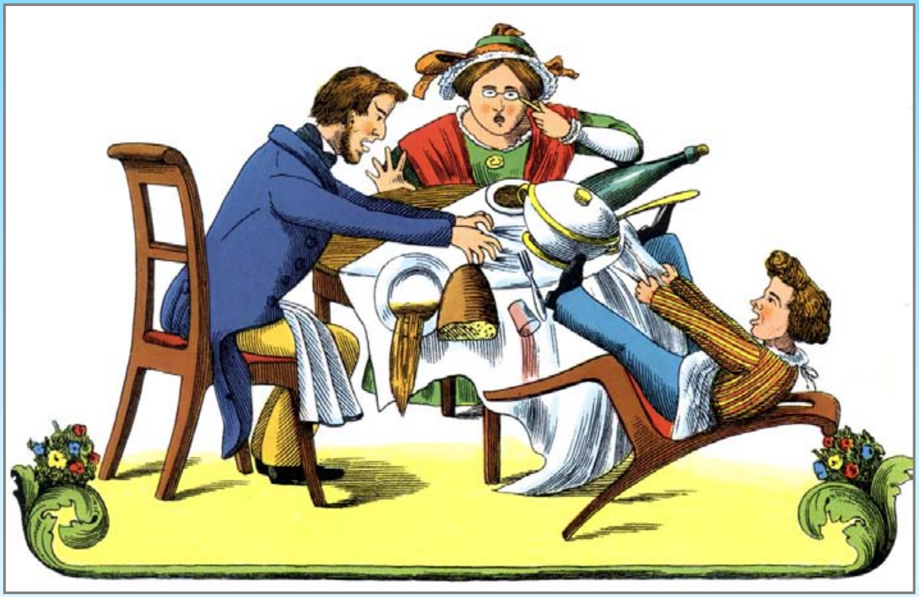
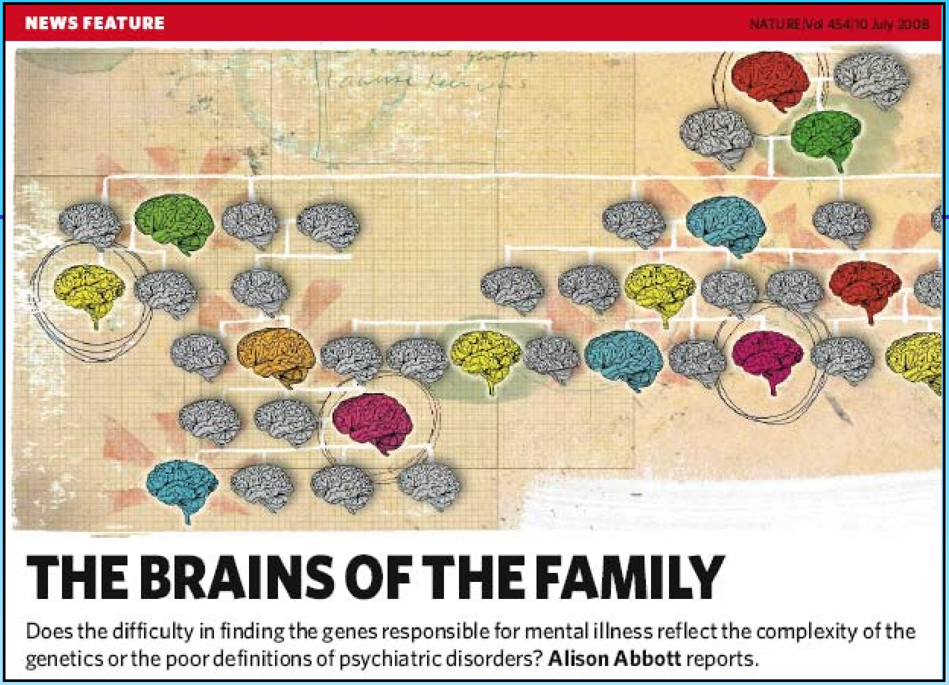
Neurobiologische Grundlagen der ADHS – Update
Teil 2



Tobias Banaschewski

Klinik für Psychiatrie und Psychotherapie des Kindes- und Jugendalters, Zentralinstitut für Seelische Gesundheit, Mannheim

Korrelate

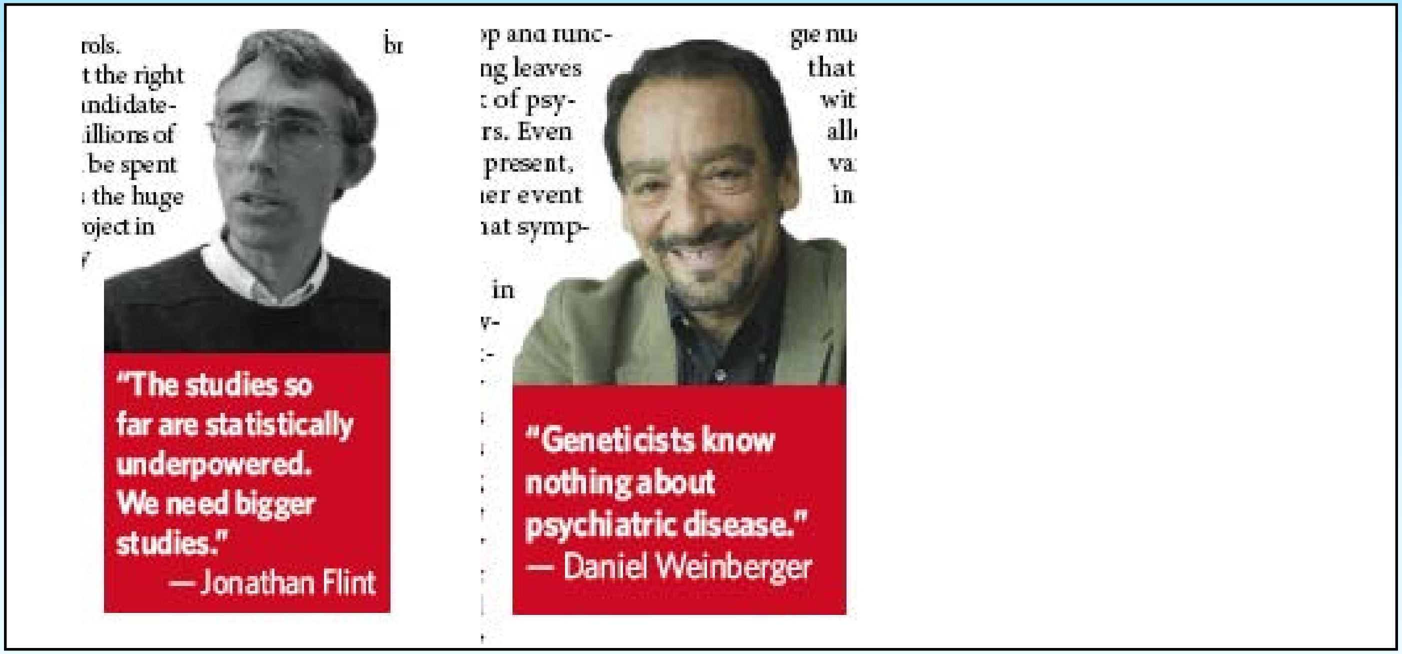


NEWS FEATURE

NATURE|Vol 454|10 July 2008

THE BRAINS OF THE FAMILY

Does the difficulty in finding the genes responsible for mental illness reflect the complexity of the genetics or the poor definitions of psychiatric disorders? **Alison Abbott** reports.



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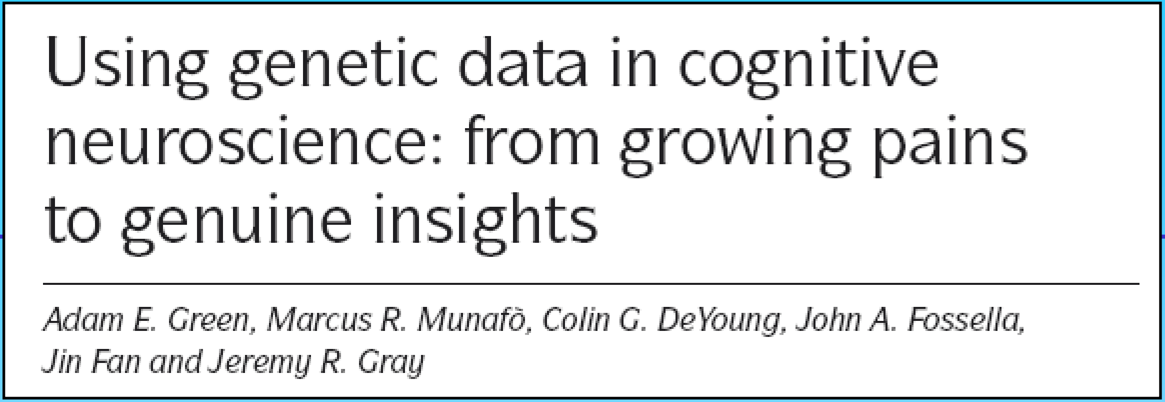
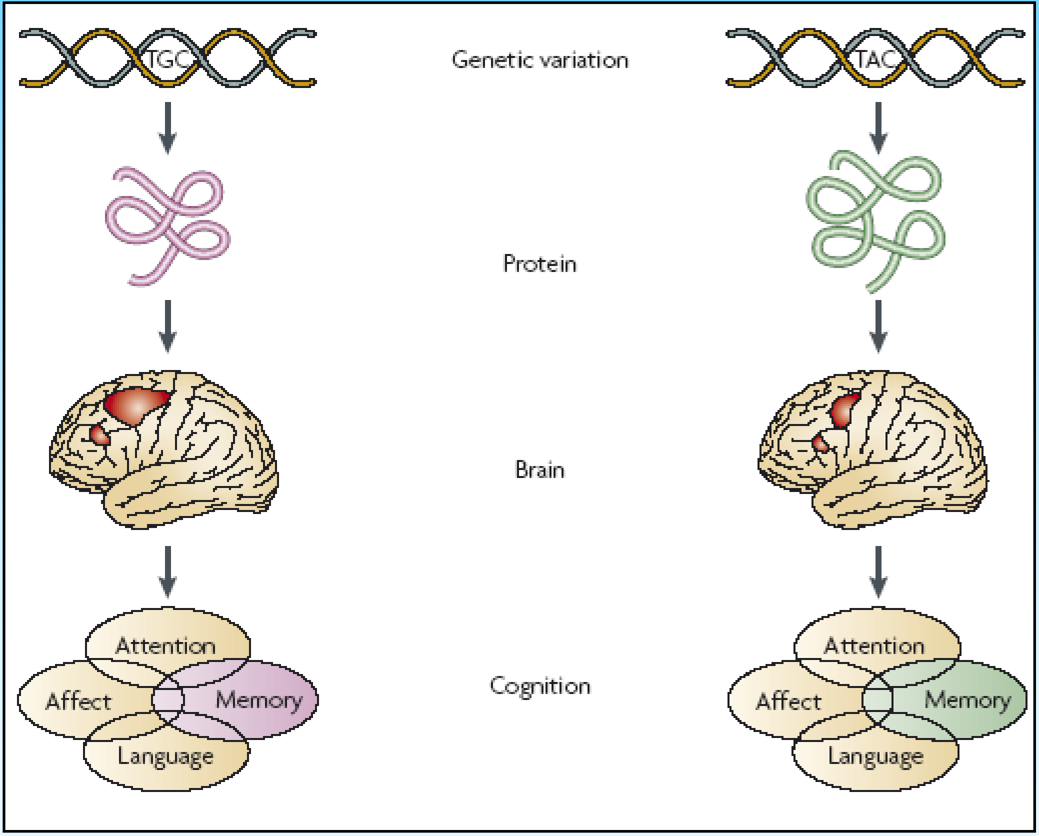
"The studies so far are statistically underpowered. We need bigger studies."
— Jonathan Flint

