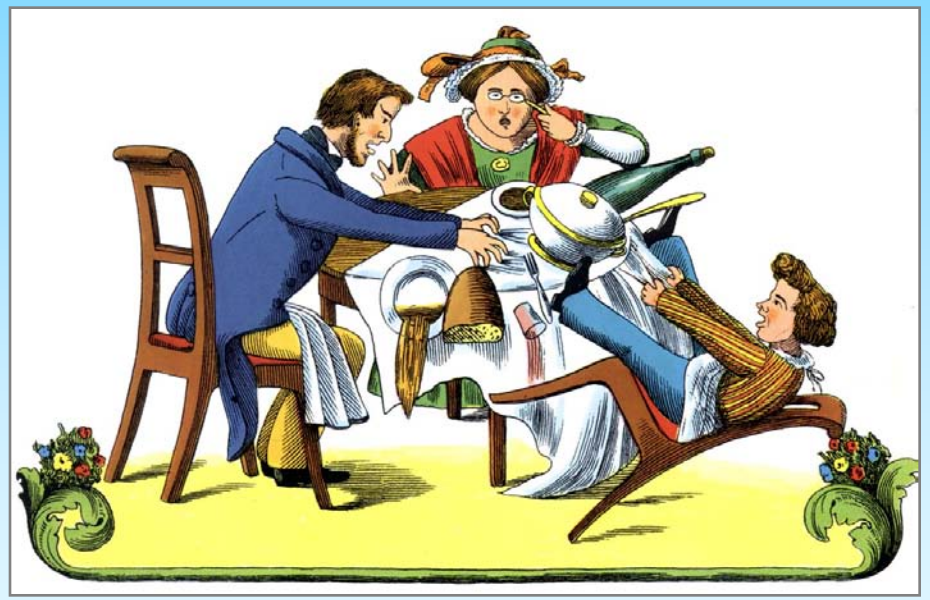
Neurobiologische Grundlagen der ADHS – Update
Teil 1



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Übersicht

- Risikofaktoren (Teil 1)
  - Genetik & Umweltfaktoren
- Korrelate (Teil 2)
  - Neuroanatomie
  - Neurochemie
  - Neuropsychologie
  - Neurophysiologie

Klinisches Bild

Definition

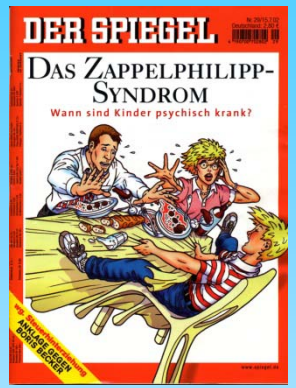
Kernsymptome

- Unaufmerksamkeit
- Motorische Hyperaktivität
- Mangelnde Impulskontrolle

- Beginn in Kindheit
- Nicht Alter, Intelligenz entsprechend
- Dauer (mindestens 6 Monate)
- Beeinträchtigungen in mind. 2 Lebensbereichen
- Nicht durch eine andere psychische Störung erklärbar

Klinische Relevanz

- ADHS ist eine häufige Störung: 3-6%
  - Hyperkinetische Störung: 1-2%
  - Jungen vs. Mädchen: (ca. 3 – 6:1)
- ADHS ist eine chronische Störung
  - 30-60% Persistenz frühes Erwachsenenalter
- ADHS führt oft zu psychosozialen Beeinträchtigungen
  - Z.B. schulische & berufliche Entwicklung, Unfallrisiko, soziale Beziehungen
- Assoziierte Störungen sind der Regelfall
  - Ca. 65-80 % mind. 1 assoziierte Störung
  - > 50 % mindestens 2 a. Störungen



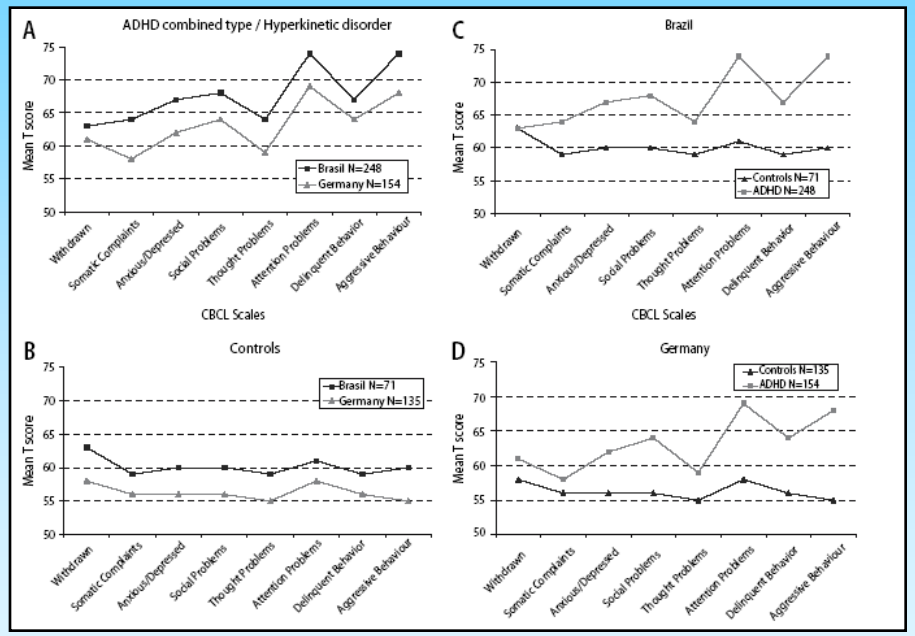
z. B.: Taylor et al., 2004

Eur Arch Psychiatry Clin Neurosci (2007) 257:352–359 DOI 10.1007/s00406-007-0738-y

