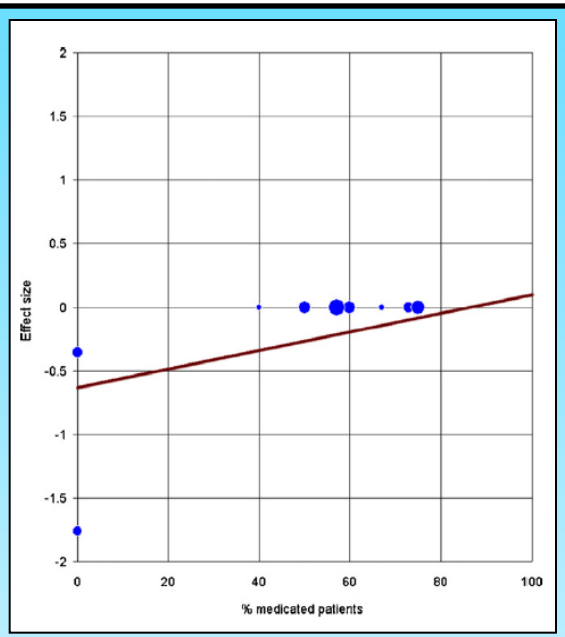


- Percentage of patients receiving long-term stimulant treatment associated with more normal right caudate activation

Meta-analysis of fMRI studies of timing in attention-deficit hyperactivity disorder (ADHD)

Heledd Hart[a], Joaquim Radua[b,c], David Mataix-Cols[b], Katya Rubia[a,*]

Neuroscience and Biobehavioral Reviews 36 (2012) 2248–2256



- Percentage of patients receiving long-term stimulant treatment associated with more normal right DLPFC activation

Article

Nonpharmacological Interventions for ADHD: Systematic Review and Meta-Analyses of Randomized Controlled Trials of Dietary and Psychological Treatments

Edmund J.S. Sonuga-Barke, Ph.D.
Daniel Brandeis, Ph.D.
Samuele Cortese, M.D., Ph.D.
David Daley, Ph.D.
Maite Ferrin, M.D., Ph.D.
Martin Holtmann, M.D.
Jim Stevenson, Ph.D.
Marina Danckaerts, M.D., Ph.D.
Saskia van der Oord, Ph.D.
Manfred Döpfner, Ph.D.
Ralf W. Dittmann, M.D., Ph.D.
Emily Simonoff, M.D.
Alessandro Zuddas, M.D.
Tobias Banaschewski, M.D., Ph.D.
Jan Buitelaar, M.D., Ph.D.
David Coghill, M.D.
Chris Hollis, M.D.
Eric Konofal, M.D., Ph.D.
Michel Lecendreux, M.D.
Ian C.K. Wong, Ph.D.
Joseph Sergeant, Ph.D.
European ADHD Guidelines Group

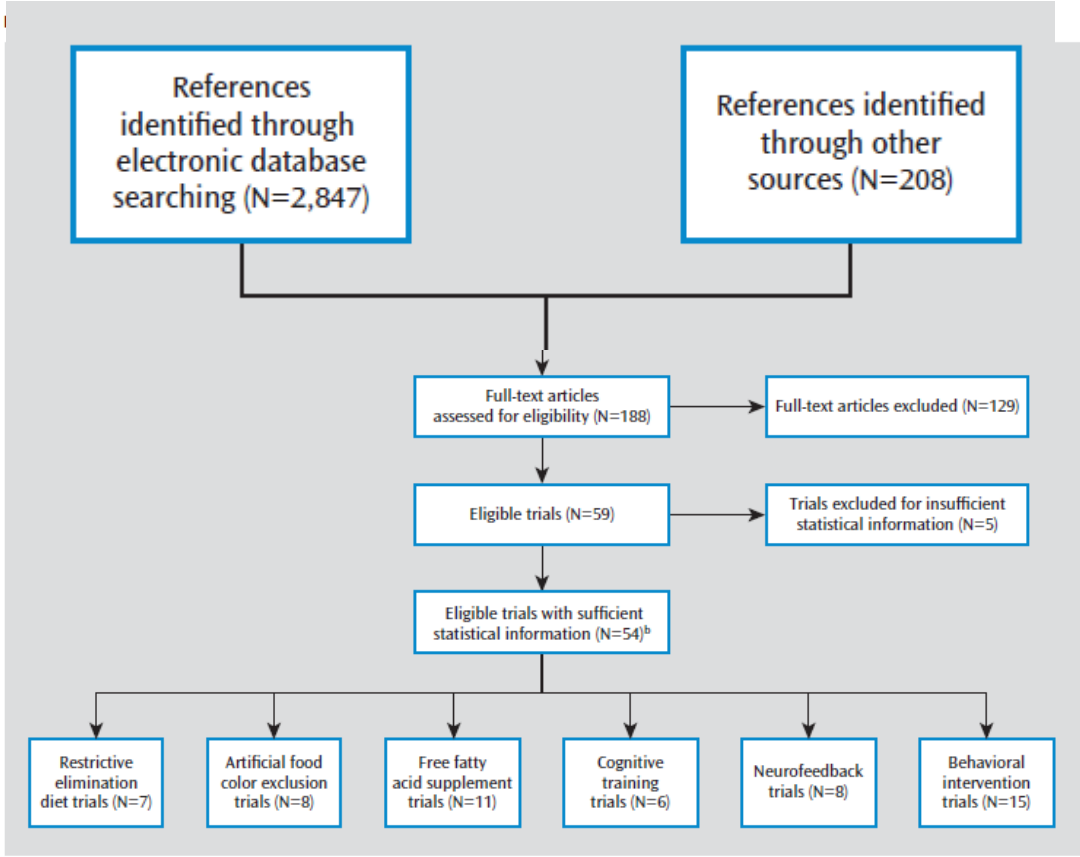
Objective: Nonpharmacological treatments are available for attention deficit hyperactivity disorder (ADHD), although their efficacy remains uncertain. The authors undertook meta-analyses of the efficacy of dietary (restricted elimination diets, artificial food color exclusions, and free fatty acid supplementation) and psychological (cognitive training, neurofeedback, and behavioral interventions) ADHD treatments.