"Geneticists know nothing about psychiatric disease."
— Daniel Weinberger

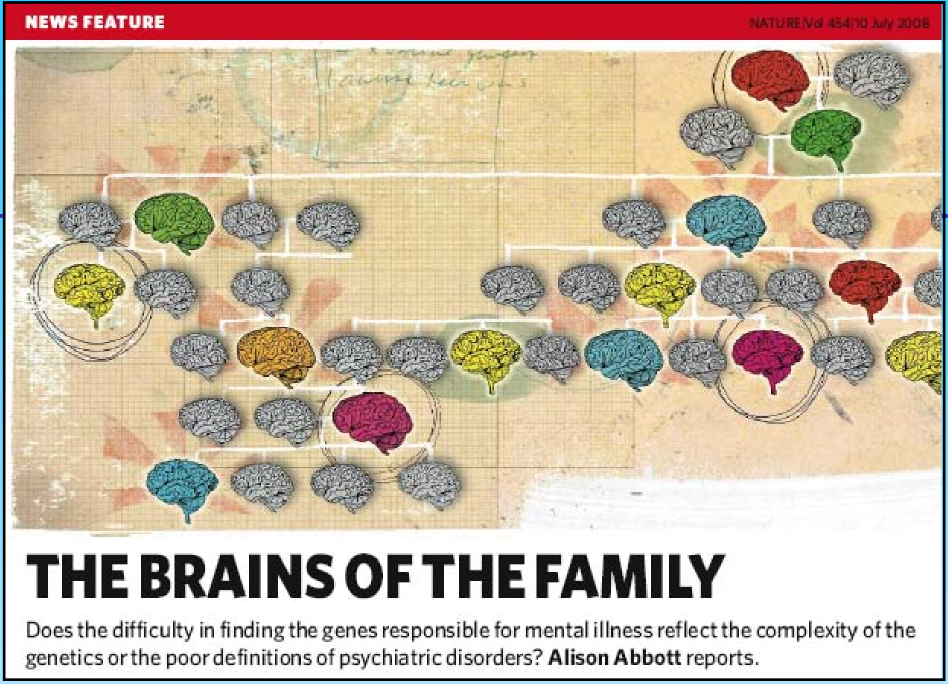


Using genetic data in cognitive neuroscience: from growing pains to genuine insights

Adam E. Green, Marcus R. Munafò, Colin G. DeYoung, John A. Fossella, Jin Fan and Jeremy R. Gray


TGC
Genetic variation
TAC
Protein
Brain
Attention
Affect
Memory
Language
Cognition
Attention
Affect
Memory
Language

NATURE REVIEWS | NEUROSCIENCE VOLUME 9 | SEPTEMBER 2008



NEWS FEATURE

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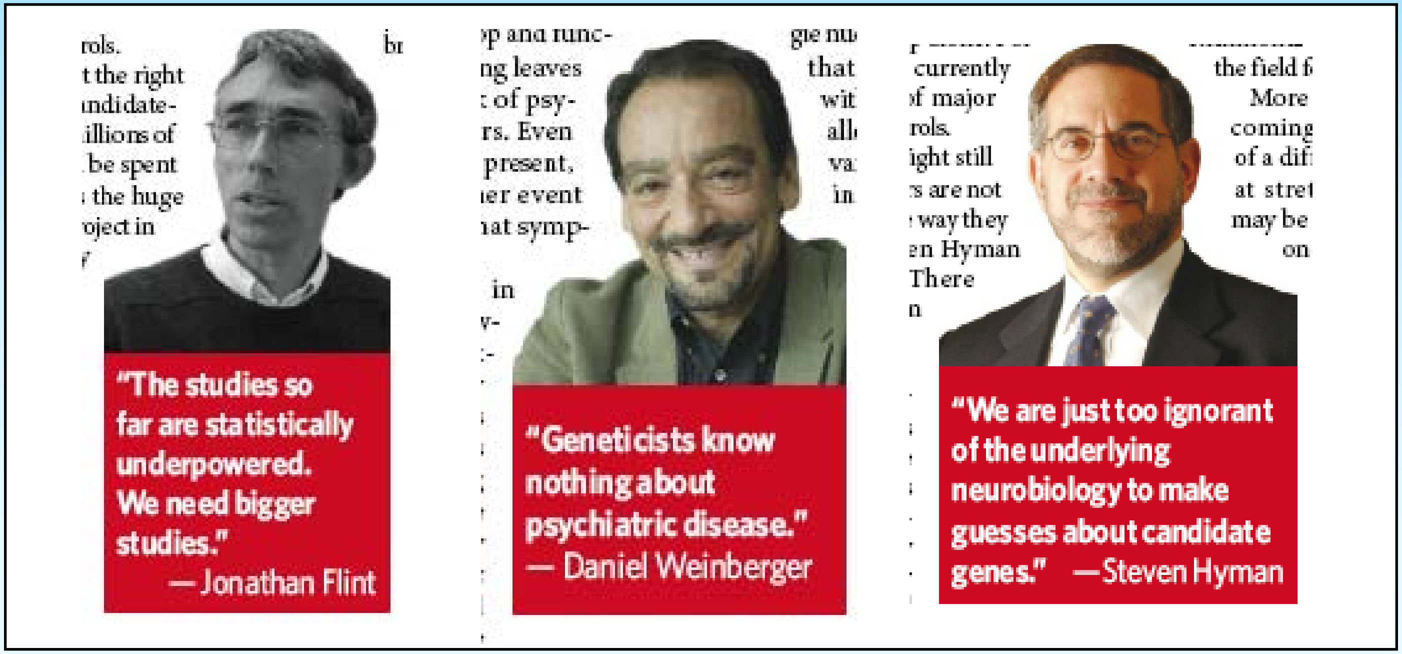


"The studies so far are statistically underpowered. We need bigger studies." — Jonathan Flint

"Geneticists know nothing about psychiatric disease." — Daniel Weinberger

"We are just too ignorant of the underlying neurobiology to make guesses about candidate genes." —Steven Hyman

Neuroanatomische Korrelate

Neuroanatomie

- Gehirn kleiner (~4%), insb. Frontallappen rechts (~8%)
- Basalganglien kleiner (~6%)
- Cerebellum kleiner (~12%)

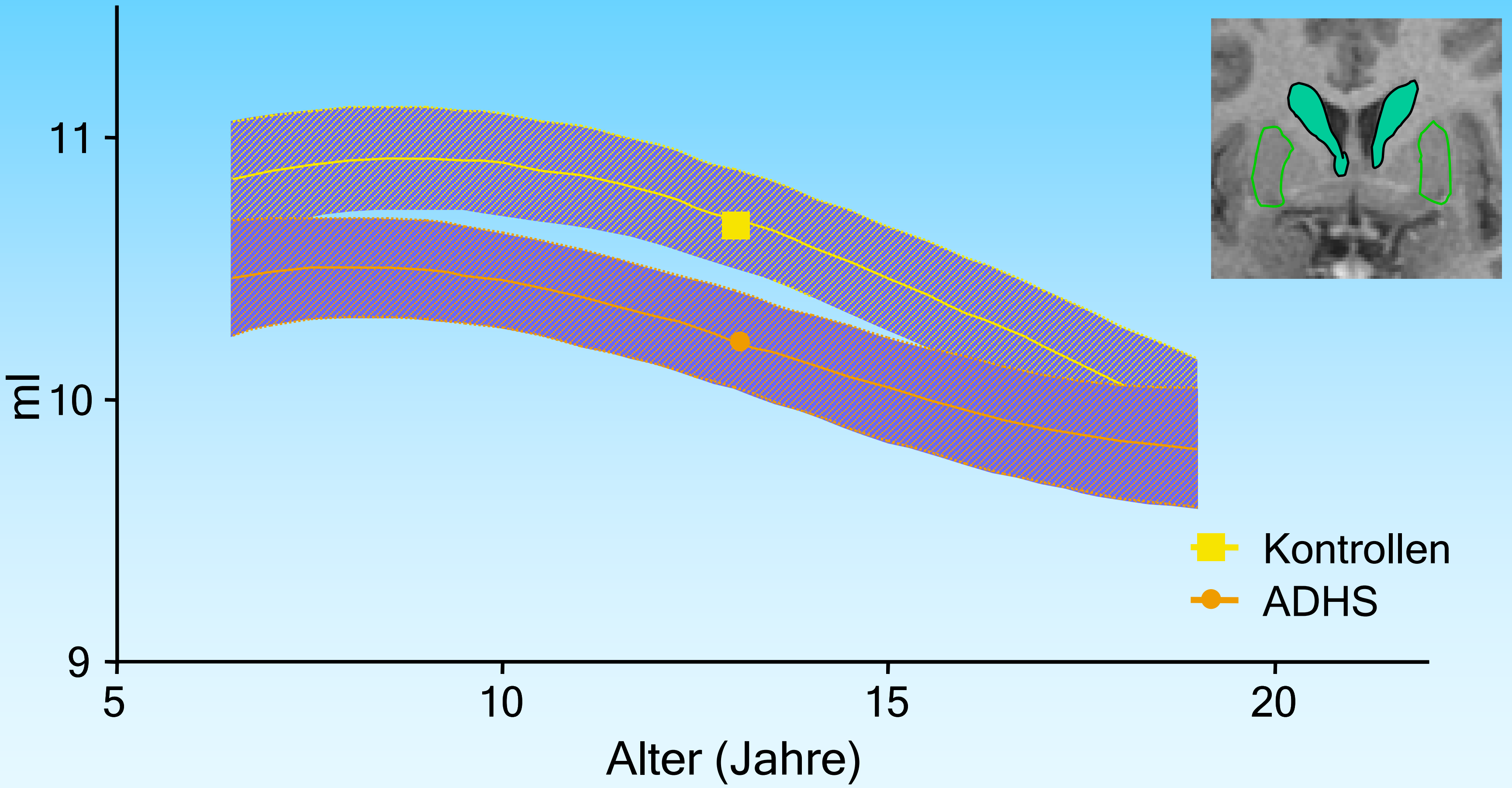
- Volumetrische Unterschiede
  - Manifestieren sich früh (~6 J.)
  - Korrelieren mit ADHS-Schweregrad
  - Unabhängig von der Stimulantienbehandlung