ORIGINAL PAPER

Veit Roessner · Andreas Becker · Aribert Rothenberger · Luis Augusto Rohde · Tobias Banaschewski

A cross-cultural comparison between samples of Brazilian and German children with ADHD/HD using the Child Behavior Checklist



- In verschiedenen Kulturen gleichen sich Kinder mit ADHS hinsichtlich ihrer Auffälligkeiten

Genetische Risikofaktoren

Familienstudien

- Hohe Prävalenz bei Verwandten
  - Geschwister: 2-4 x häufiger
    - Biederman et al., 1990, 1992; Pauls, 1991
  - Eltern: bis 8 x häufiger
    - Biedermann et al., 1990, 1991; Faraone, et al., 1994, 1995
  - Kinder betroffener Erwachsener: ca. 40-60%
    - Biederman et al., 1995

Adoptionsstudien

Höhere Prävalenz bei biologischen Eltern als bei Adoptiveltern

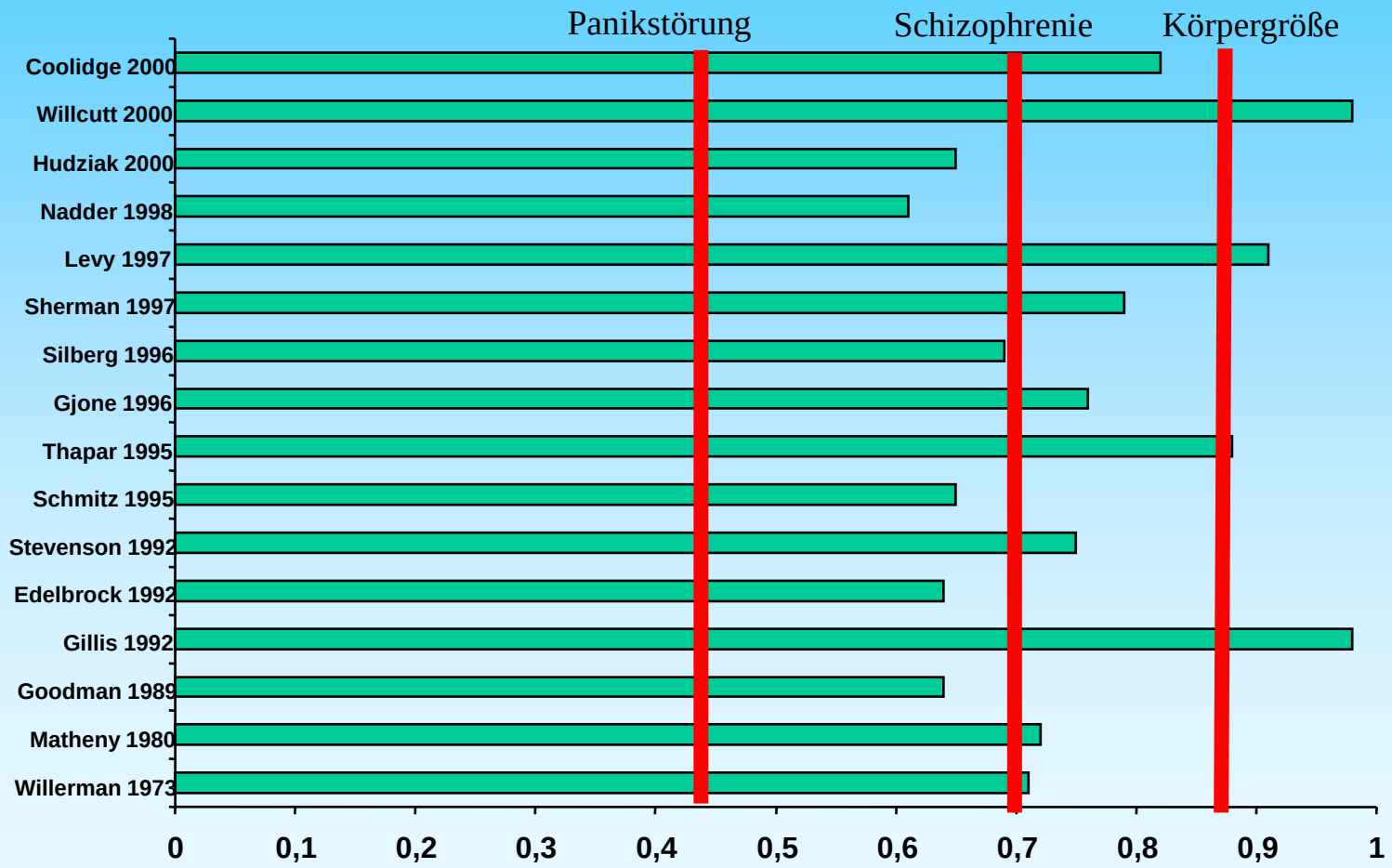
- Cantwell, 1975; Morrison & Stewart, 1973

