Was sagen uns die Ergebnisse der Pharmakotherapie über die Ursachen der ADHS?

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‘ Ursachen von ADHS – Was wissen wir wirklich? Causes of ADHD – what do we really know? ’

Disclosure

	Former employee	Current employee	Stockholder	Research Funding	Speaker Bureau	Advisory Board	
DFG				X			
Volkswagenstiftung				X			
NIMH				X			
Public funding agencies				X			
Private non-profit funding agencies				X			
E. Lilly & Co.; Lilly Deutschland	X		X	X (as former employee and current investigator)	X	X	
Ferring Pharmaceuticals				X			
Shire Pharmaceuticals				X		(x)	
Central Institute of Mental Health Mannheim, Univ. of Heidelberg		X					

R.W. Dittmann, Status March 2009

Gliederung

Beispielhafte Darstellung zu:

- Präklinische Befunde
- Klinik/Wirksamkeit
- Schlaf
- Neurophysiologie
- Neuropsychologie
- Pharmakogenetik
- Neuroimaging

- Zusammenfassung/Schlussfolgerungen

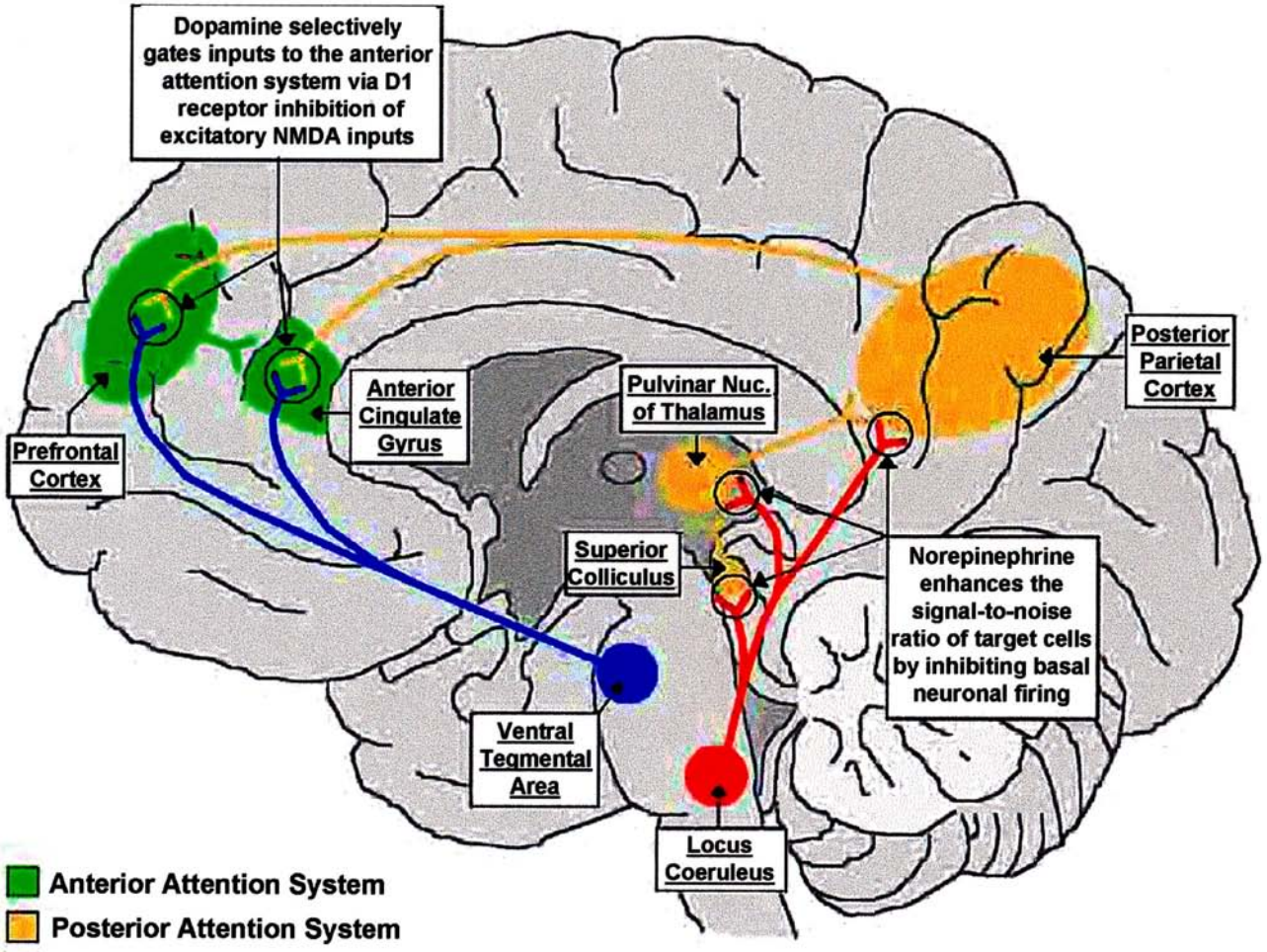


Figure 2. Mid-sagittal view of the brain illustrating Plitzska et al. (1996) multi-stage model of attention-deficit hyperactivity disorder (ADHD). Red lines indicate noradrenergic pathways and blue lines represent dopaminergic pathways.Himelstein et al.(2001)

Präklinische Befunde

Atomoxetine Increases Extracellular Levels of Norepinephrine and Dopamine in Prefrontal Cortex of Rat: A Potential Mechanism for Efficacy in Attention Deficit/Hyperactivity Disorder

Frank P. Bymaster, M.S., Jason S. Katner, B.S., David L. Nelson, Ph.D., Susan K. Hemrick-Luecke, M.S., Penny G. Threlkeld, M.S., John H. Heiligenstein, M.D., S. Michelle Morin, M.S., Donald R. Gehlert, Ph.D., and Kenneth W. Perry, M.S.

The selective norepinephrine (NE) transporter inhibitor atomoxetine (formerly called tomoxetine or LY139603) has been shown to alleviate symptoms in Attention Deficit/Hyperactivity Disorder (ADHD). We investigated the mechanism of action of atomoxetine in ADHD by evaluating the interaction of atomoxetine with monoamine transporters, the effects on extracellular levels of monoamines, and the expression of the neuronal activity marker Fos in brain regions. Atomoxetine inhibited binding of radioligands to clonal cell lines transfected with human NE, serotonin (5-HT) and dopamine (DA) transporters with dissociation constants (K_i) values of 5, 77 and 1451 nM, respectively, demonstrating selectivity for NE transporters. In microdialysis studies, atomoxetine increased extracellular (EX) levels of NE in prefrontal cortex (PFC) 3-fold, but did not alter 5-HT_{EX} levels. Atomoxetine also increased DA_{EX} concentrations in PFC 3-fold, but did not alter DA_{EX} in striatum or nucleus accumbens. In contrast, the psychostimulant methylphenidate, which is used in ADHD therapy, increased NE_{EX} and DA_{EX} equally in PFC, but also increased DA_{EX} in the striatum and nucleus accumbens to the same level. The expression of the neuronal activity marker Fos was increased 3.7-fold in PFC by atomoxetine administration, but was not increased in the striatum or nucleus accumbens, consistent with the regional distribution of increased DA_{EX}. We hypothesize that the atomoxetine-induced increase of catecholamines in PFC, a region involved in attention and memory, mediates the therapeutic effects of atomoxetine in ADHD. In contrast to methylphenidate, atomoxetine did not increase DA in striatum or nucleus accumbens, suggesting it would not have motoric or drug abuse liabilities.

[Neuropsychopharmacology X:X–X, XXXX]

Table 1. Affinity of Atomoxetine and Other Uptake Inhibitors for Human Monoamine Transporters.