Vor allem Fronto-striatale und cerebelläre Abweichungen

z.B. Giedd et al., 2001, Castellanos et al., 2002

Neuroanatomie

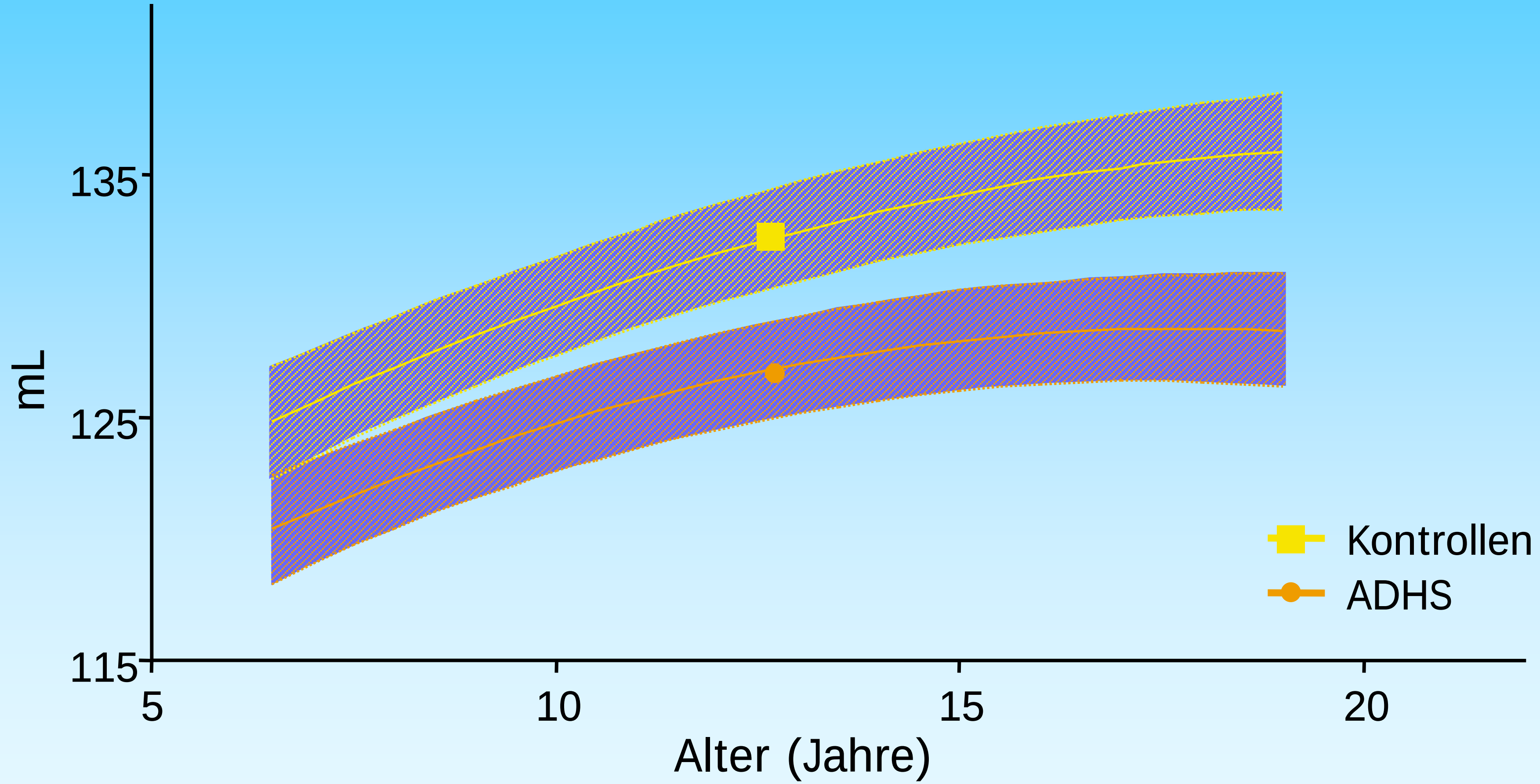
Caudatusvolumen



Castellanos et al., 2002

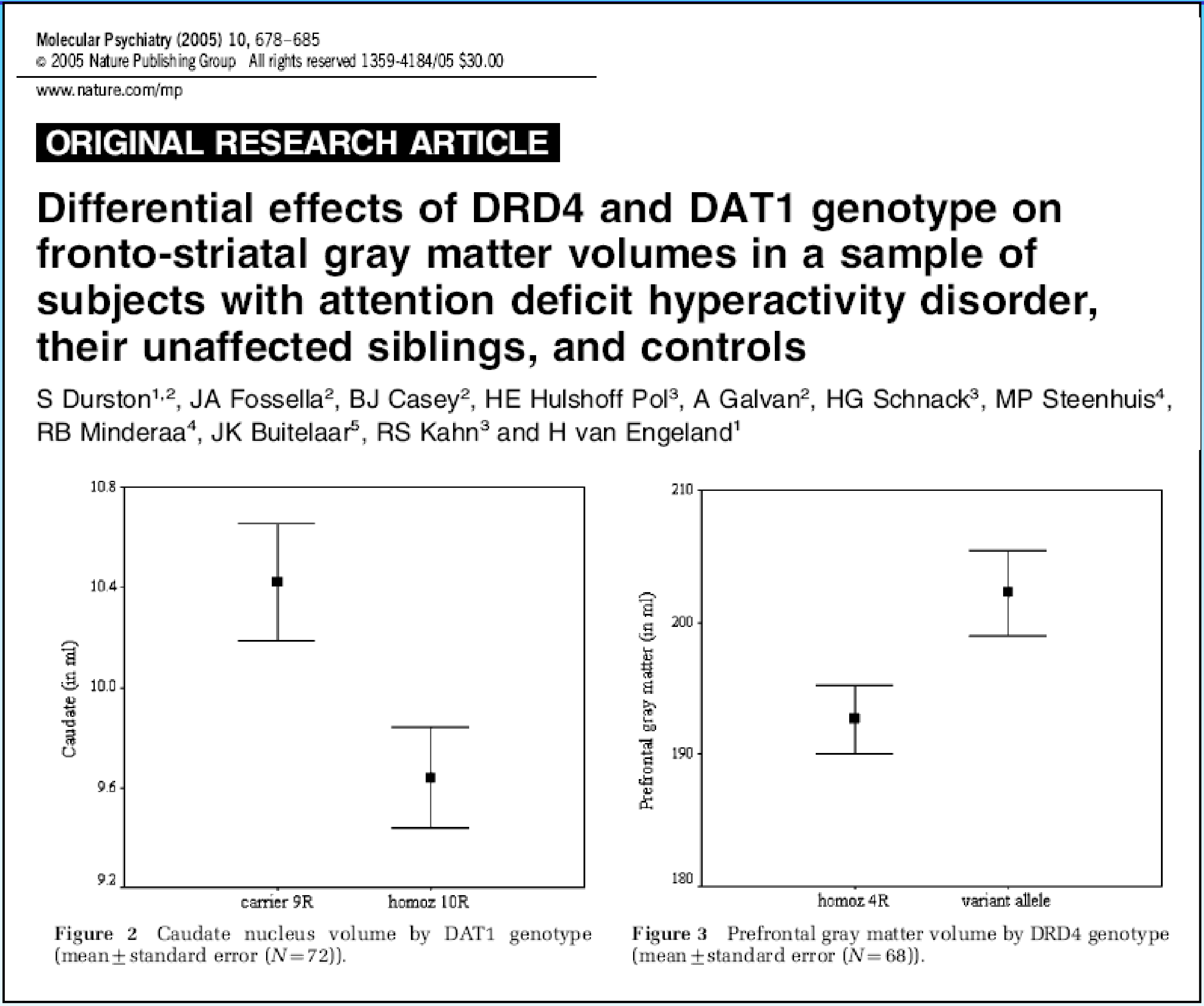
Neuroanatomie

Cerebelläres Volumen



Castellanos et al., 2002

Gen – Struktur - Relationen



Molecular Psychiatry (2005) 10, 678–685

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www.nature.com/mp

ORIGINAL RESEARCH ARTICLE

Differential effects of DRD4 and DAT1 genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls

S Durston[1,2], JA Fossella[2], BJ Casey[2], HE Hulshoff Pol[3], A Galvan[2], HG Schnack[3], MP Steenhuis[4], RB Minderaa[4], JK Buitelaar[5], RS Kahn[3] and H van Engeland[1]

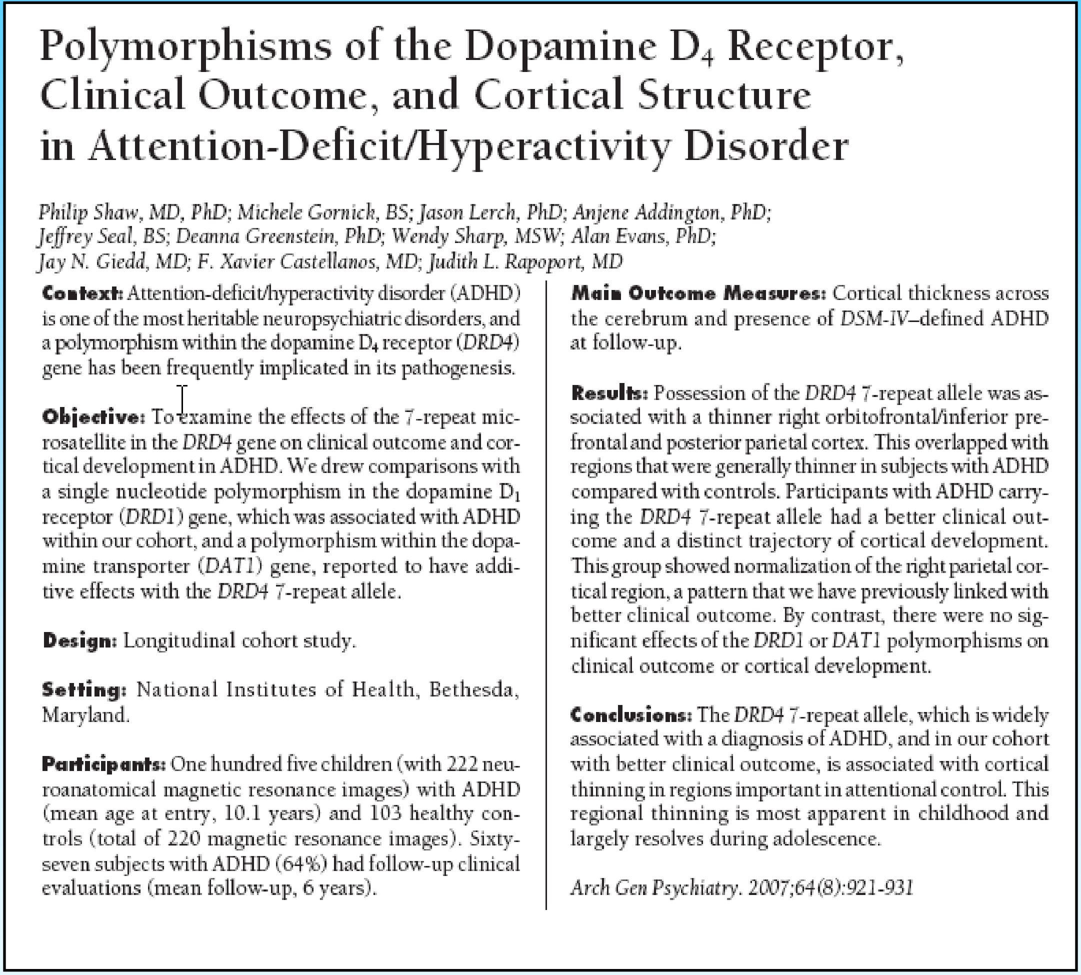
10.8
10.4
10.0
9.6
9.2
Caudate (in ml)
carrier 9R
homoz 10R

Figure 2 Caudate nucleus volume by DAT1 genotype (mean ± standard error ($N = 72$)).