Höhere Konkordanz bei - getrennt lebenden - biologischen Geschwistern als bei Halbgeschwistern

- Alberts-Corush et al., 1986; Cantwell, 1975; Morrison & Stewart, 1973

Heritabilität

Erblichkeitskoeffizienten: 0.6-0.9, mean = 0,76



Genetische Faktoren sind bedeutsam

Faraone et al., 1998

Kopplungsuntersuchungen

- Replizierte positive Kopplungsbefunde
  - z.B. 5p13, 11q22-25, 17p11
- Aber: keine Region konsistent identifiziert & Mehrzahl der Befunde bislang nicht repliziert

Existenz von Hauptgenen mit starken Effekten unwahrscheinlich

- Überlappende Kopplungsbefunde:
- ADHS und Autismus z. B. 16p, 15q
- ADHS und Legasthenie z.B. 1p, 14q , 13q, 15q 16p, 17q 20q

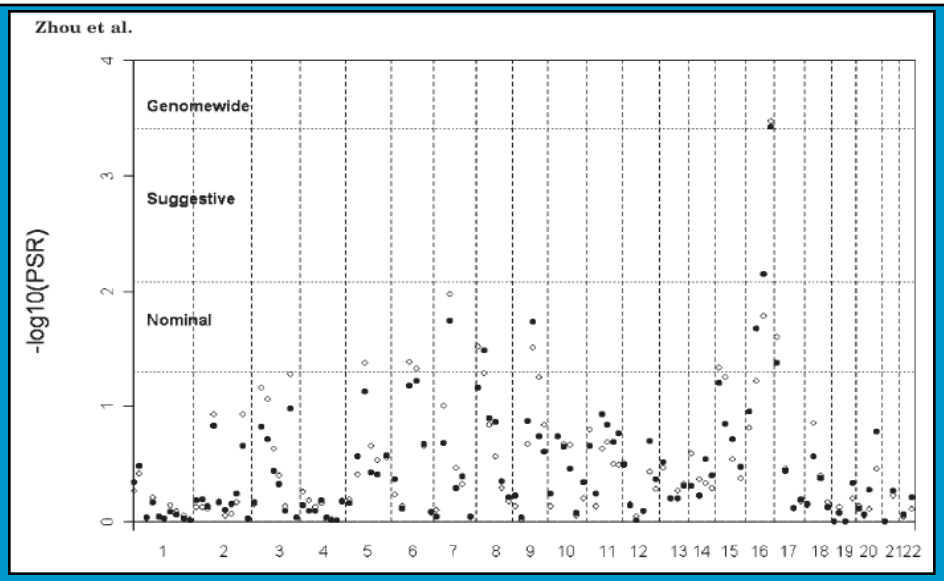
Risikoallele für ADHS könnten pleiotrope Effekte haben

Kopplungsuntersuchungen

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] Johannes Hebebrand,[16] Anke Hinney,[16] Christian Jacob,[18] Klaus Peter Lesch,[18] Sandra K. Loo,[19] Francisco Lopera,[20] James T. McCracken,[19] James J. McGough,[19] Jobst Meyer,[21] Eric Mick,[7] Ana Miranda,[22] Maximilian Muenke1,[4] Fernando Mulas,[23] Stanley F. Nelson,[11] T.Trang Nguyen,[2] Robert D. Oades,[24] Matthew N. Ogdie,[25] Juan David Palacio,[20] David Pineda,[20] Andreas Reif,[18] Tobias J. Renner,[26] Herbert Roeyers,[27] Marcel Romanos,[26] Aribert Rothenberger,[28] Helmut Schäfer,[2] Joseph Sergeant,[29] Richard J. Sinke,[5] Susan L. Smalley,[19,30] Edmund Sonuga-Barke,[1,9,31] Hans-Christoph Steinhausen,[32] Emma van der Meulen,[33] Susanne Walitza,[26] Andreas Warnke,[26] Cathryn M Lewis,[1,12] Stephen V. Faraone,[7,34] and Philip Asherson[1]*



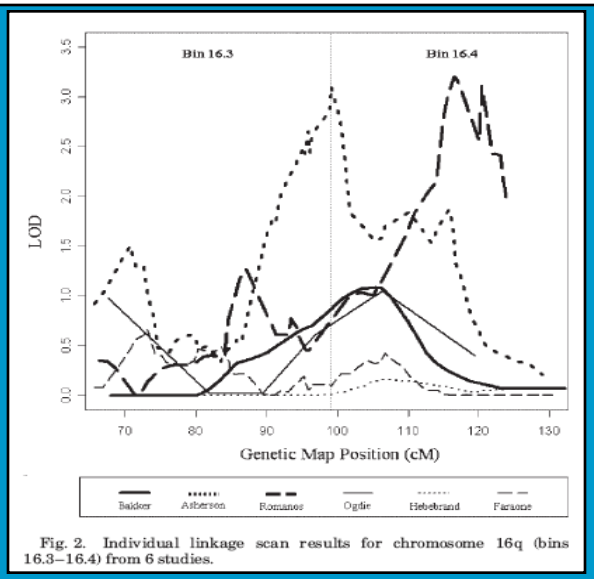


Fig. 2. Individual linkage scan results for chromosome 16q (bins 16.3–16.4) from 6 studies.