Compound	Norepinephrine	Serotonin K_i, nM	Dopamine
Atomoxetine	5	77	1451
Reboxetine	11	440	>10000
Desipramine	3.8	179	>10000
Methylphenidate	339	>10000	34
Bupropion	>10000	>10000	562
Nomifensine	29	4872	53
Imipramine	98	19	>10000
Fluoxetine	1022	7	4752

K_i values were determined from at least six concentrations in triplicate in three separate assays.

Bymaster et al. , 2002, contin.

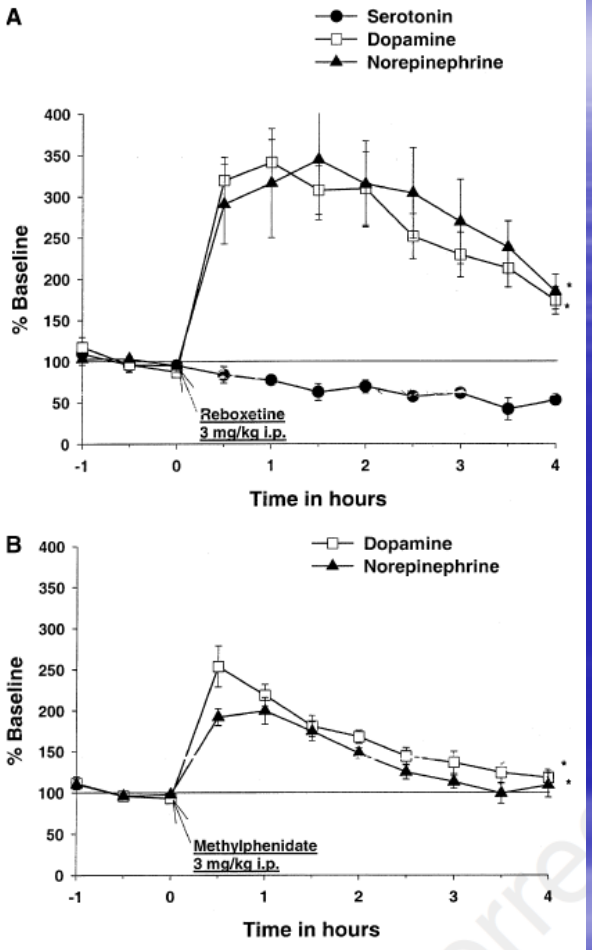


Figure 5. Time course of the effects of reboxetine (3 mg/kg i.p.) (A) and methylphenidate (3 mg/kg i.p.) administration (B) on extracellular monoamine levels in prefrontal cortex of freely moving rat. Values are the mean ± SEM of the % of pre-drug baseline determined at −1, −0.5 and 0 h. Administration of reboxetine or methylphenidate at time 0 h is indicated by the arrow. Reboxetine significantly increased extracellular norepinephrine (NE) and dopamine (DA) concentrations throughout the 4-h period ($^{*}p < .05$, Duncan's post hoc test) whereas methylphenidate significantly increased NE and DA for the first 2.5 h ($^{*}p < .05$, Duncan's post hoc test).

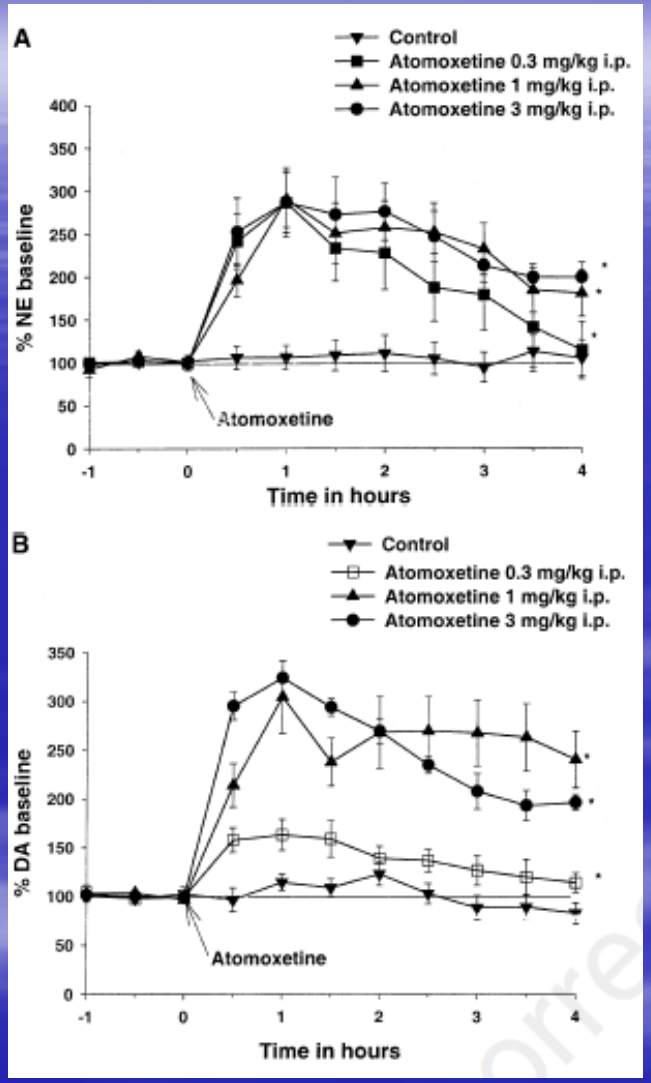


Figure 2. Time course of the effects of control (vehicle) or atomoxetine (0.3, 1, 3 mg/kg i.p.) administration on extracellular concentrations of norepinephrine (NE) (A), dopamine (DA) (B) and serotonin (5-HT) (C) in prefrontal cortex of freely moving rat. Values are the mean ± SEM of the % of pre-drug baseline determined at −1, −0.5 and 0 h. Administration of vehicle or atomoxetine at time 0 h is indicated by the arrow. Atomoxetine significantly increased extracellular NE and DA concentrations throughout the 4-h period ($^{*}p < .025$, Duncan's post hoc test).

- Mikrodialyse
- frei laufende Ratten
- präfrontaler Kortex
- DA, NE; 5-HT

Bymaster et al. , 2002, contin.

- Mikrodialyse
- DA
- PFC, Striatum, N. acc.

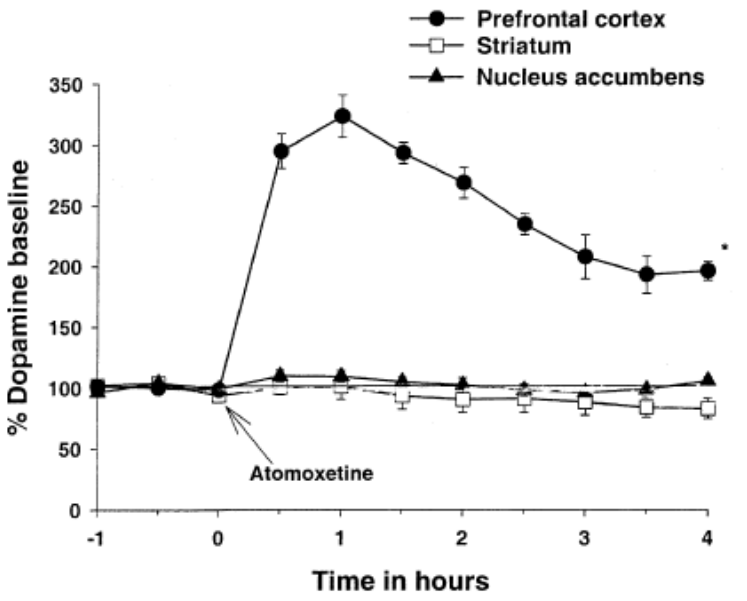


Figure 3. Time course of the effects of atomoxetine administration on extracellular dopamine levels in prefrontal cortex (PFC), striatum and nucleus accumbens of freely moving rat. Values are the mean ± SEM of the % of pre-drug baseline determined at −1, −0.5 and 0 h. Administration of vehicle or atomoxetine (3 mg/kg i.p. in PFC and nucleus accumbens and 10 mg/kg i.p. in striatum) at time 0 h is indicated by the arrow. Atomoxetine significantly increased extracellular norepinephrine and dopamine concentrations throughout the 4-h period only in the PFC ($^{*}p < .05$, Duncan's post hoc test).