210
200
190
180
Prefrontal gray matter (in ml)
homoz 4R
variant allele

Figure 3 Prefrontal gray matter volume by DRD4 genotype (mean ± standard error ($N = 68$)).

Gen – Struktur - Relationen



Polymorphisms of the Dopamine D₄ Receptor, Clinical Outcome, and Cortical Structure in Attention-Deficit/Hyperactivity Disorder

Philip Shaw, MD, PhD; Michele Gornick, BS; Jason Lerch, PhD; Anjene Addington, PhD;
Jeffrey Seal, BS; Deanna Greenstein, PhD; Wendy Sharp, MSW; Alan Evans, PhD;
Jay N. Giedd, MD; F. Xavier Castellanos, MD; Judith L. Rapoport, MD

Context: Attention-deficit/hyperactivity disorder (ADHD) is one of the most heritable neuropsychiatric disorders, and a polymorphism within the dopamine D_4 receptor (*DRD4*) gene has been frequently implicated in its pathogenesis.

Objective: To examine the effects of the 7-repeat microsatellite in the *DRD4* gene on clinical outcome and cortical development in ADHD. We drew comparisons with a single nucleotide polymorphism in the dopamine D_1 receptor (*DRD1*) gene, which was associated with ADHD within our cohort, and a polymorphism within the dopamine transporter (*DAT1*) gene, reported to have additive effects with the *DRD4* 7-repeat allele.

Design: Longitudinal cohort study.

Setting: National Institutes of Health, Bethesda, Maryland.

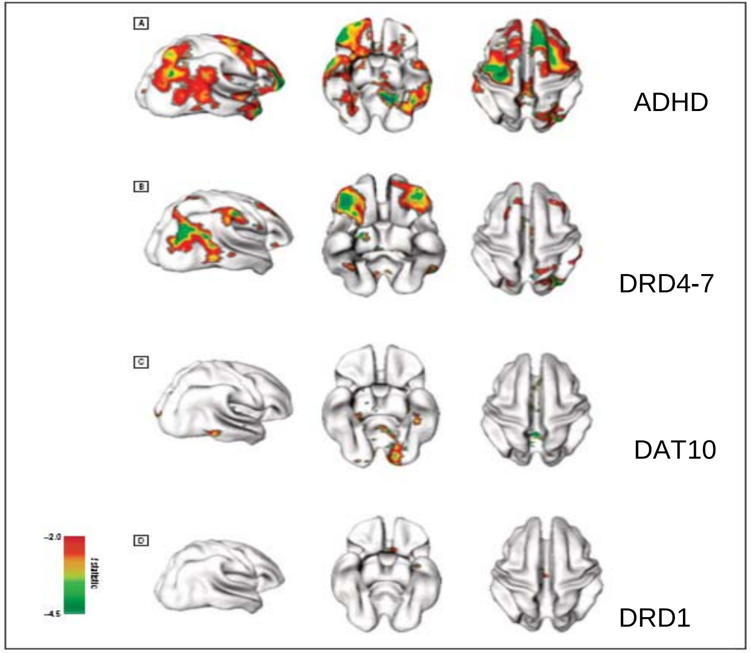
Participants: One hundred five children (with 222 neuroanatomical magnetic resonance images) with ADHD (mean age at entry, 10.1 years) and 103 healthy controls (total of 220 magnetic resonance images). Sixty-seven subjects with ADHD (64%) had follow-up clinical evaluations (mean follow-up, 6 years).

Main Outcome Measures: Cortical thickness across the cerebrum and presence of *DSM-IV*–defined ADHD at follow-up.

Results: Possession of the *DRD4* 7-repeat allele was associated with a thinner right orbitofrontal/inferior prefrontal and posterior parietal cortex. This overlapped with regions that were generally thinner in subjects with ADHD compared with controls. Participants with ADHD carrying the *DRD4* 7-repeat allele had a better clinical outcome and a distinct trajectory of cortical development. This group showed normalization of the right parietal cortical region, a pattern that we have previously linked with better clinical outcome. By contrast, there were no significant effects of the *DRD1* or *DAT1* polymorphisms on clinical outcome or cortical development.

Conclusions: The *DRD4* 7-repeat allele, which is widely associated with a diagnosis of ADHD, and in our cohort with better clinical outcome, is associated with cortical thinning in regions important in attentional control. This regional thinning is most apparent in childhood and largely resolves during adolescence.

Arch Gen Psychiatry. 2007;64(8):921-931



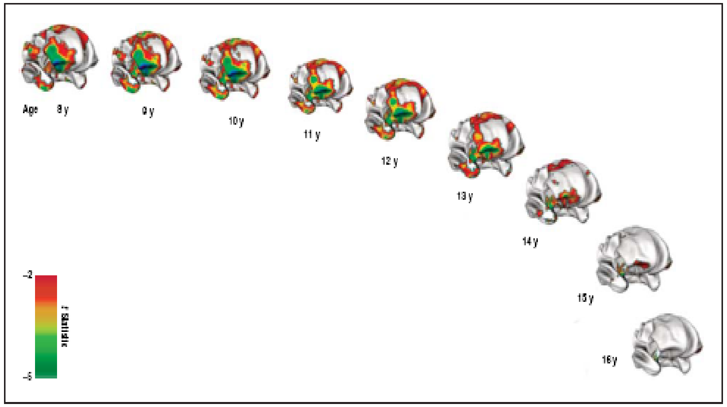
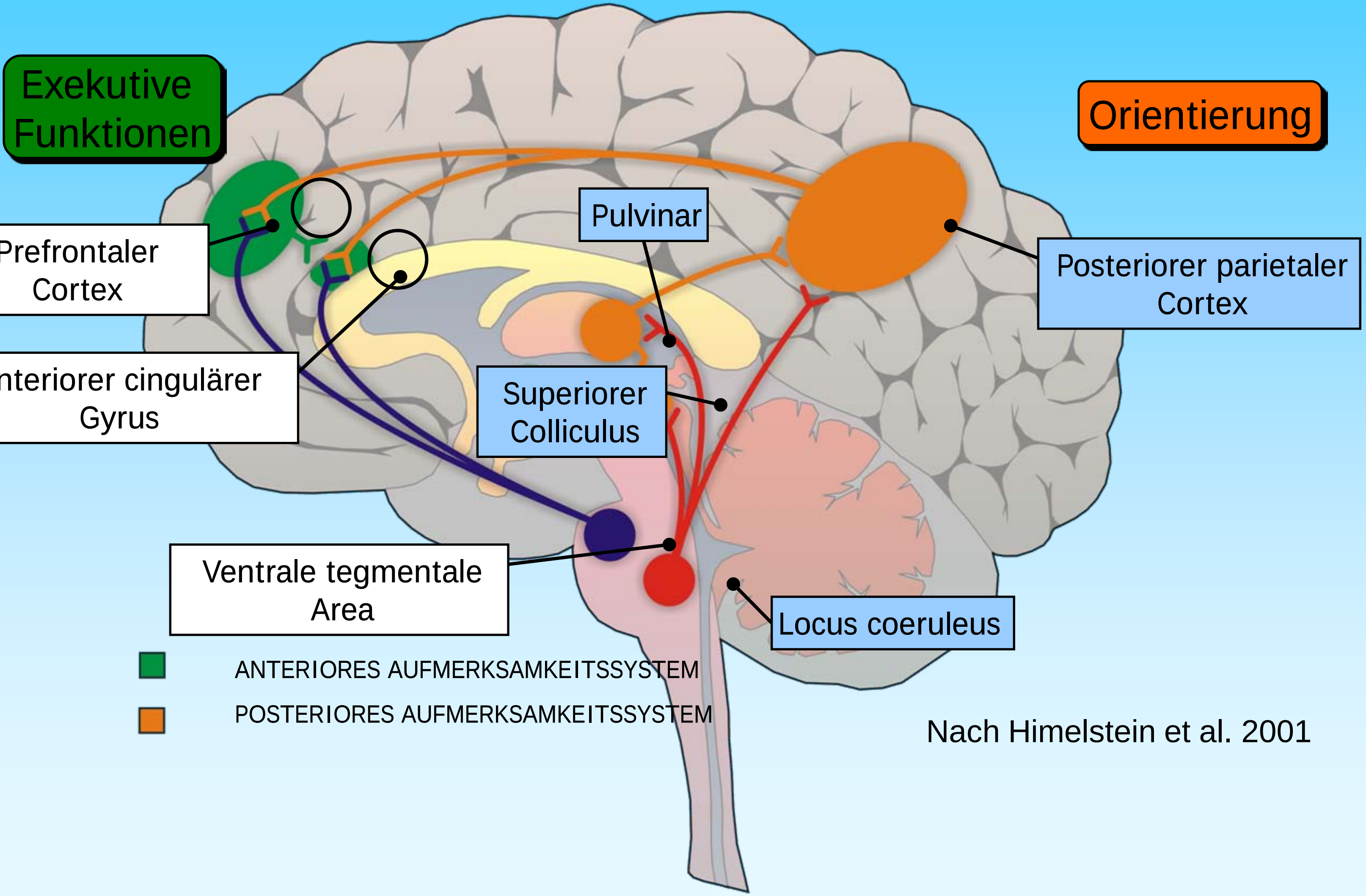


Figure 5. Cortical thinning at baseline in attention-deficit/hyperactivity disorder (ADHD) carriers of the 7-repeat allele corrects with age. Contrast between ADHD carriers and healthy controls without the 7-repeat allele from age 8 years through 16 years illustrating the resolution of regional cortical thinning with age (contrasts set at $t > 2$).