Assoziationsuntersuchungen

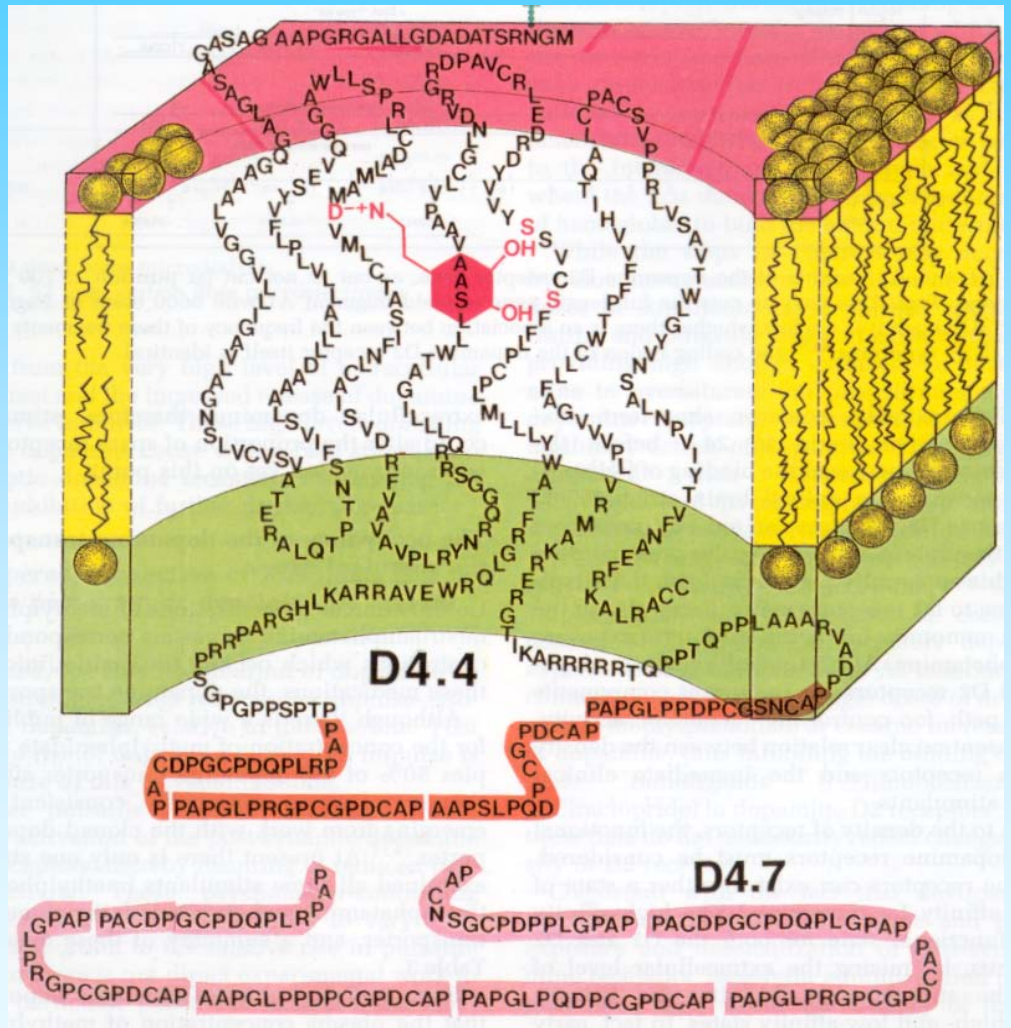
Gene	Study design	Pooled OR	95% CI
Dopamine D4 receptor (exon III VNTR, 7-repeat)	family	1.16	1.03-1.31
Dopamine D4 receptor (exon III VNTR, 7-repeat)	case-control	1.45	1.27-1.65
Dopamine D5 receptor (CA repeat, 148 bp)	family	1.24*	1.12-1.38
Dopamine transporter (VNTR, 10-repeat)	family	1.13	1.03-1.24
Dopamine beta-hydroxylase (TaqI A)	case-control	1.33	1.11-1.59
SNAP25 (T1065G)	family	1.19	1.03-1.38
Serotonin transporter (5HTTLPR long)	case-control	1.31	1.09-1.59
HTR1B (G861C)	family	1.44	1.14-1.83

Table 1. Significant Pooled Odds Ratios for Gene Variants examined in Three or More Case-Control or Family-Based Studies*