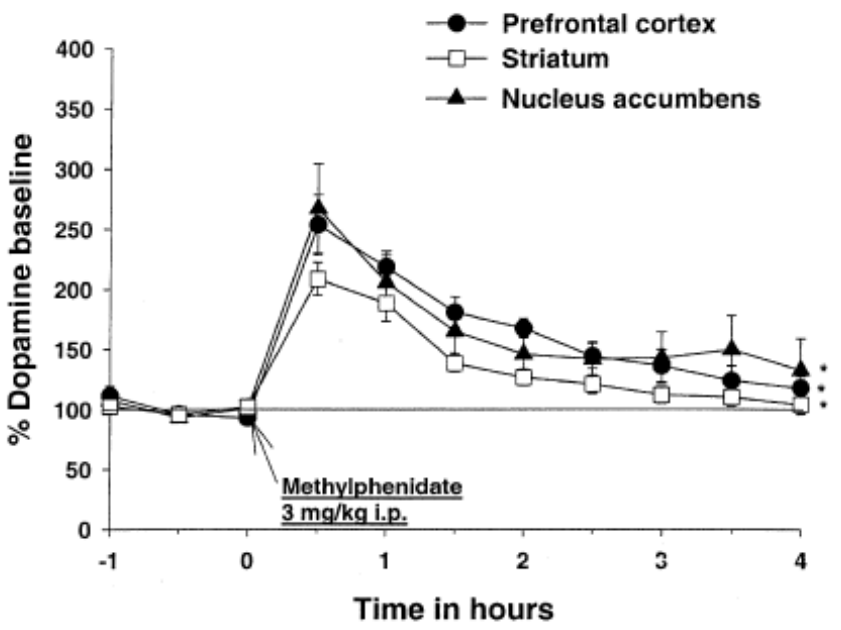


Figure 6. Time course of the effects of methylphenidate (3 mg/kg i.p.) administration on extracellular dopamine levels in prefrontal cortex, striatum, and nucleus accumbens of freely moving rat. Values are the mean± SEM of the % of pre-drug baseline determined at −1, −0.5 and 0 h. Administration of methylphenidate at time 0 h is indicated by the arrow. Methylphenidate significantly increased extracellular dopamine concentrations through the 2.5-h period in all brain regions ($^{*}p < .05$, Duncan's post hoc test).

Klinik / Wirksamkeit

ORIGINAL ARTICLE

A 14-Month Randomized Clinical Trial of Treatment Strategies for Attention-Deficit/ Hyperactivity Disorder

The MTA Cooperative Group

Background: Previous studies have demonstrated the short-term efficacy of pharmacotherapy and behavior therapy for attention-deficit/hyperactivity disorder (ADHD), but no longer-term (ie, >4 months) investigations have compared these 2 treatments or their combination.

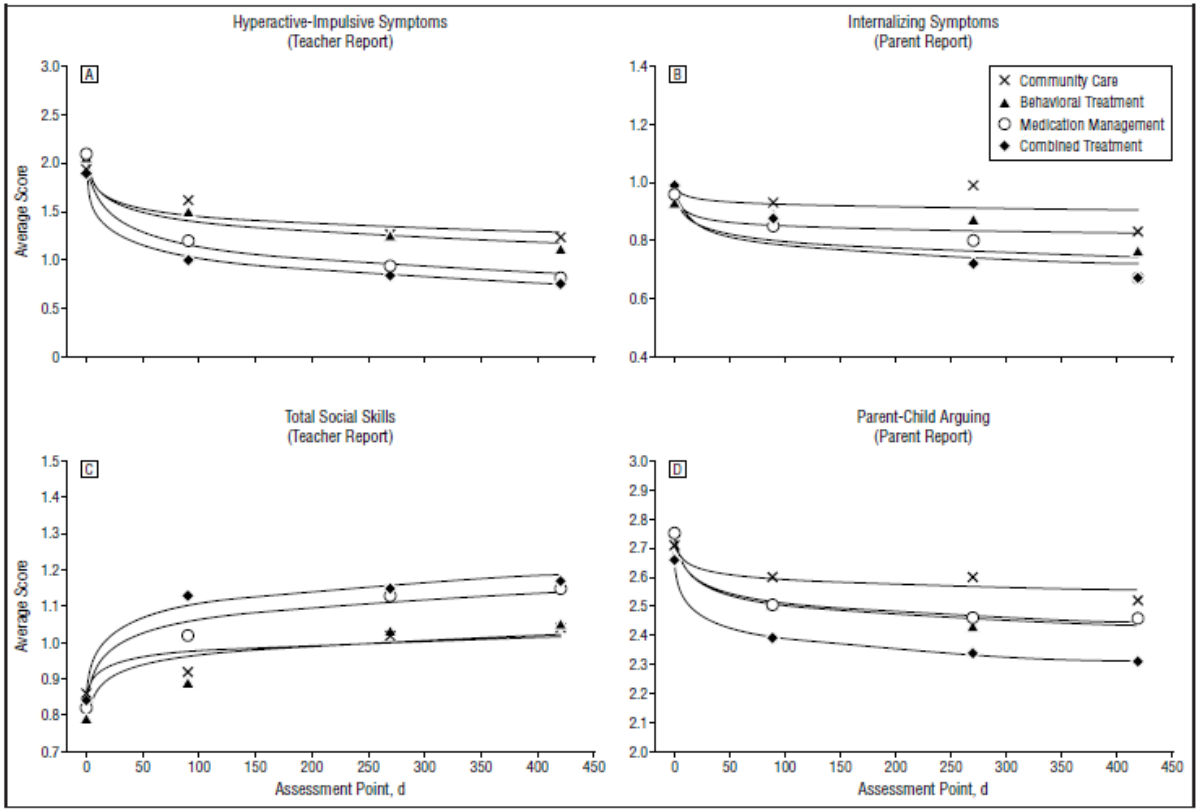
Methods: A group of 579 children with ADHD Combined Type, aged 7 to 9.9 years, were assigned to 14 months of medication management (titration followed by monthly visits); intensive behavioral treatment (parent, school, and child components, with therapist involvement gradually reduced over time); the two combined; or standard community care (treatments by community providers). Outcomes were assessed in multiple domains before and during treatment and at treatment end point (with the combined treatment and medication management groups continuing medication at all assessment points). Data were analyzed through intent-to-treat random-effects regression procedures.

Results: All 4 groups showed sizable reductions in symptoms over time, with significant differences among them in degrees of change. For most ADHD symptoms, children in the combined treatment and medication management groups showed significantly greater improvement than those given intensive behavioral treatment and community care. Combined and medication management treatments did not differ significantly on any direct comparisons, but in several instances (oppositional/aggressive symptoms, internalizing symptoms, teacher-rated social skills, parent-child relations, and reading achievement) combined treatment proved superior to intensive behavioral treatment and/or community care while medication management did not. Study medication strategies were superior to community care treatments, despite the fact that two thirds of community-treated subjects received medication during the study period.

Conclusions: For ADHD symptoms, our carefully crafted medication management was superior to behavioral treatment and to routine community care that included medication. Our combined treatment did not yield significantly greater benefits than medication management for core ADHD symptoms, but may have provided modest advantages for non-ADHD symptom and positive functioning outcomes.