Neurochemische Korrelate

Neurochemie


Exekutive Funktionen
Orientierung
Prefrontaler Cortex
Anteriorer cingulärer Gyrus
Pulvinar
Posteriorer parietaler Cortex
Superiorer Colliculus
Ventrale tegmentale Area
Locus coeruleus
🟩 ANTERIORES AUFMERKSAMKEITSSYSTEM
🟧 POSTERIORES AUFMERKSAMKEITSSYSTEM

Nach Himelstein et al. 2001

Dysregulation dopaminerger & noradrenerger Transmittersysteme

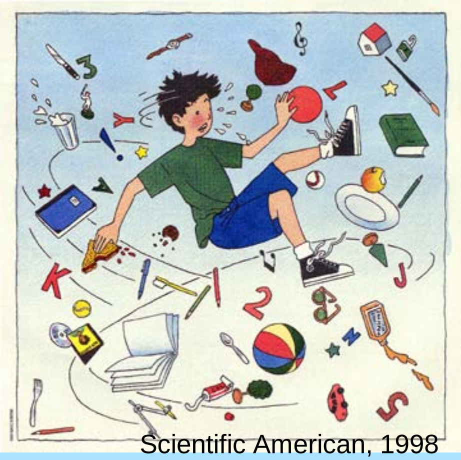
z. B. Arnsten, 2001; Goldman-Racik et al., 2004

Neuropsychologische Korrelate

Neuropsychologie

Störung exekutiver Funktionen

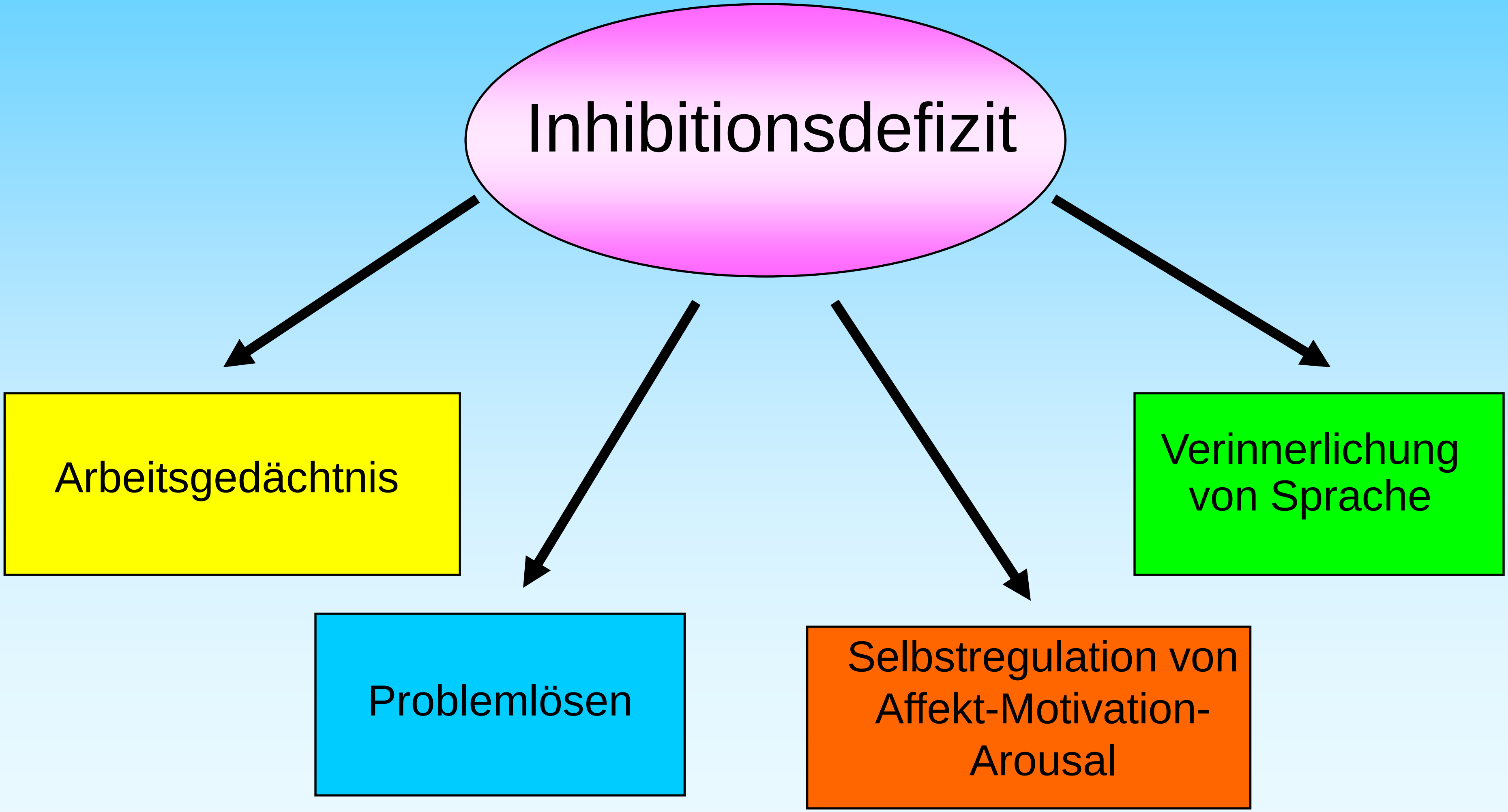
- Hemmung (motorisch, kognitiv + emotional)
- Planungsfähigkeit
- Arbeitsgedächtnis
- Aufmerksamkeit & Flexibilität



Scientific American, 1998

z. .B.: Nigg et al., 2005; Doyle et al., 2005

ADHS - primäres Inhibitionsdefizit?



Inhibitionsdefizit

Arbeitsgedächtnis

Problemlösen

Selbstregulation von Affekt-Motivation-Arousal

Verinnerlichung von Sprache

Barkley, 1997, 1998

Neuropsychologie

Störung exekutiver Funktionen

- Hemmung (motorisch, kognitiv + emotional)
- Planungsfähigkeit
- Arbeitsgedächtnis
- Aufmerksamkeit & Flexibilität

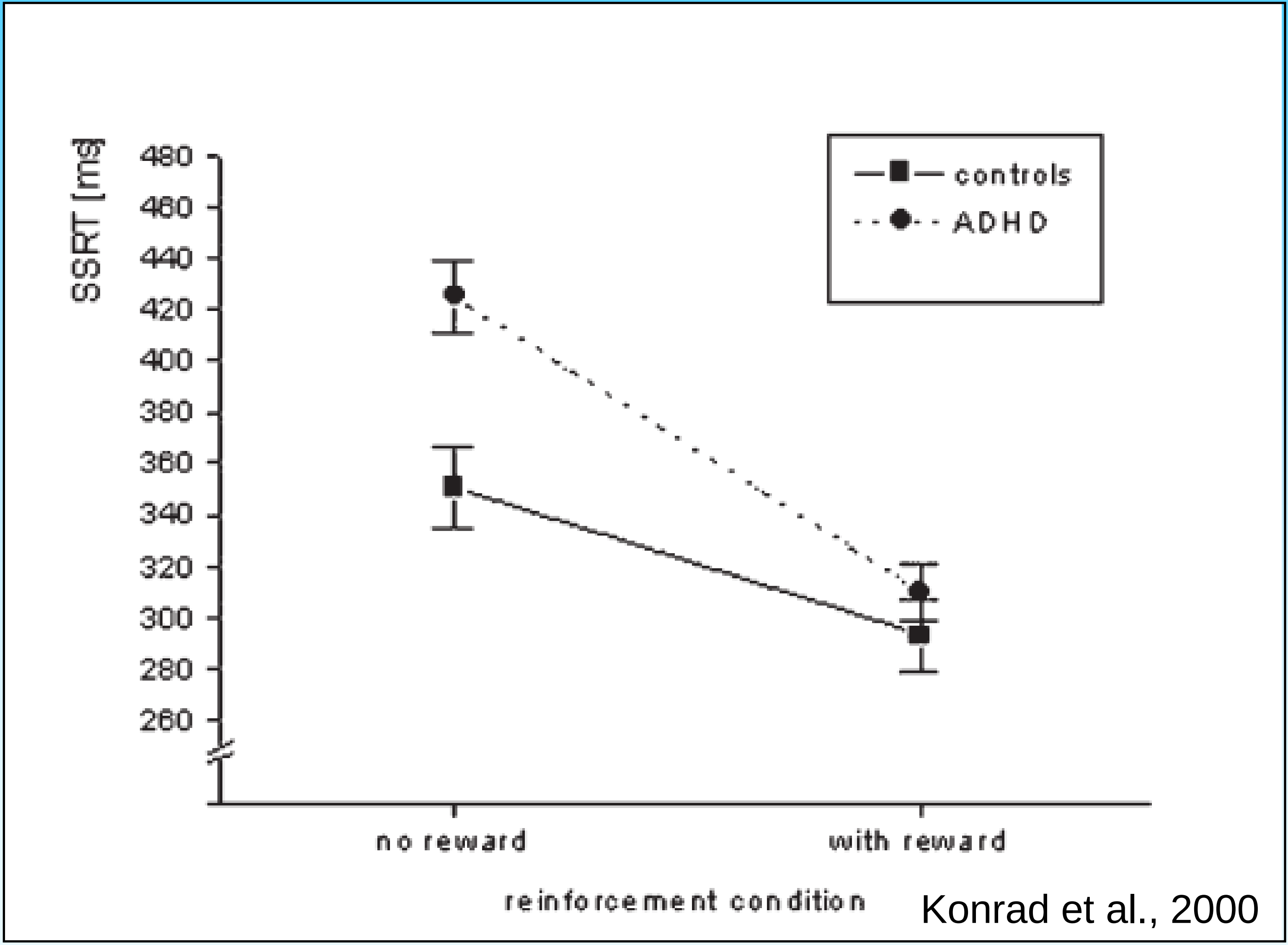
Scientific American, 1998

1. Exekutive Dysfunktionen: nicht störungsspezifisch
2. 50% der Betroffenen: ausgeprägte exekutive Auffälligkeiten
3. Aber auch beeinträchtigte Motivations- & Lernprozesse

z. .B.: Nigg et al., 2005; Doyle et al., 2005

Motivationale Abweichungen & Beeinträchtigte Lernmechanismen

Motivational modulation of inhibitory control performance



Konrad et al., 2000

Neuropsychologische Modelle

Scientific American, 1998

Kognitive M.
- Exekutive Funktionen (Pennington & Ozonoff)
- Inhibitionskontrolle (Barkley)
- Arbeitsgedächtnis (Denney & Rapport)

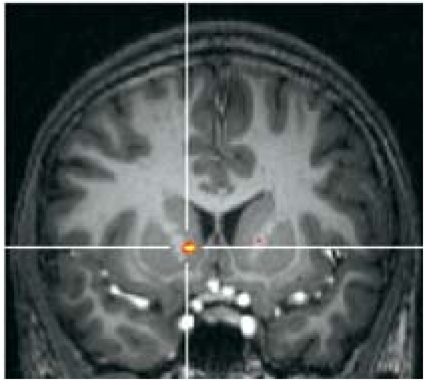
Motivationale M.
- Abneigung geg. Belohnungsaufschub (Sonuga-Barke)
- Reduzierte Dauer der Verstärkerwirksamkeit (Sagvolden)

Kombinierte M.
- Kognitiv-energetisches M. (Sergeant)

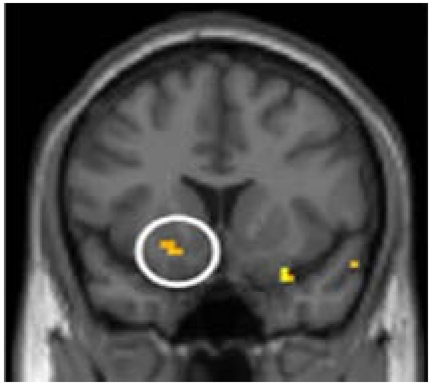
ADHD: A disorder of impaired reward-learning?