Faraone et al., 2005

Dopamin-D_4 Receptor (DRD-4)

- 48-bp VNTR-Polymorphismus im Exon III
  - 7-repeat Allel assoziiert mit Neugierverhalten
  - abgeschwächte Sensitivität des DRD4-7 Rezeptors



Molecular Psychiatry (2006) 11, 934–953

www.nature.com/mp

ORIGINAL ARTICLE

The analysis of 51 genes in DSM-IV combined type attention deficit hyperactivity disorder: association signals in *DRD4, DAT1* and 16 other genes

K Brookes[1], X Xu[1], W Chen[1], K Zhou[1], B Neale[1], N Lowe[2], R Aneey[2], B Franke[3], M Gill[2], R Ebstein[4], J Buitelaar[3], P Sham[1], D Campbell[1], J Knight[1], P Andreou[1], M Altink[3], R Arnold[5], F Boer[6], C Buschgens[3], L Butler[2], H Christiansen[7], L Feldman[8], K Fleischman[1], E Fliers[3], R Howe-Forbes[1], A Goldfarb[8], A Heise[9], I Gabriëls[10], I Korn-Lubetzki[11], R Marco[12], S Medad[8], R Minderaa[13], F Mulas[12], U Müller[14], A Mulligan[2], K Rabin[8], N Rommelse[15], V Sethna[1], J Sorohan[2], H Uebel[9], L Psychogiou[16], A Weeks[16], R Barrett[16], I Craig[1], T Banaschewski[9], E Sonuga-Barke[16], J Eisenberg[8], J Kuntsi[1], I Manor[8], P McGuffin[1], A Miranda[12], RD Oades[7], R Plomin[1], H Roeyers[10], A Rothenberger[9], J Sergeant[15], H-C Steinhausen[14], E Taylor[1], M Thompson[16], SV Faraone[17], P Asherson[1] and L Johansson[1]

Table 2 Table of results for the 18 genes found to be suggestive of association in the SNP screen

Gene	*Nominal* P-*value*	*T*	*NT*	*OR*	*Global* P-*value*	*P_SUM Statistic*
TPH2	0.003	207	151	1.37	0.036	0.106
ARRB2	0.004	103	66	1.56	0.022	0.209
DAT1	0.005	349	278	1.26	0.119	0.014
PNMT	0.008	70	42	1.67	0.012	0.024
SLC9A9	0.01	74	46	1.61	0.485	0.114
NET	0.012	133	95	1.4	0.349	0.786
ADRB2	0.013	210	162	1.3	0.088	0.485
HES1	0.016	300	244	1.23	0.076	0.096
ADRA1A	0.017	283	229	1.24	0.443	0.387
PER2	0.017	31	15	2.07	0.124	0.419
MAOA	0.02	175	134	1.31	0.082	—
SNAP25	0.035	155	120	1.29	0.529	0.198
DDC	0.039	161	126	1.28	0.537	0.597
FADS2	0.039	284	237	1.2	0.389	0.727
SYP	0.045	180	114	1.25	0.034	—
CHRNA4	0.05	116	88	1.32	0.503	0.663
HTR1E	0.051	75	53	1.42	0.509	0.214
DRD4	0.055	34	20	1.7	0.199	0.321

- 18 Gene signifikant assoziiert, inklusive DRD4 & DAT1
- TPH2, ARRB2, SYP, DAT1, ADRB2, HES1, MAOA & PNMT

Genetische Heterogenität

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]*

ADHS + Störung des Sozialverhaltens

genetisch verschieden von

ADHS - Störung des Sozialverhaltens?

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.