Arch Gen Psychiatry. 1999;56:1073-1086

- **579 ADHD Pat., 7 – 9.9 J**
- **4 Behandlungsarme**
- **„ ..medication management superior .. „**

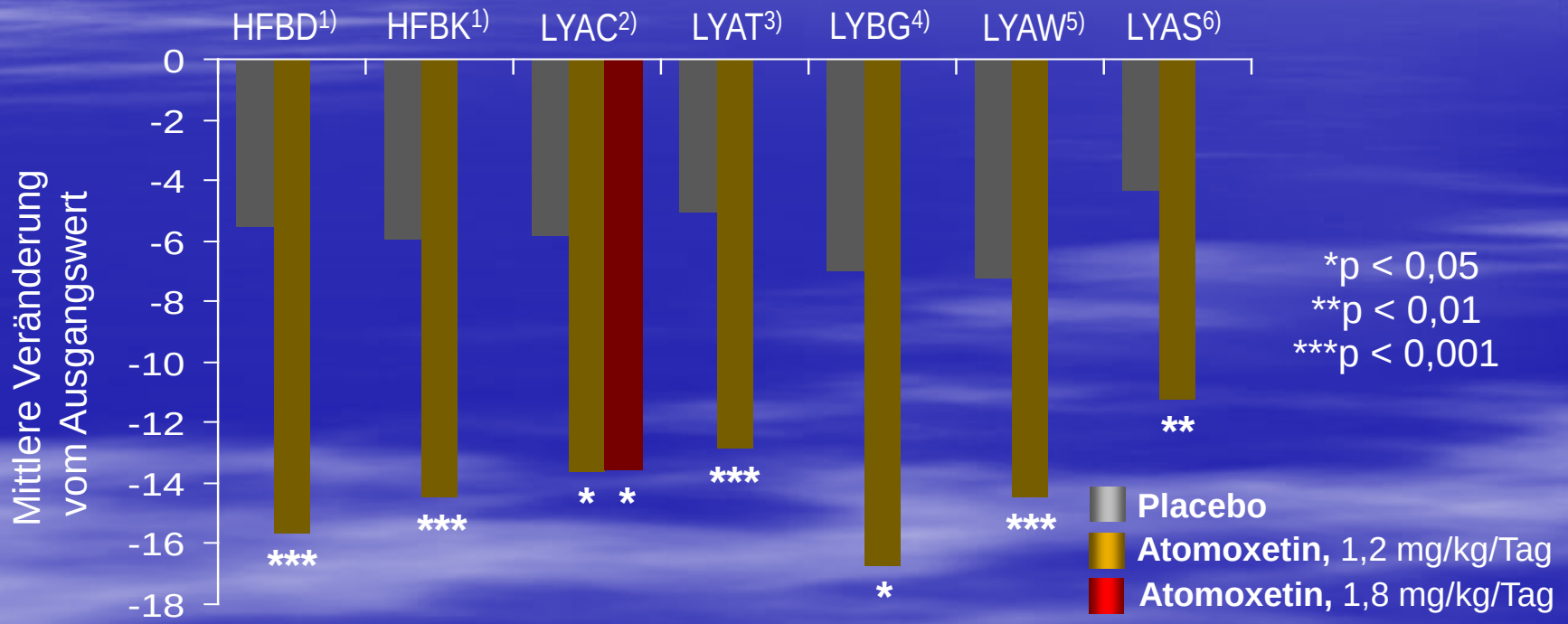


For internalizing symptoms (parent reported), combined treatment and medication management symbols overlapped at the 14-month data point. For parent-child arguing (power assertion, parent reported), medication management and intensive behavioral treatment symbols overlapped at the 3-month and 14-month data points. A, Combined treatment and medication management were more effective than community care. B, Combined treatment was more effective than behavioral treatment and community care. C, Combined treatment and medication management were more effective than community care. D, Combined and behavioral treatment were more effective than community care.

Atomoxetin Studienergebnisse

ADHD-RS: Gesamtwert

doppelblind, 6-18 Wochen



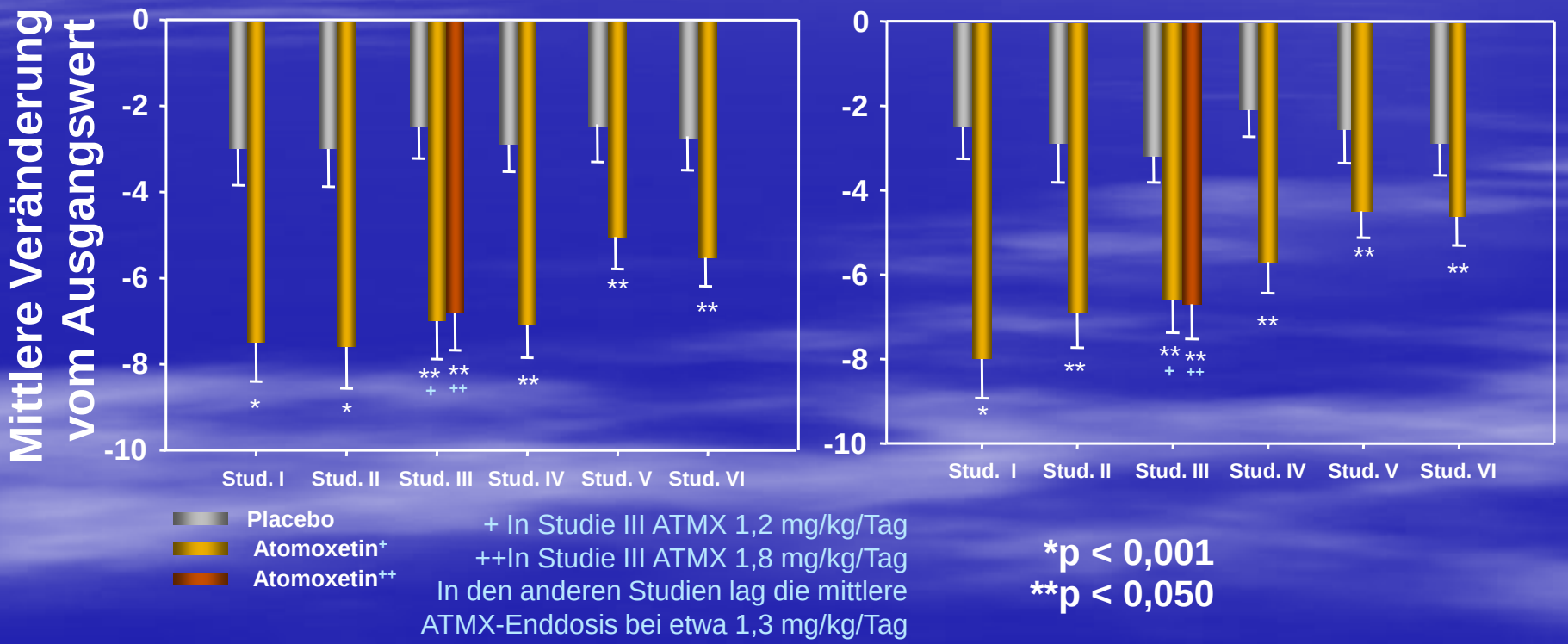
1. Spencer et al., J. Clin Psychiatry 2002; 63(12):1140-47
2. Michelson et al., Pediatrics 2001; 108(5):e83-e91
3. Michelson et al., Am J Psychiatry 2002; 159:1896-1901
4. Kelsey et al., Pediatrics 2004; 108(5):e1-38
5. Weiss et al., J Am Acad Child Adolesc Psychiatry 2005; 44(7):647-655
6. McCracken et al., Posterpräsentation, AACAP, 2003, Miami

Atomoxetin Studienergebnisse

ADHD-RS: Subskalen

Unaufmerksamkeit Subskala

Hyperaktivität/Impulsivität Subskala



\+ In Studie III ATMX 1,2 mg/kg/Tag
++In Studie III ATMX 1,8 mg/kg/Tag
In den anderen Studien lag die mittlere ATMX-Enddosis bei etwa 1,3 mg/kg/Tag

***p < 0,001**
****p < 0,050**

Atomoxetine and Osmotically Released Methylphenidate for the Treatment of Attention Deficit Hyperactivity Disorder: Acute Comparison and Differential Response

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Christopher J. Kratochvil, M.D.
Albert J. Allen, M.D., Ph.D.
Charles D. Casat, M.D.
Dustin D. Ruff, Ph.D.
Rodney J. Moore, Ph.D.
David Michelson, M.D.
Atomoxetine/Methylphenidate Comparative Study Group

Objective: Response to atomoxetine, a nonstimulant norepinephrine-specific reuptake inhibitor, was compared with the effect of osmotic-release oral methylphenidate, a long-acting methylphenidate preparation, in patients with attention deficit hyperactivity disorder (ADHD).