Brain activation in **reward system (ventral striatum)** reduced in ADHD

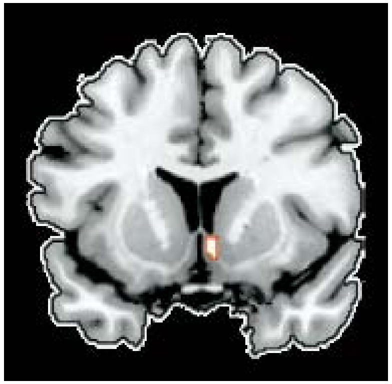
ADHD < healthy controls



Scheres et al. 2007
Biological Psychiatry



Ströhle et al. 2007
Neuroimage



Plichta et al. 2008
Biological Psychiatry

Dual pathway model of ADHD
Impaired reward processing

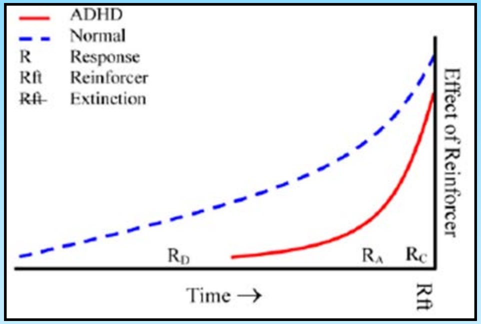
Dysfunctional reward system

Impaired signaling of delayed reward

Altered reinforcement mechanisms

Dysfunctional learning of contingencies

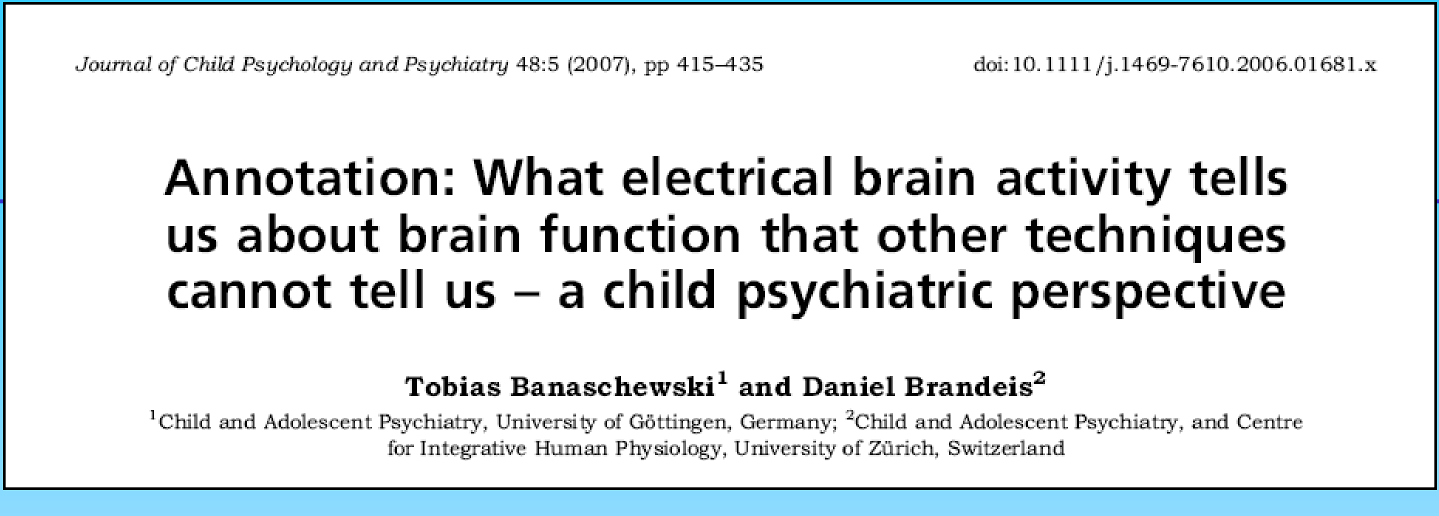
Impulsivity



e.g., Sonuga-Barke, 2005

Neurophysiologie

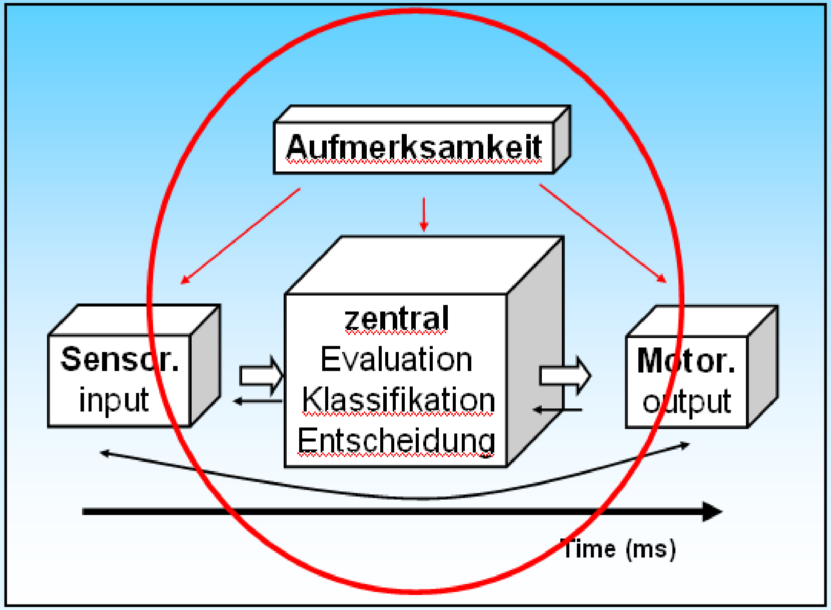
Funktionelle Bildgebung



Journal of Child Psychology and Psychiatry 48:5 (2007), pp 415–435 doi:10.1111/j.1469-7610.2006.01681.x

Annotation: What electrical brain activity tells us about brain function that other techniques cannot tell us – a child psychiatric perspective

Tobias Banaschewski[1] and Daniel Brandeis[2]
[1]Child and Adolescent Psychiatry, University of Göttingen, Germany; [2]Child and Adolescent Psychiatry, and Centre for Integrative Human Physiology, University of Zürich, Switzerland



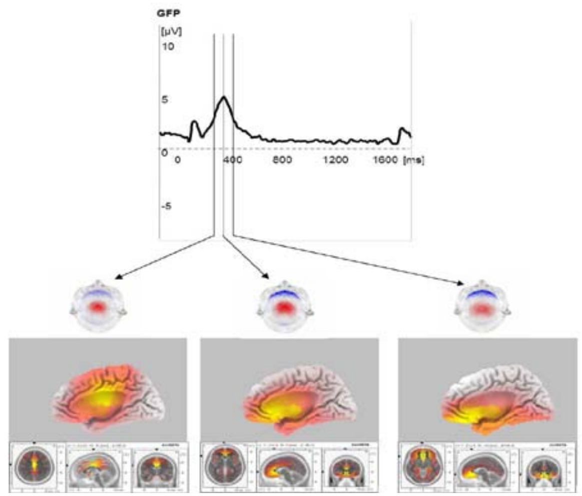
Aufmerksamkeit

Sensor. input

zentral
Evaluation
Klassifikation
Entscheidung

Motor. output

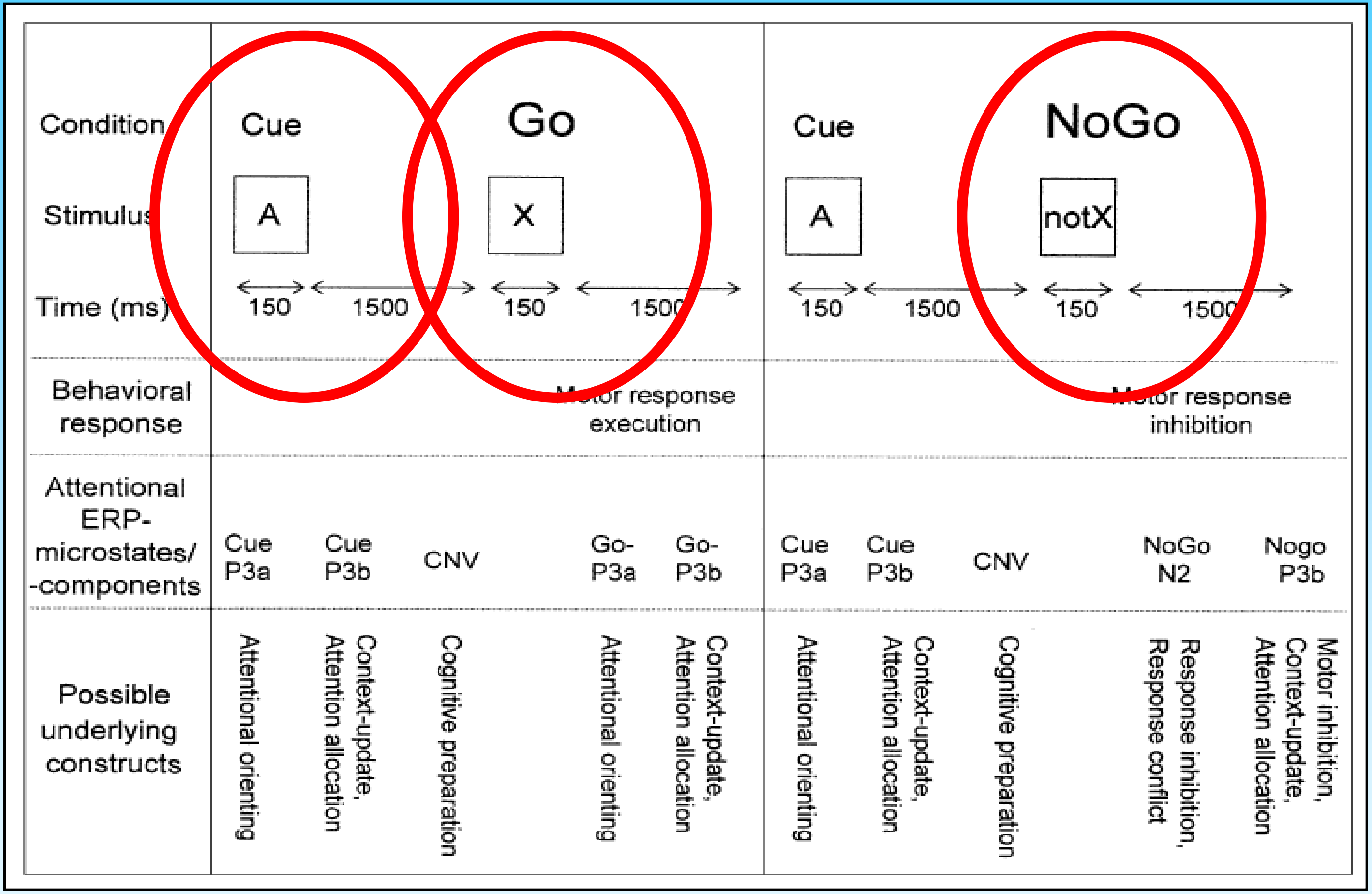
Time (ms)