Method: Using a common systematic search and a rigorous coding and data extraction strategy across domains, the authors searched electronic databases to identify published randomized controlled trials that involved individuals who were diagnosed with ADHD (or who met a validated cutoff on a recognized rating scale) and that included an ADHD outcome.

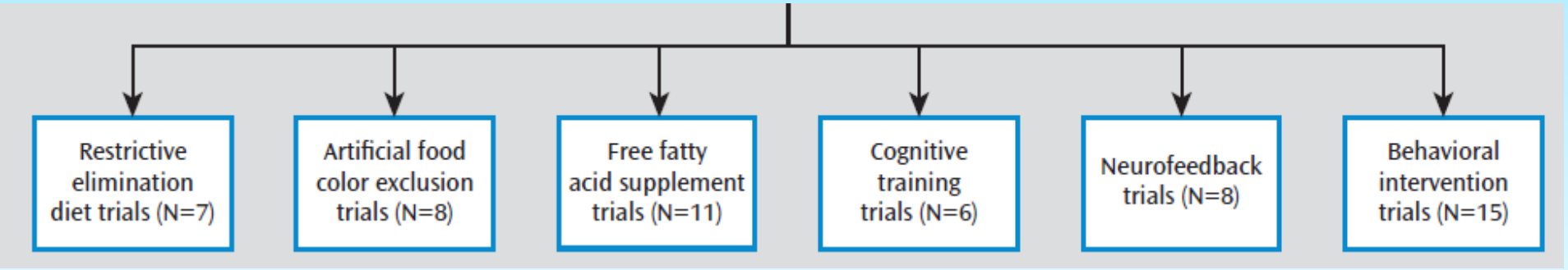
Results: Fifty-four of the 2,904 cate screened records were inc the analyses. Two different anal performed. When the outcome was based on ADHD assessmen ers closest to the therapeutic s dietary (standardized mean diff 0.21–0.48) and psychological (ized mean differences=0.40–0. ments produced statistically s effects. However, when the best blinded assessment was employe remained significant for free f supplementation (standardized r ference=0.16) and artificial fo exclusion (standardized mea ence=0.42) but were substantial ated to nonsignificant levels f treatments.

Conclusions: Free fatty acid sup tation produced small but signi ductions in ADHD symptoms e probably blinded assessments, the clinical significance of thes remains to be determined. Artif color exclusion produced large but often in individuals selected sensitivities. Better evidence fo from blinded assessments is for behavioral interventions, ne back, cognitive training, and elimination diets before they supported as treatments for co symptoms.