Method: In a large placebo-controlled, double-blind study, patients ages 6–16 with ADHD, any subtype, were randomly assigned to receive 0.8–1.8 mg/kg per day of atomoxetine (N=222), 18–54 mg/day of osmotically released methylphenidate (N=220), or placebo (N=74) for 6 weeks. The a priori specified primary analysis compared response (at least 40% decrease in ADHD Rating Scale total score) to osmotically released methylphenidate with response to atomoxetine and placebo. After 6 weeks, patients treated with methylphenidate were switched to atomoxetine under double-blind conditions.

Results: The response rates for both atomoxetine (45%) and methylphenidate (56%) were markedly superior to that for placebo (24%), but the response to osmotically released methylphenidate was superior to that for atomoxetine. Each medication was well tolerated, with completion rates and discontinuations for adverse events not significantly different from those for placebo. Of the 70 subjects who did not respond to methylphenidate, 30 (43%) subsequently responded to atomoxetine. Likewise, 29 (42%) of the 69 patients who did not respond to atomoxetine had previously responded to osmotically released methylphenidate.

Conclusion: Response was significantly greater with osmotically released methylphenidate than with atomoxetine. One-third of patients who received methylphenidate followed by atomoxetine responded better to one or the other, suggesting that there may be preferential responders.

(Am J Psychiatry 2008; 165:721–730)

- 516 ADHD Pat., 6 – 16 J.
- Atx vs. Oros-MPH
- Stimulanzien-Nonresp. ausgeschlossen
- Atx, hohe Dosis
- Hinweise für ‚preferential responders‘

TABLE 2. Baseline ADHD Rating Scale Scores and Change to Endpoint for Children and Adolescents With ADHD in a 6-Week Comparison of Atomoxetine, Osmotically Released Methylphenidate, and Placebo

	Atomoxetine (N=222)				Osmotically Released Methylphenidate (N=220)				Difference in Mean Change Between Atomoxetine and Methylphenidate (p)[b]
	Baseline Score		Change in Score[a]		Baseline Score		Change in Score[a]		
ADHD Rating Scale Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Total scale									
All patients (N=492)	40.9	8.8	−14.4	12.7	40.0	8.8	−16.9	13.1	0.02
Prior stimulant users (N=301)	41.2	9.1	−12.4	12.2	39.7	8.8	−15.1	13.1	0.04
Stimulant-naive (N=191)	40.4	8.3	−17.9	13.0	40.4	8.9	−19.7	12.6	0.26
Inattentive subscale									
All patients (N=492)	22.3	4.0	−7.3	7.1	22.1	4.2	−9.0	7.7	0.006
Prior stimulant users (N=301)	22.3	4.0	−5.9	6.8	21.8	4.2	−7.8	7.8	0.02
Stimulant-naive (N=191)	22.4	4.1	−9.7	7.1	22.5	4.0	−11.0	7.2	0.19
Impulsivity/hyperactivity subscale									
All patients (N=492)	18.6	6.6	−7.1	6.9	17.9	6.7	−7.9	6.8	0.09
Prior stimulant users (N=301)	18.8	6.7	−6.5	6.6	17.9	6.5	−7.3	6.7	0.17
Stimulant-naive (N=191)	18.1	6.6	−8.2	7.2	17.9	7.0	−8.7	7.0	0.42

[a] With the last observation carried forward.
[b] Determined with analysis of covariance. Baseline measures were not statistically different between treatment groups. Atomoxetine and methylphenidate differed significantly from placebo in the mean change to endpoint for all groups on all measures. ANCOVA model included independent effects for investigator, treatment, CYP2D6 metabolizer status, and baseline score.

Newcorn et al., Am J Psychiat, 2008, 165, 721-30; contin.

TABLE 3. Change to Endpoint in Scores on Secondary Measures for Children and Adolescents With ADHD in a 6-Week Comparison of Atomoxetine, Osmotically Released Methylphenidate, and Placebo

	Atomoxetine			Osmotically Released Methylphenidate			Placebo			Difference in Mean Change Between Atomoxetine and Methylphenidate
		Change in Score[a]			Change in Score[a]			Change in Score[a]		
Secondary Measure	N	Mean	SD	N	Mean	SD	N	Mean	SD	(p)[b]
CGI ADHD severity index										
All patients	213	−1.2	1.2	211	−1.5	1.3	68	−0.7	1.0	0.004
Prior stimulant users	134	−0.9	1.2	127	−1.3	1.2	40	−0.6	1.0	0.008
Stimulant-naive	79	−1.5	1.2	84	−1.8	1.3	28	−0.8	1.1	0.26
Conners Parent Rating Scale ADHD index										
All patients	208	−7.8	9.2	195	−10.2	9.1	66	−2.3	8.4	0.003
Prior stimulant users	130	−5.9	8.8	119	−8.2	9.0	39	−1.1	7.3	0.02
Stimulant-naive	78	−10.9	9.2	76	−13.5	8.2	27	−3.9	9.7	0.052
Daily Parent Ratings of Evening and Morning Behavior—Revised										
Morning	135	−0.31	0.65	134	−0.25	0.67	37	0.01	0.61	0.54
Evening	135	−0.48	0.58	134	−0.53	0.66	37	0.01	0.60	0.21
Child Health Questionnaire psychosocial summary score										
All patients	193	5.4	11.9	193	7.8	12.7	64	1.0	12.0	0.02
Prior stimulant users	121	2.7	11.4	118	6.5	13.1	37	0.7	12.1	0.008
Stimulant-naive	72	9.9	11.5	75	9.8	11.8	27	1.4	12.0	0.82

[a] With the last observation carried forward.

[b] Determined with analysis of covariance. Atomoxetine and methylphenidate differed significantly from placebo in the mean change to endpoint for all groups on all measures with the exception of the Child Health Questionnaire psychosocial summary score for patients with prior stimulant exposure (atomoxetine versus placebo: p=0.65) and the Daily Parent Ratings of Evening and Morning Behavior morning subscore (methylphenidate versus placebo: p=0.053). ANCOVA model included independent effects for investigators, treatment, CYP2D6 metabolizer status, and baseline score.