Erfolgreiche Antworthemmung während eines NoGo-Trials

Neurophysiologie

Continuous Performance Test – AX



Condition	Cue	Go	Cue	NoGo
Stimulus	A	X	A	notX
Time (ms)	150 1500	150 1500	150 1500	150 1500
Behavioral response		Motor response execution		Motor response inhibition
Attentional ERP-microstates/ -components	Cue P3a Cue P3b CNV	Go-P3a Go-P3b	Cue P3a Cue P3b CNV	NoGo N2 Nogo P3b
Possible underlying constructs	Attentional orienting Context-update, Attention allocation Cognitive preparation	Attentional orienting Context-update, Attention allocation	Attentional orienting Context-update, Attention allocation Cognitive preparation	Response inhibition, Response conflict Motor inhibition, Context-update, Attention allocation

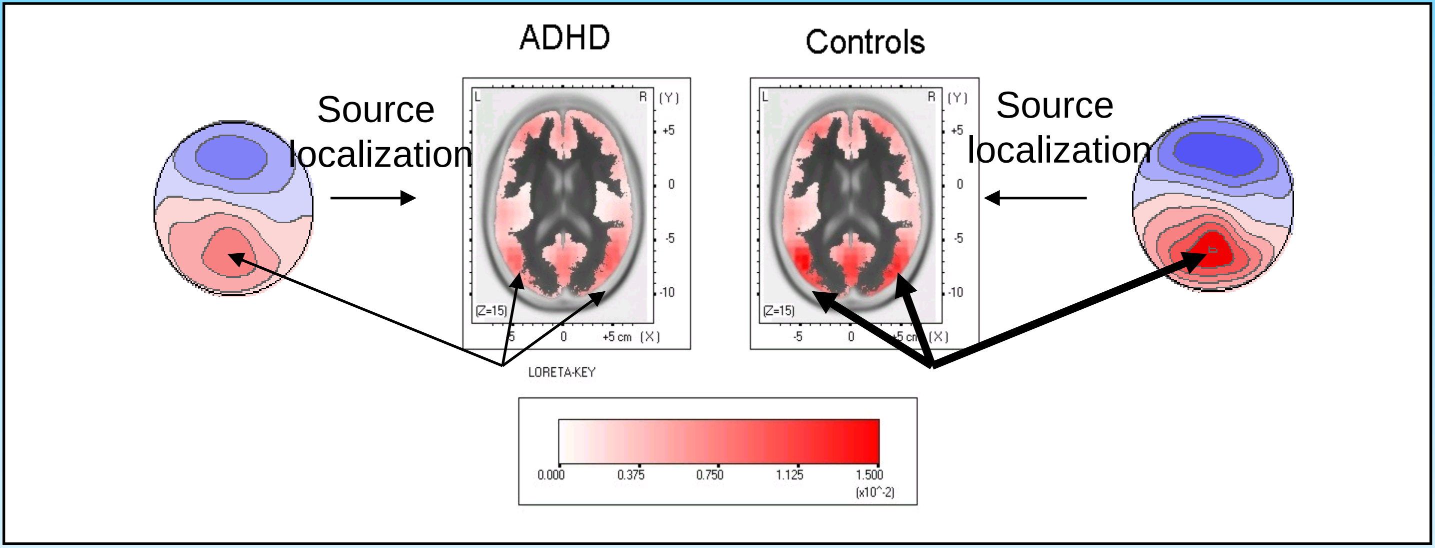
Aufmerksamkeitsorientierung, Antwortvorbereitung, Antwortausführung & -hemmung lassen sich trennen

Banaschewski et al 2004

Neurophysiologie

Abweichende Aufmerksamkeitsprozesse

Aktivierung nach Präsentation von A bei CPT A-X (P300)

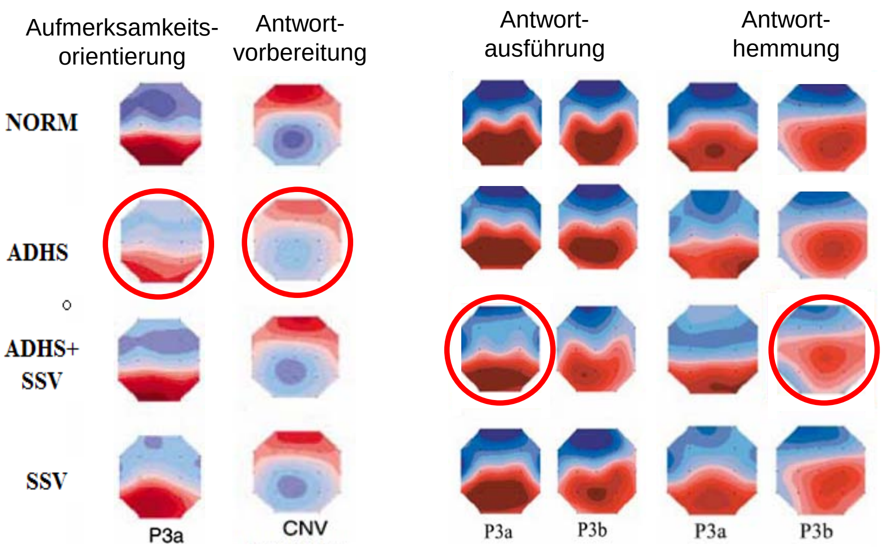

ADHD
Controls
Source localization
Source localization
L
R
(Y)
+5
0
-5
-10
(Z=15)
-5
0
+5 cm (X)
LORETA-KEY
0.000
0.375
0.750
1.125
1.500
(x10^-2)

- ➢ Beeinträchtige Aufmerksamkeitsorientierung
- ➢ Posteriores Aufmerksamkeitssystem schwächer

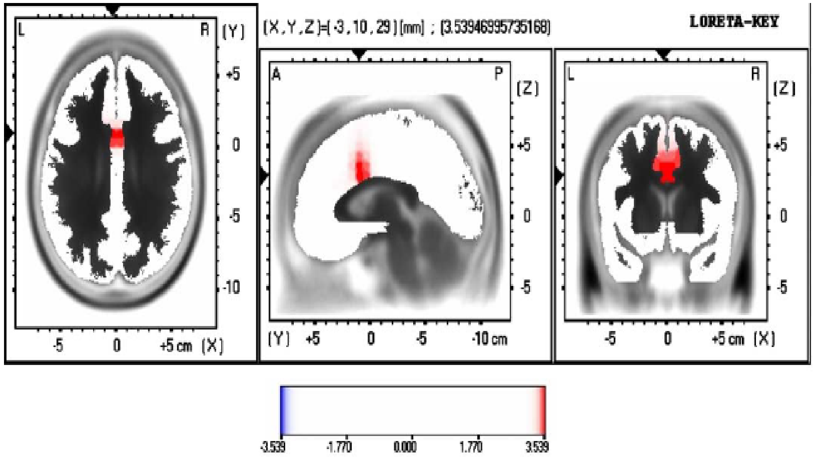
Brandeis, Banaschewski et al., 2002: Multizenterstudie; Banaschewski, Brandeis et al., 2003

Neurophysiologie

Defizite von Vorbereitung & Antwortkontrolle


Aufmerksamkeits-orientierung
Antwort-vorbereitung
Antwort-ausführung
Antwort-hemmung
NORM
ADHS
ADHS+ SSV
SSV
P3a
CNV
P3a
P3b
P3a
P3b

Banaschewski et al., 2003

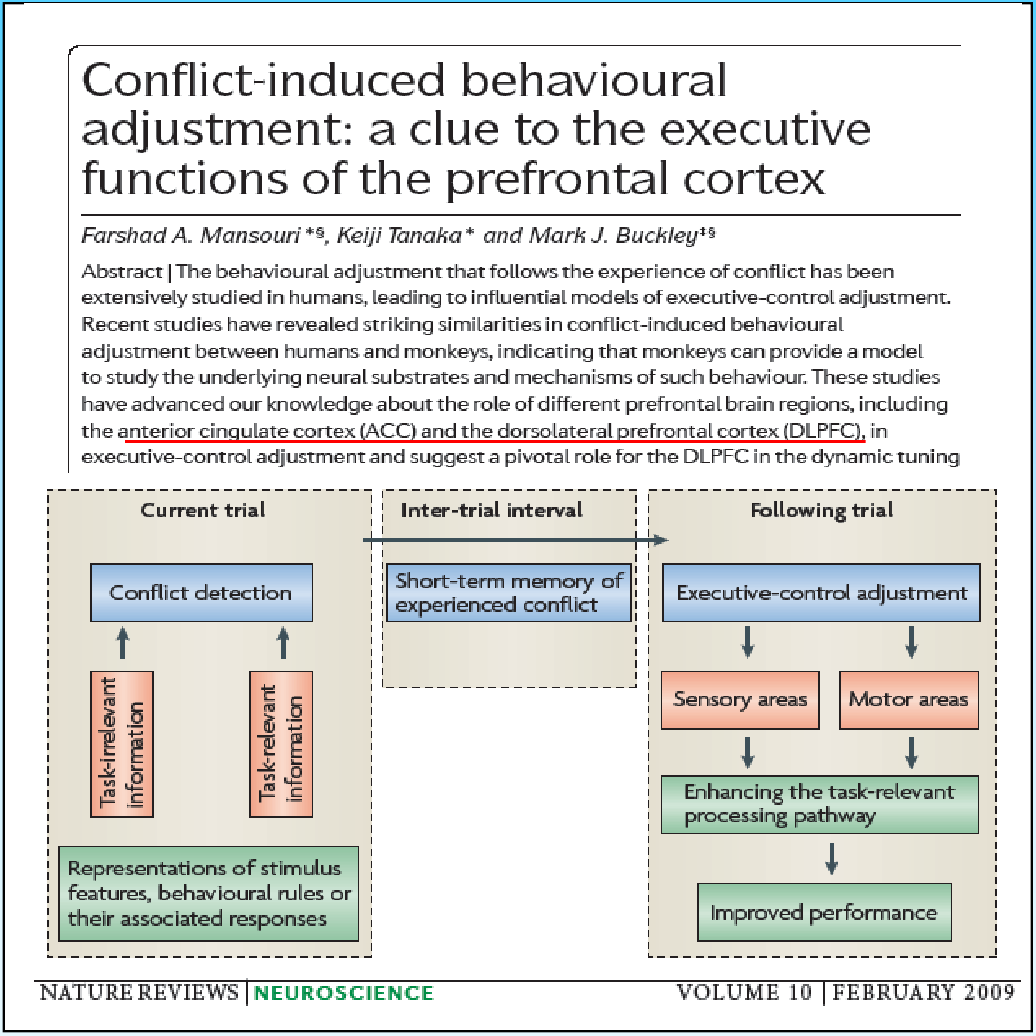

(X,Y,Z)=(-3,10,29)[mm] ; (3.53946995735168)
LORETA-KEY
L
R
(Y)
+5
0
-5
-10
-5
0
+5 cm (X)
A
P
(Z)
+5
0
-5
(Y) +5
0
-5
-10 cm
L
R
(Z)
+5
0
-5
-5
0
+5 cm (X)
-3.539
-1.770
0.000
1.770
3.539