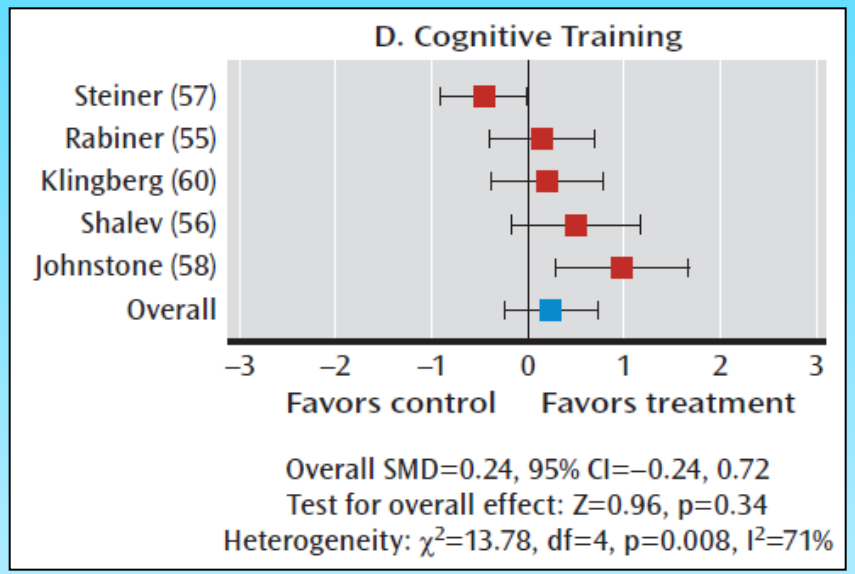
(Am J Psychiatry 2012;

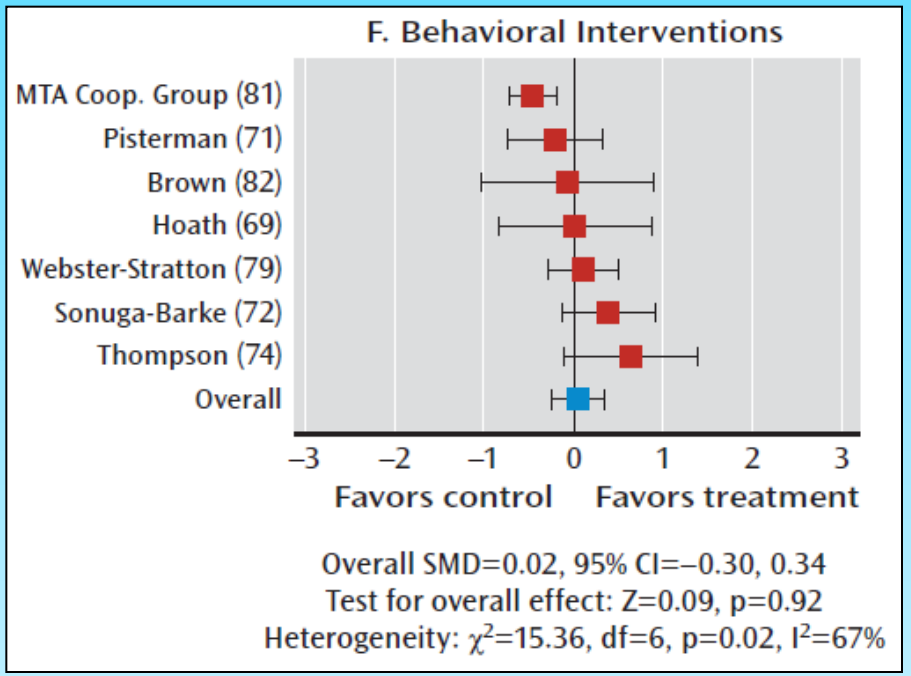


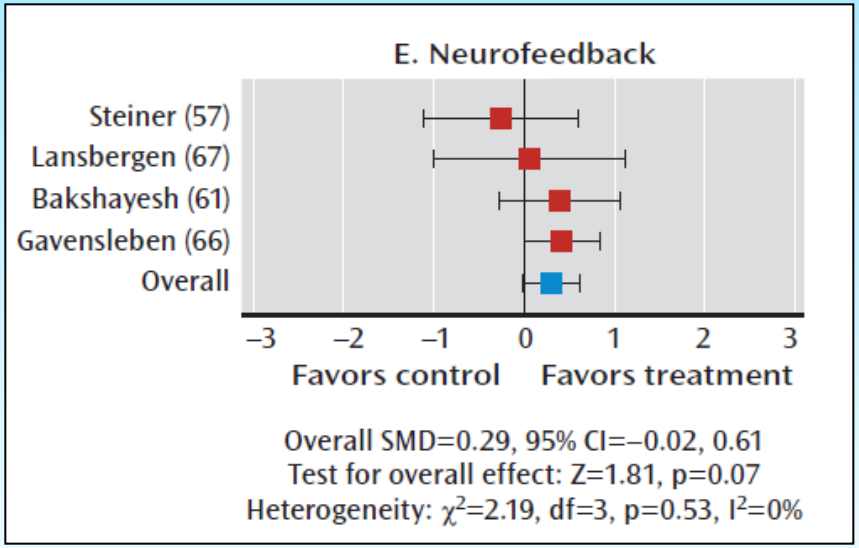
a PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses (www.prisma-statement.org).
b Data from one three-arm trial are included in both neurofeedback and cognitive training analyses.



Probably Blinded Assessments







Thank you

for your attention!