Schlaf

ADHD

Effects of Atomoxetine and Methylphenidate on Sleep in Children With ADHD

R. Bart Sangal, MD[1]; Judith Owens, MD[2]; Albert J. Allen, MD[3]; Virginia Sutton, PhD[3]; Kory Schuh, PhD[3]; Douglas Kelsey, MD[3]

[1]Clinical Neurophysiology Services, PC, Troy, MI; [2]Child and Family Psychiatry, Rhode Island Hospital, Providence, RI; [3]Lilly Research Laboratories, Indianapolis, IN

Study Objectives: This study compared the effects of atomoxetine and methylphenidate on the sleep of children with attention-deficit/hyperactivity disorder (ADHD). This study also compared the efficacy of these medications for treating ADHD in these children.
Design: Randomized, double-blind, crossover trial.
Setting: Two sleep disorders centers in the United States; 1 in a private-practice setting and 1 in a hospital setting.
Patients: 85 children diagnosed with ADHD.
Interventions: Twice-daily atomoxetine and thrice-daily methylphenidate, each for approximately 7 weeks.
Measurements and Results: Relative to baseline, the actigraphy data indicated that methylphenidate increased sleep-onset latency significantly more than did atomoxetine (39.2 vs 12.1 minutes, $p < .001$). These results were consistent with the polysomnography data. Child diaries indicated that it was easier to get up in the morning, it took less time to fall asleep, and the children slept better with atomoxetine, compared with methylphenidate. Parents reported that it was less difficult getting their children up and getting them ready in the morning and that the children were less irritable, had less difficulty getting ready for bed, and had less difficulty falling asleep with atomoxetine, compared with methylphenidate. There were no significant differences between medications using the main measures of efficacy for ADHD treatment. Atomoxetine was superior on some secondary ADHD treatment-efficacy measures, based on parent reports. The only significant differences in treatment-emergent adverse events were greater incidence of decreased appetite and greater incidence of insomnia with methylphenidate.
Conclusions: Patients receiving twice-daily atomoxetine had shorter sleep-onset latencies, relative to thrice-daily methylphenidate, based on objective actigraphy and polysomnography data. Although both medications decreased nighttime awakenings, the decrease was greater for methylphenidate.
Keywords: Atomoxetine, methylphenidate, attention-deficit/hyperactivity disorder, child, sleep
Citation: Sangal RB; Owens J; Allen AJ et al. Effects of atomoxetine and methylphenidate on sleep in children with ADHD. *SLEEP* 2006;29(12):1573-1585.

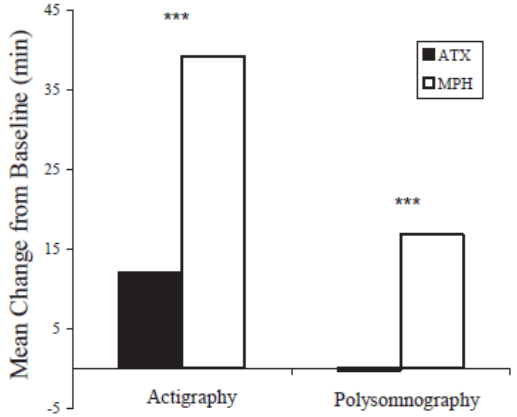

Figure 3—Effects of atomoxetine (ATX) and methylphenidate (MPH) on mean change from baseline in sleep onset, in minutes. ***$p < .001$ for comparison of change scores between ATX and MPH.

- **85 ADHD Pat., 6 – 14 J.**
- **db cross-over**
- **sleep diaries**

Table 3—Actigraphic Sleep Measures During Atomoxetine and Methylphenidate Treatment[a]

Sleep Measure	Baseline	Atomoxetine		Methylphenidate		Atomoxetine vs Methylphenidate		
		Endpoint	Change	Endpoint	Change	p Value	Effect Size	95% CI
Sleep-onset latency, min	30.11 ± 24.84	42.17 ± 31.61	12.06 ± 27.07	69.35 ± 43.86	39.24 ± 40.77	< .001[b]	-.79	-12.82, -6.49
Total nap time, min	3.47 ± 5.32	7.97 ± 10.11	4.49 ± 10.41	6.51 ± 7.30	3.04 ± 7.92	.475	.16	-1.68, 3.55
Total sleep interval, min	518.82 ± 44.13	503.82 ± 50.97	-15.00 ± 45.10	482.93 ± 62.64	-35.89 ± 56.10	.004[b]	.41	6.81, 34.15
Assumed sleep time, min	457.41 ± 47.34	442.14 ± 50.63	-15.26 ± 44.25	427.80 ± 57.20	-29.61 ± 53.00	.016	.29	2.73, 25.73
Interrupted sleep time, min	61.41 ± 20.85	61.67 ± 20.00	0.26 ± 15.04	55.13 ± 20.61	-6.28 ± 17.48	.025	.40	0.80, 11.69
Sleep interruptions, no.	31.78 ± 7.79	30.47 ± 10.42	-1.31 ± 6.83	27.42 ± 9.62	-4.36 ± 6.33	.011	.46	0.70, 5.19

[a]Data are from 50 subjects, except sleep interruptions, which were from 48 subjects both effect sizes; 95% confidence intervals computed based on methylphenidate subtracted from atomoxetine. Baseline, endpoint, and change data are presented as mean ± SD. CI refers to confidence interval.
[b]p Value remained significant after a Bonferroni adjustment for multiple comparisons.

Neurophysiologie

DOI 10.1007/s00702-003-0818-8
J Neural Transm (2003) 110: 821–829

Journal of Neural Transmission
Printed in Austria

Electrophysiological investigation of the effectiveness of methylphenidate in children with and without ADHD

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[1]EEG-Ep-Mapping Laboratory, Department of Child and Adolescent Psychiatry, and [2]EEG-EP-Mapping Laboratory, Department of Psychiatry, University Hospital of Würzburg, Germany

- ***A significant medication effect was detected following MPH treatment: segment 3 amplitudes in MPH-treated hyperactive children were not significantly different from those of healthy controls. MPH exerts a highly potent effect on stimulus recognition and resulting consequences.***
- ***Application of the CPT-OX enables the reliable measurement of electrophysiological correlates of the clinical effectiveness of MPH under different stimulus conditions.***

- **17 ADHD Pat., 20 Kontrollen, 7 – <12 J.**
- **MPH 10 mg/d, für 7 Tage**

Mean MPH dose was 0.34 mg/kg (range: 0.27–0.47 mg/kg).

- **verschiedene Reiz-/Aufgabenbedingungen**

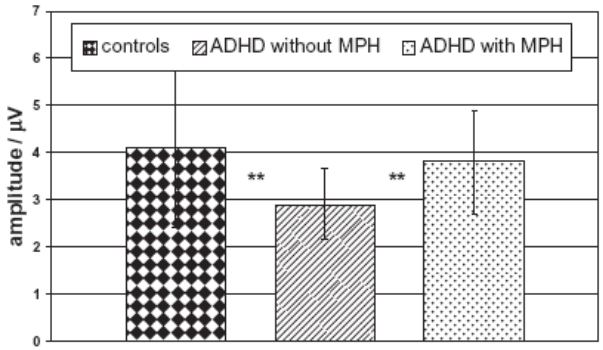

Fig. 3. Primer-amplitude maxima and SD in the time segment 3 for each ex group (**difference is very significant, $p < 0.01$)

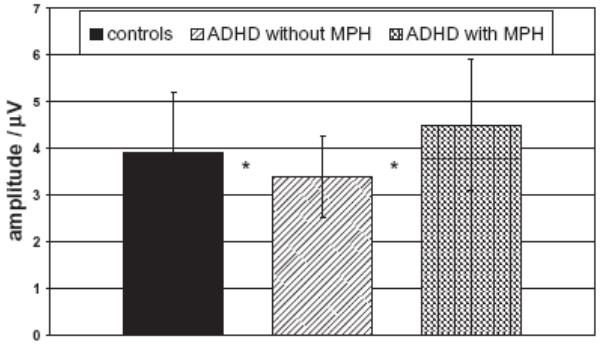

Fig. 4. NoGo-amplitude maxima and SD in the time segment 3 for each experimental group (*difference is significant, $p < 0.05$)

Neuropsychologie

J Neural Transm (2008) 115: 357–362
DOI 10.1007/s00702-008-0871-4
Printed in The Netherlands

Journal of Neural Transmission

Acute effects of methylphenidate on neuropsychological parameters in adults with ADHD: possible relevance for therapy

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- retrospektive Untersuchung
- N = 34 erw. ADHD Pat., 19 – 51 J.
- N = 23 bei Studienende
- Testdosis 10 mg MPH
- Tagesdosen 40 – 60 mg; 3 – 6 Mo
- signif. Verbesserungen div. neuropsycholog. Tests (Aufmerksamkeit, Gedächtnis, exek. Funktionen)
- r = 0.48, p < 0,011, mittl. Verbesserungen bei T2 u. T4
- keine signif. Korrel.: GAF Verb. mit kognit. Verbesserungen