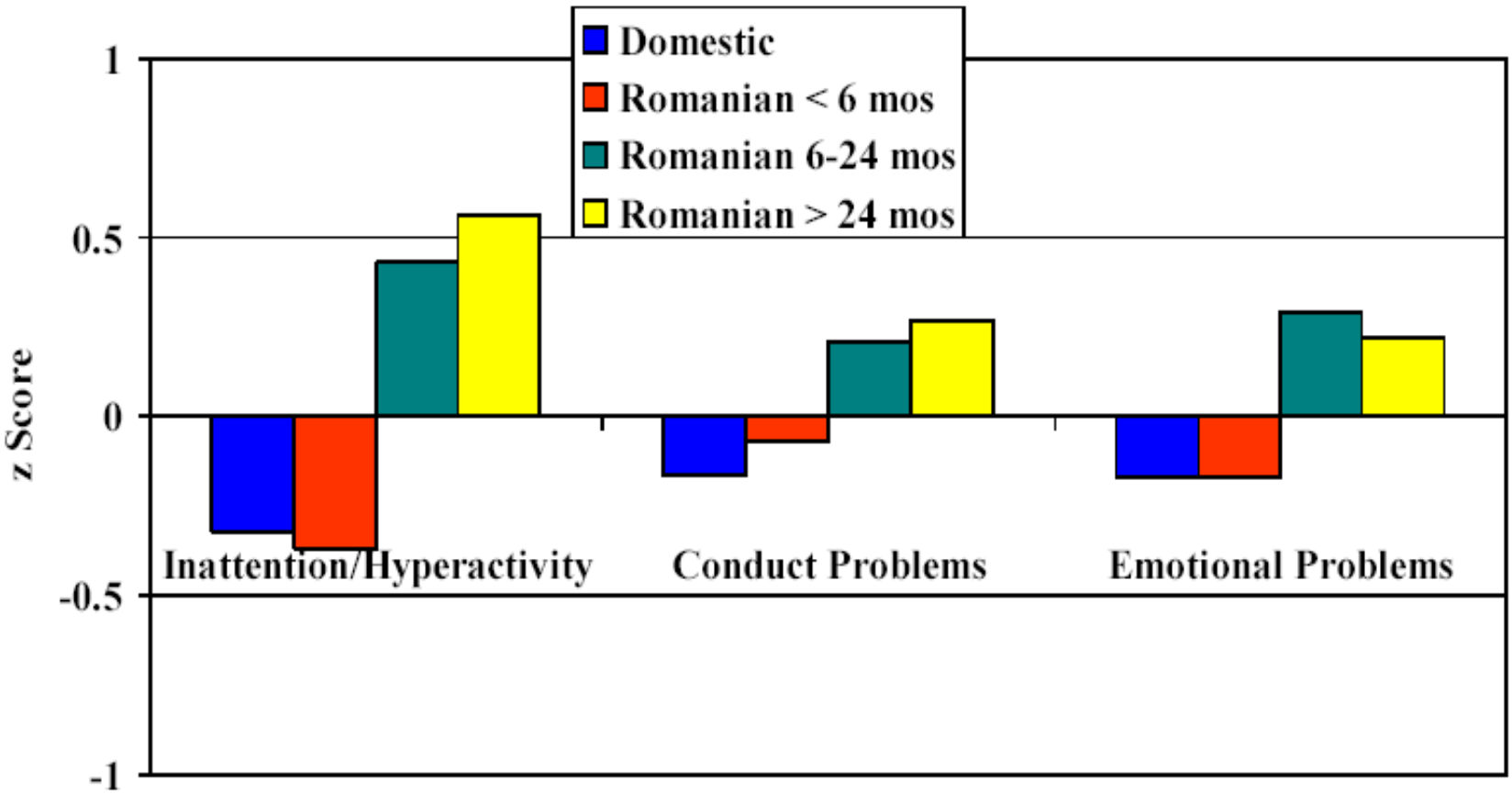
(Am J Psychiatry 2007; 164:674–677)

Umweltrisiken

Exogene Risikofaktoren

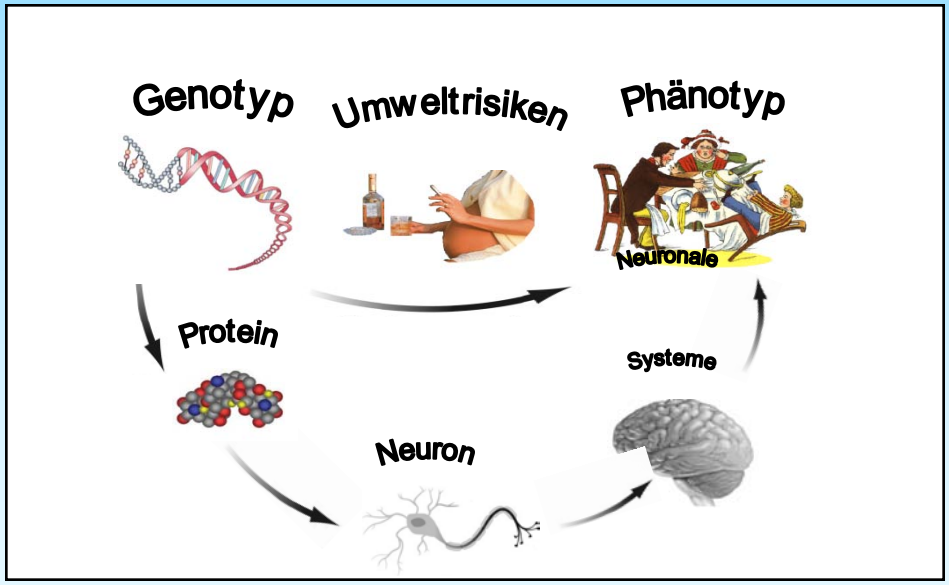
- Schwangerschafts- und Geburtskomplikationen
- Extreme Frühgeburt und niedriges Geburtsgewicht
- Infektionen & traumatische Hirnschädigungen
  - (z.B. Enzephalitis, Gehirntrauma)
- Toxine
  - (z.B. pränatale Alkohol- und Nikotinexposition, chronische Bleiexposition)
- Ungünstige psychosoziale Umstände
  - (z.B. frühe Deprivation)
- Allergien & Nahrungsmittelunverträglichkeiten spielen eine untergeordnete Rolle

Frühkindliche Deprivation



Kreppner, J.M. (2001). *J Abnorm Child Psychol*, 29: 513-528.