Fallgatter et al., 2004

Antwortvorbereitung, sowie Hemmung **und** Ausführung betroffen: Beeinträchtigte Antwortkontrolle

Beeinträchtigte Antwortkontrolle aufgrund Funktionsstörung des anterioren cingulären Kortex

Handlungskontrolle & Fehlerverarbeitung



Conflict-induced behavioural adjustment: a clue to the executive functions of the prefrontal cortex

Farshad A. Mansouri§, Keiji Tanaka* and Mark J. Buckley‡§*

Abstract | The behavioural adjustment that follows the experience of conflict has been extensively studied in humans, leading to influential models of executive-control adjustment. Recent studies have revealed striking similarities in conflict-induced behavioural adjustment between humans and monkeys, indicating that monkeys can provide a model to study the underlying neural substrates and mechanisms of such behaviour. These studies have advanced our knowledge about the role of different prefrontal brain regions, including the anterior cingulate cortex (ACC) and the dorsolateral prefrontal cortex (DLPFC), in executive-control adjustment and suggest a pivotal role for the DLPFC in the dynamic tuning

Current trial

Conflict detection

Task-irrelevant information

Task-relevant information

Representations of stimulus features, behavioural rules or their associated responses

Inter-trial interval

Short-term memory of experienced conflict

Following trial

Executive-control adjustment

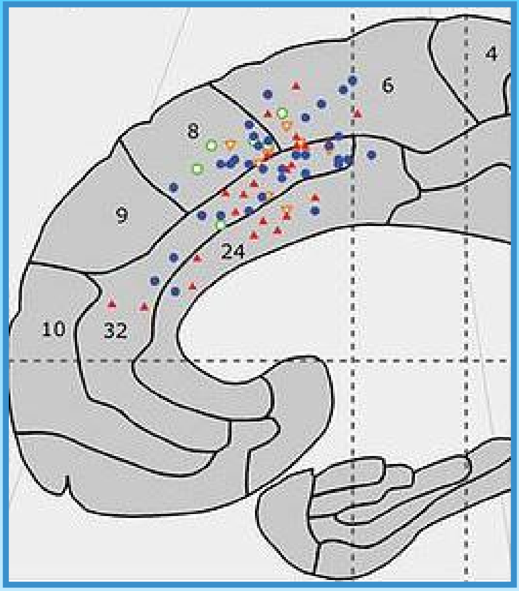
Sensory areas

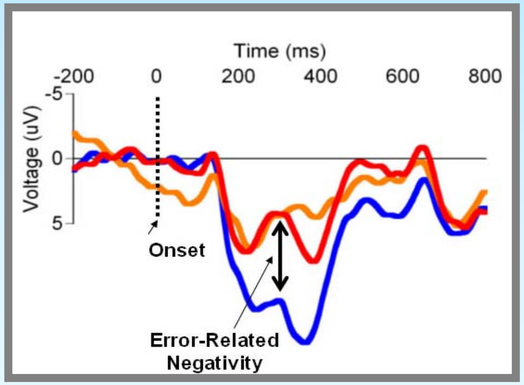
Motor areas

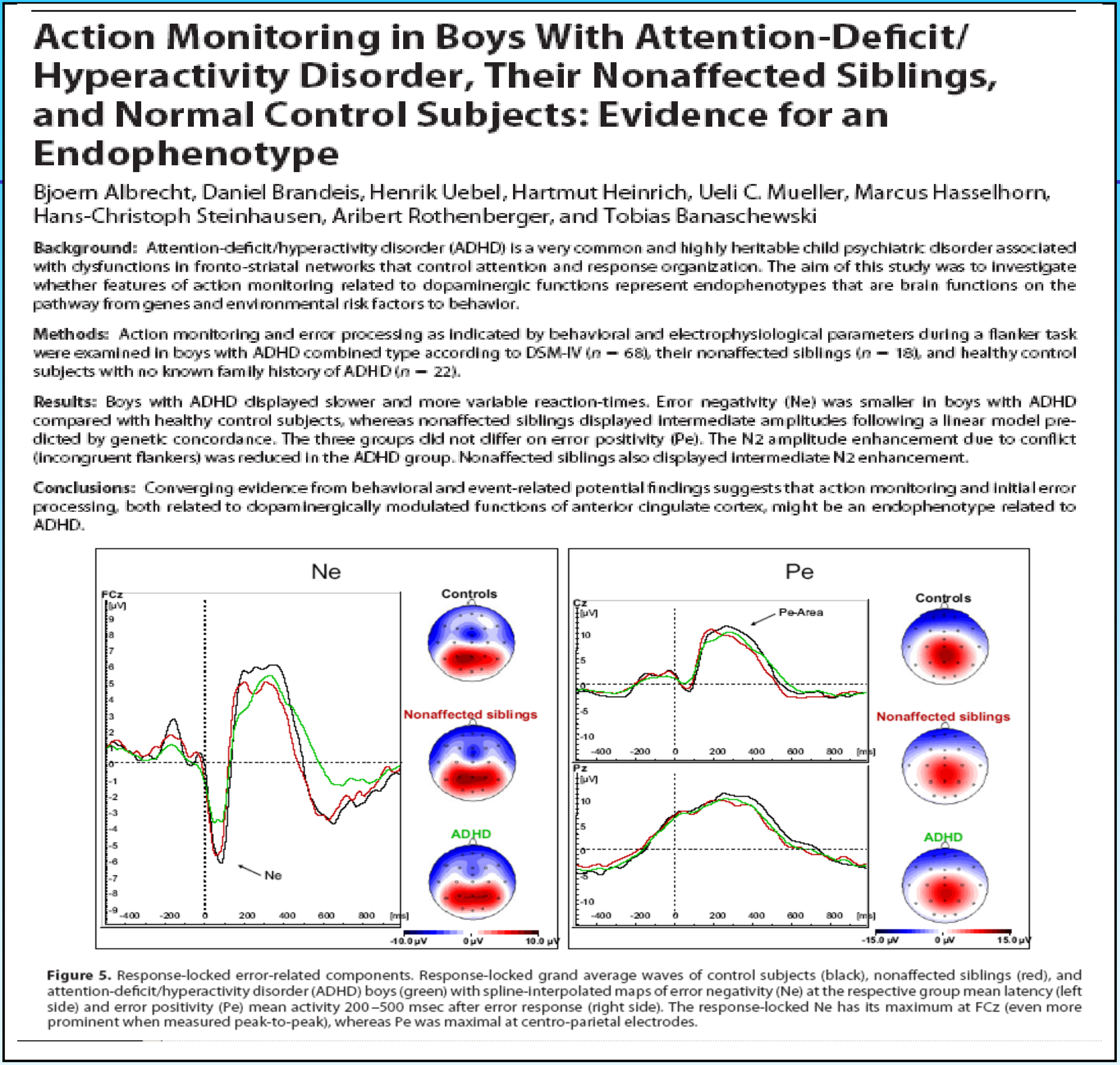
Enhancing the task-relevant processing pathway

Improved performance

NATURE REVIEWS | NEUROSCIENCE VOLUME 10 | FEBRUARY 2009






Ne
FCz
[µV]
Controls
Nonaffected siblings
ADHD
Ne
-400
-200
0
200
400
600
800
[ms]
-10.0 µV
0 µV
10.0 µV
Pe
Cz
Pz
Pe-Area
-15.0 µV
0 µV
15.0 µV

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.

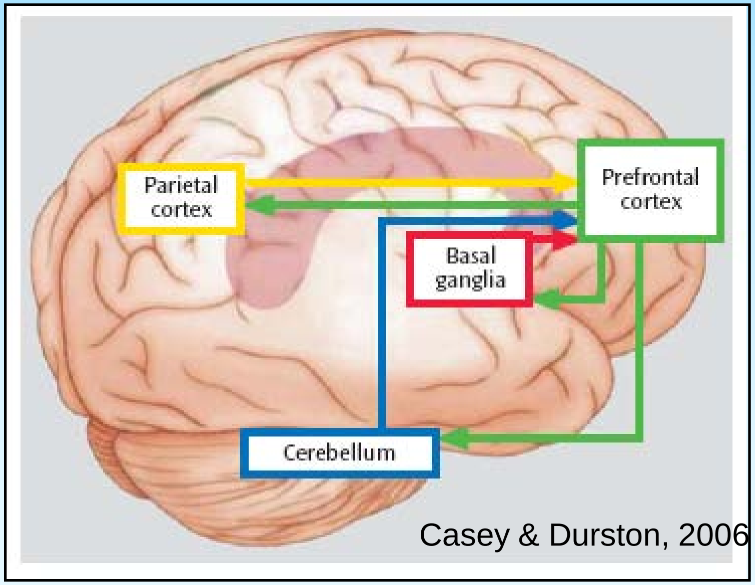
Figure 5. Response-locked error-related components. Response-locked grand average waves of control subjects (black), nonaffected siblings (red), and attention-deficit/hyperactivity disorder (ADHD) boys (green) with spline-interpolated maps of error negativity (Ne) at the respective group mean latency (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.

ERN: Kognitive Kontrolle bei ADHS und auch bei nicht-betroffenen Geschwistern abweichend

Zusammenfassung

Multiple Auffälligkeiten

Strukturell:	Fronto-striatale und cerebelläre Abweichungen
Biochemisch:	Dysregul. dopamin. & noradrenerge Transmittersysteme
Neuropsychol.:	Kognitive und motivationale Abweichungen, beeinträchtigte Lernmechanismen
Neurophysiol.:	Mehrere Aufmerksamkeitsnetzwerke beeinträchtigt


Parietal cortex
Prefrontal cortex
Basal ganglia
Cerebellum

Casey & Durston, 2006

Dysregulated top-down control & bottom-up systems

Vielen Dank für

Ihre Aufmerksamkeit !