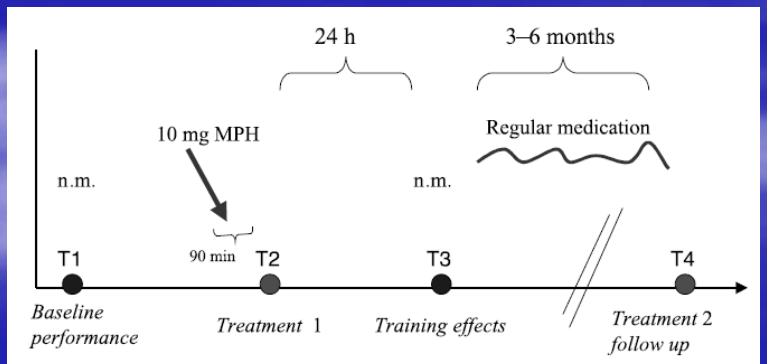

Fig. 1. Time points of neuropsychological testing. *T1* first test battery, baseline performance; *T2* second test battery, measurement of medication effects; *T3* third test battery, control for training effects; *T4* fourth test battery, follow up; *n.m* no medication; *MPH* methylphenidate

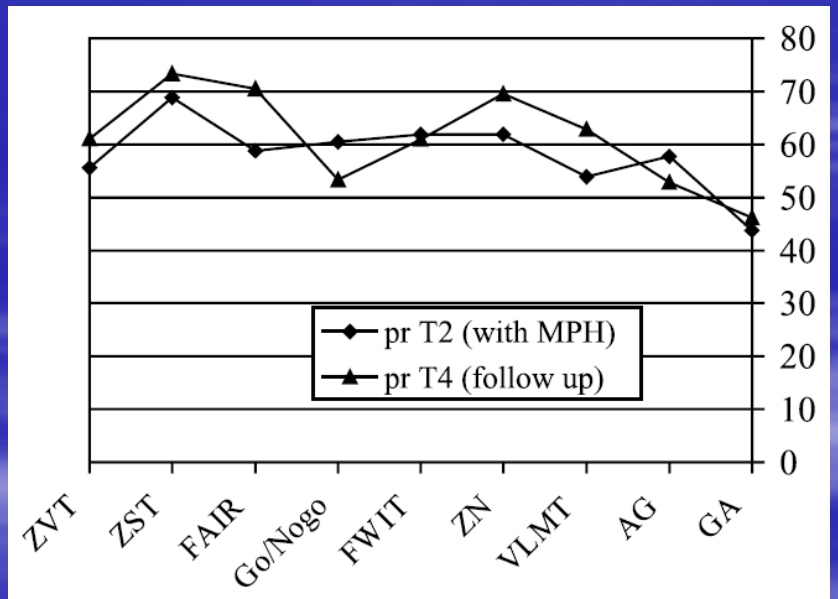

Fig. 3. Test results at T2 and T4 ($N = 23$). *ZVT* Trail-Making-Test; *ZST* digit symbol; *FAIR* Frankfurt Attention Inventory; *Go/Nogo* test of Test-battery for Attentional Performance; *FWIT* Color-Word-Interference Test; *ZN* digit span; *VLMT* Verbal Learning and Memory Test; *TAP-AG* working attention; *TAP-GA* divided attention; *MPH* methylphenidate; *follow up* 3–6 months regular intake of MPH; *pr* percentile rank score (0–100)

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Pharmacogenetics of Methylphenidate Response in Attention Deficit/Hyperactivity Disorder: Association With the Dopamine Transporter Gene (*SLC6A3*)

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- 141 ADHD Pat. , mittl. Alter ca. 10 J.
- 10-R homozygote Pat.: N = 70
- Mittl. Enddosis MPH ca. ≥ 30 mg/d; Behandlungsdauer ca. 50 – 60 Tage
- signif. Verbesserung div. Parameter, Stroop u. CPT
- kein Genotyp-Effekt für kognit. Parameter
- keine Korrelationen: Kognition mit klin. Wirksamkeit

Pharmacogenetic studies investigating the 40-bp VNTR polymorphism at *SLC6A3* and methylphenidate response have shown conflicting results and large differences in study design and efficacy endpoints. Our objective was to investigate the relation between the 3′-VNTR at *SLC6A3* and variability in methylphenidate response in a sample of 141 ADHD children and adolescents, assessed before and after methylphenidate treatment with both clinical and neuropsychological outcome measures. 10-R homozygotes were significantly overrepresented in the low response group, but no genotype effect was shown in cognitive variables improvement. A meta-analysis of genetic studies with comparable data (responders vs. non-responders) on a total of 475 subjects showed a significant association between the 10-10 genotype and low rates of methylphenidate response (mean Odds Ratio = 0.46; 95% CI [0.28–0.76]). Heterogeneity between these studies did not reach a significant level but, as publications with different endpoints were excluded from this meta-analysis, our results do not rule out a possible influence of study design.

Purper-Ouakil et al.

TABLE III. Pre- and Post-Treatment Cognitive Parameters

	Pre-treatment	Post-treatment	Statistics	
TMTA	20.89 (10.35)	20.01 (8.62)	$F_{1,221} = 0.45$	$P = 0.5$
TMTB	51.64 (35.71)	45.93 (36.76)	$F_{1,220} = 1.35$	$P = 0.25$
TMT B-A	29.71 (28.25)	25.92 (31.22)	$F_{1,220} = 0.88$	$P = 0.35$
Stroop CW	28.78 (10.85)	32.44 (10.99)	$F_{1,214} = 6.06$	$P = 0.01$*
Stroop Inter	23.78 (10.85)	23.61 (9.83)	$F_{1,214} = 13.00$	$P = 0.91$
CPT Om	56.51 (22.16)	48.09 (13.26)	$F_{1,108} = 5.25$	$P = 0.02$*
CPT Com	47.30 (11.71)	39.82 (11.42)	$F_{1,108} = 11.00$	$P < 0.01$*
CPT RT	54.17 (13.72)	51.30 (11.12)	$F_{1,108} = 1.36$	$P = 0.24$
CPT RTSE	55.20 (121.64)	47.99 (9.86)	$F_{1,108} = 10.37$	$P < 0.01$*
CPT Var	54.14 (11.47)	48.08 (9.76)	$F_{1,108} = 8.41$	$P < 0.01$*
CPT Det	49.47 (11.90)	41.58 (12.31)	$F_{1,108} = 11.34$	$P < 0.01$*
CPT Block RT	54.38 (14.29)	48.48 (8.72)	$F_{1,108} = 6.15$	$P = 0.01$*
CPT ISIRT	57.54 (15.14)	91.70 (49.54)	$F_{1,108} = 9.50$	$P < 0.01$*

TMT, Trail Making Test; Stroop CW, Stroop Color Word condition; Stroop Inter, Stroop Interference score; CPT OM, T score Ommission Errors; CPT Com, T score Commission Errors; CPT RT, T score Reaction Time; CPT RTSE, T score Reaction Time Standard Error; CPT Var, T score Variability; CPT Det, T score Detectability; CPT Block RT, T score Block change Reaction Time; CPT ISI RT, CPT T score Interstimulus Intervall change Reaction Time.
*$P < 0.05$.

The Effect of Discontinuation of Methylphenidate on Neuropsychological Performance of Children with Attention Deficit Hyperactivity Disorder

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Objective To use Cambridge Neuropsychological Test Automated Battery (CANTAB) test battery to assess the effects of discontinuation of treatment with methylphenidate on the neuropsychological performance of children with attention deficit hyperactivity disorder (ADHD) and to compare this performance with normative data.