Gen – Umwelt Interaktionen



Gen – Umwelt Interaktionen
Psychosoziale Belastung & 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

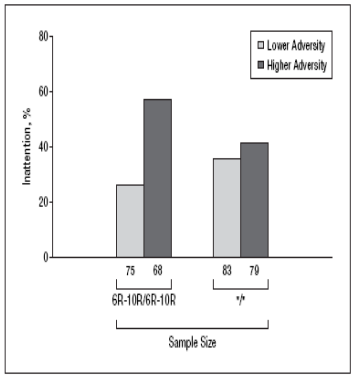


Figure 1. Percentage of inattention in adolescents grouped by the presence or absence of the *DAT1* 6-repeat allele–10-repeat allele (6R-10R) haplotype and exposure to psychosocial adversity. The 6R-10R/6R-10R haplotype exposed to higher adversity is significantly different from all other groups. */*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

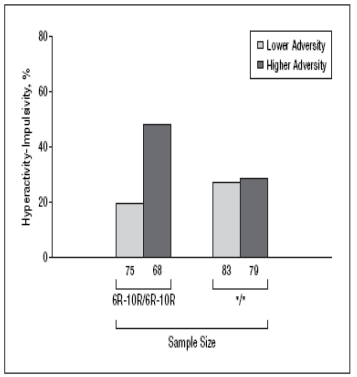


Figure 2. Percentage of hyperactivity-impulsivity in adolescents grouped by the presence or absence of the *DAT1* 6-repeat allele–10-repeat allele (6R-10R) haplotype and exposure to psychosocial adversity. The 6R-10R/6R-10R haplotype exposed to higher adversity is significantly different from all other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

Gen – Umwelt Interaktionen
Alkohol & DAT

A Common Haplotype of the Dopamine Transporter Gene Associated With Attention-Deficit/Hyperactivity Disorder and Interacting With Maternal Use of Alcohol During Pregnancy

Keeley-Joanne Brookes, BSc; Jon Mill, PhD; Camilla Guindalini, BSc; Sarah Curran, MRCPsych, PhD; Xiaohui Xu, MD; Jo Knight, PhD; Chih-Ken Chen, MD, PhD; Yu-Shu Huang, MD; Vaheshta Sethna, BSc; Eric Taylor, FRCP, FRCPsych, PhD; Wai Chen, MRCPsych; Gerome Breen, PhD; Philip Asherson, MRCPsych, PhD

Context: Attention-deficit/hyperactivity disorder (ADHD) is a common heritable childhood behavioral disorder. Identifying risk factors for ADHD may lead to improved intervention and prevention. The dopamine transporter gene (*DAT1*) is associated with ADHD in several studies, with an average 1.2 odds ratio and evidence of heterogeneity across data sets.

Objective: To investigate sources of heterogeneity by refining the *DAT1* association using additional markers and investigating gene-environment interaction between *DAT1* and maternal use of alcohol and tobacco during pregnancy.

Design: Prospective study.

Setting and Patients: Children with ADHD from child behavior clinics in the southeast of England and in the Taipei area of Taiwan.

Interventions: Within-family tests of association using 2 repeat polymorphisms in the 3′ untranslated region and intron 8 plus additional markers in the English sample.

Main Outcome Measures: Transmission ratios of risk alleles from heterozygote parents to affected offspring and comparison of the transmission ratios in high- and low-exposure groups for the environmental variables.

Results: A novel association was identified between ADHD, the intron 8 polymorphism, and a specific risk haplotype in both English and Taiwanese samples. The risk haplotype showed significant interactions with maternal use of alcohol during pregnancy.

Conclusions: The identification of a common haplotype in 2 independent populations is an important step toward identifying functionally significant regions of *DAT1*. Interaction between *DAT1* genotypes and maternal use of alcohol during pregnancy suggests that *DAT1* moderates the environmental risk and has implications for the prevention of ADHD. Further studies are required to delineate the precise causal risk factor involved in this interaction.

Arch Gen Psychiatry. 2006;63:74-81

Gen – Umwelt Interaktionen
Nikotin & DAT

Kahn et al. 2003

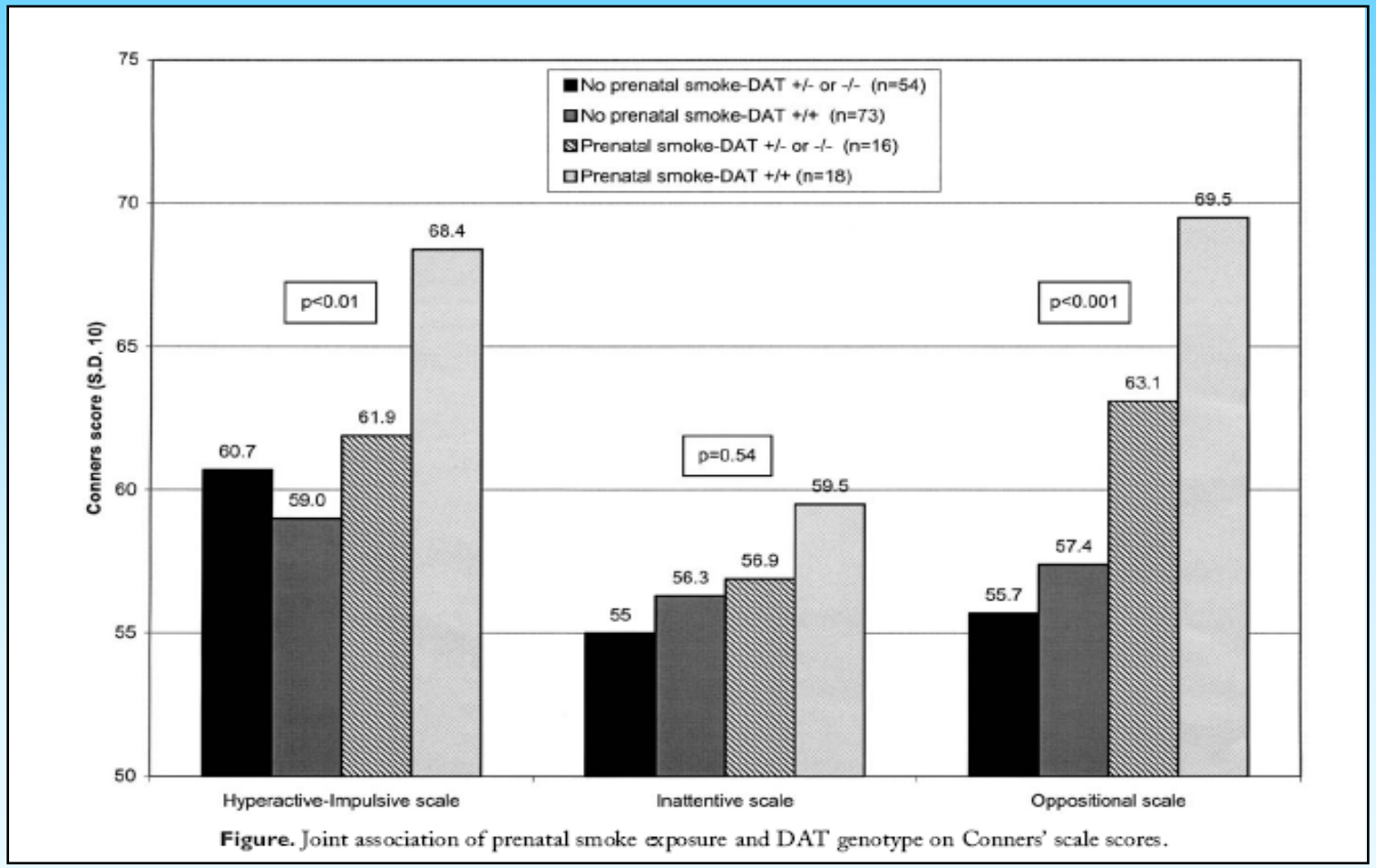
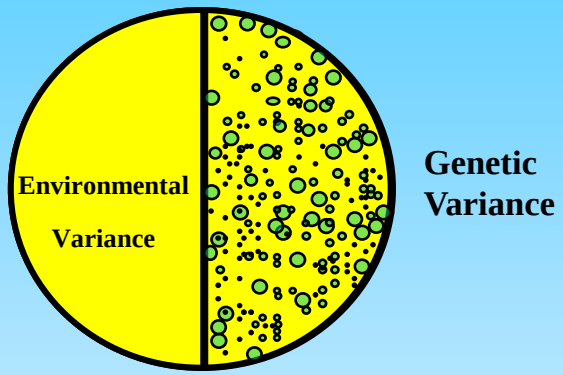


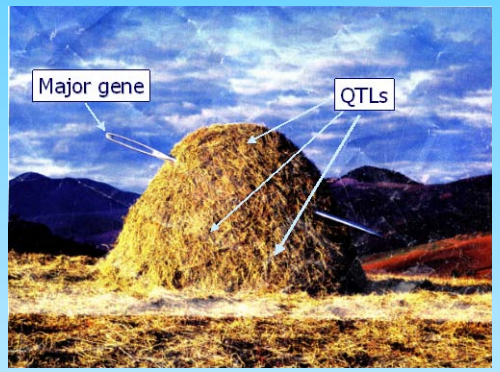
Figure. Joint association of prenatal smoke exposure and DAT genotype on Conners' scale scores.

480-bp DAT allele (DAT +/+)

Zusammenfassung

- Genetische Faktoren sind bedeutsam





- **Aber**: wahrscheinlich multiple Gene mit jeweils kleinem Effekt
- Risiko stammt von normalen Genvarianten, nicht von seltenen Mutationen
- Risikoallele nicht spezifisch
- Umweltfaktoren, Gen-Gen- und Gen-Umweltinteraktionen relevant
- Genetische Heterogenität?
- Epigenetische Prozesse
- Genetische Kontinuität über den Entwicklungsverlauf?

Vielen Dank für

Ihre Aufmerksamkeit !