Methods Fifteen boys meeting criteria for Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV ADHD aged between 4.5−14.6 yrs were selected. The CANTAB test battery was conducted after discontinuation of methylphenidate for a minimum of 24 hours and was repeated one week after the recommencement of treatment.

Results Performance differences between the unmedicated/medicated groups were found on the pattern recognition memory task ($F=0.37$, $p=0.041$) and intra/extra-dimensional (IED) Set-Shifting task [number of stages completed ($z=-4.572$, $p=0.001$) and total errors ($F=1.36$, $p=0.046$)]. In the unmedicated group, total errors made on IED Set-Shifting correlated with a lower strategy score on the Spatial Working Memory (SWM) task ($r=0.518$, $p=0.048$). In the medicated group, greater Spatial Span Length correlated with fewer "between search" errors made on the SWM test ($r=0.657$, $p=0.008$).

Conclusion Discontinuation of methylphenidate impairs performance on the CANTAB test battery in children with ADHD. These impairments, primarily in executive function, could be indicative of dysfunction in fronto-striatal networks, that methylphenidate can improve through manipulation of catecholaminergic pathways in the brain.

KEY WORDS: Discontinuation, Methylphenidate, Performance, Attention deficit hyperactivity disorder.

Psychiatry Invest 2007;4:76-83

- **15 Jungen mit ADHD, 4 – 15 J.**
- **MPH behandelt mind 3 Mo,**
- **Absetzen für 24 h: 1. Messung**
- **Wiederbehandlung 1 Wo: 2. Messung**
- **CANTAB: pattern recognition, set-shifting, (spatial working memory)**
- **Absetzen führte zu signif. Beeinträchtigung exekut. Funktionen (vorher durch MPH verbessert)**

Pharmakogenetik

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Pharmacogenetics of Methylphenidate Response in Attention Deficit/Hyperactivity Disorder: Association With the Dopamine Transporter Gene (*SLC6A3*)

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- 141 ADHD Pat. , mittl. Alter ca. 10 J.
- 10-R homozygote Pat.: N = 70
- Mittl. Enddosis MPH ca. ≥ 30 mg/d; Behandlungsdauer ca. 50 – 60 Tage
- signif. Genotyp-Effekt für klinische Parameter (Response, CGI-S, ADHD-RS)

TABLE II. Genotypes in the 3′-VNTR of the SLC6A3 Gene and Methylphenidate Response Status Assessed With CGI and ADHD-RS

	Genotype in the 3′-UTR VNTR of the SLC6A3 gene		
	10-R homozygotes (n = 70)	Other genotypes (n = 71)	Statistics (df); *P*-value
Response criteria I			
CGI-S improvement <2 points N (%)	23 (32.86%)	11 (15.49%)	$\chi^2(1) = 5.81$; $P = 0.02$
CGI-S improvement ≥2 points N (%)	47 (67.14%)	60 (84.51%)	
Response criteria II			
ADHD-RS <40% N (%)	27 (38.57%)	15 (21.13%)	$\chi^2(1) = 5.13$; $P = 0.02$
ADHD-RS ≥40% N (%)	43 (61.43%)	56 (78.87%)	

Re: Metaanalysis 40 bp VNTR, 3-UTR, *SLC6A3 (DAT1)*
(Purper-Oukil et al., 2008)

Lit:

10-10 R Pat. (homozygote) und Wirksamkeit

- **erniedrigt: 3 Arbeiten** (Winsberg, Comings, 1999; Roman et al., 2002; Cheon et al., 2005)
- **erhöht: 2 retrospektive Arbeiten** (Kirley et al., 2003; Bellgrove et al., 2005)

- **keine Assoziation (div. Allele u. Wirksamkeit): 5 Arbeiten** (Langley et al., 2005; Van der Meulen et al., 2005; McGough et al.; 2006, Mick et al., 2006; Zeni et al., 2007)
- **signif. Zusammenhang: 10-10 und schlechter Response, OR = 0.46**

TABLE IV. Meta-Analysis of DAT1 Pharmacogenetic Data of the 10/10 Genotype in the 3′-VNTR of the SLC6A3 Gene Based on Published Numbers of Methylphenidate Responders and Non-Responders

	Responders		Non-responders		Statistics		
	10-10	Other	10-10	Other	Effect size		
					(ln OR)	Var(ln OR)	OR
Winsberg and Comings [1999]	5	11	12	2	−2.14	0.53	0.12
Roman et al. [2002]	14	15	16	5	−1.28	0.34	0.32
Stein et al. [2005]	16	17	19	11	−0.59	0.25	0.55
Bellgrove et al. [2005]	12	9	7	8	0.41	0.45	1.51
Langley et al. [2005]	67	67	20	12	−0.50	0.15	0.60
Current sample	47	60	23	11	−0.94	0.15	0.39

Mean effect size (ln OR) = −0.78; 95% CI [−1.29 to −0.27].
Mean OR = 0.46; 95% CI [0.28–0.76].
[illegible] al; df = 5; $P = 0.16$.
Spearman correlation (effect vs. sample size): rs = 0.37; $P = 0.47$.

OR = Wahrscheinlichkeit für mittlere bis gute Response, Pat mit 10-10 Genotyp vs. Pat mit allen anderen

Neuroimaging

Neuroimaging

Langzeiteffekte (strukturell, Volumetrie)

Developmental Trajectories of Brain Volume Abnormalities in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

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Context Various anatomic brain abnormalities have been reported for attention-deficit/hyperactivity disorder (ADHD), with varying methods, small samples, cross-sectional designs, and without accounting for stimulant drug exposure.

Objective To compare regional brain volumes at initial scan and their change over time in medicated and previously unmedicated male and female patients with ADHD and healthy controls.

Design, Setting, and Participants Case-control study conducted from 1991-2001 at the National Institute of Mental Health, Bethesda, Md, of 152 children and adolescents with ADHD (age range, 5-18 years) and 139 age- and sex-matched controls (age range, 4.5-19 years) recruited from the local community, who contributed 544 anatomic magnetic resonance images.

Main Outcome Measures Using completely automated methods, initial volumes and prospective age-related changes of total cerebrum, cerebellum, gray and white matter for the 4 major lobes, and caudate nucleus of the brain were compared in patients and controls.

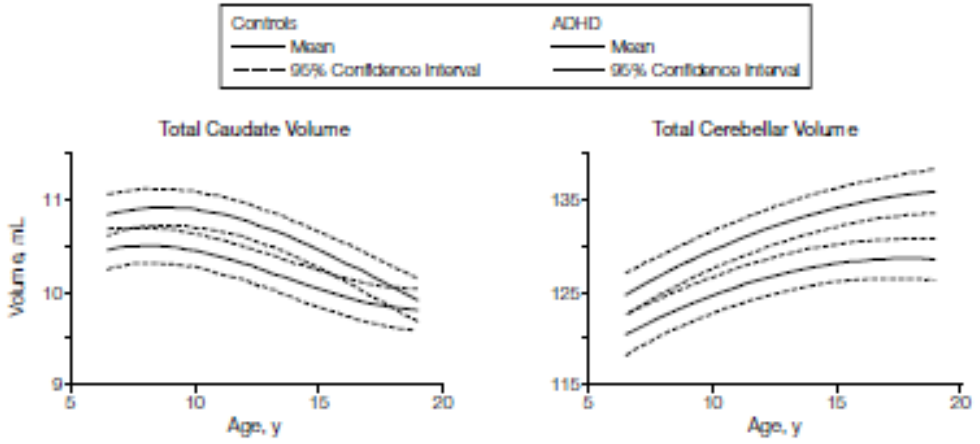
Results On initial scan, patients with ADHD had significantly smaller brain volumes in all regions, even after adjustment for significant covariates. This global difference was reflected in smaller total cerebral volumes (−3.2%, adjusted $F_{1,280}$=8.30, P=.004) and in significantly smaller cerebellar volumes (−3.5%, adjusted $F_{1,280}$=12.29, P=.001). Compared with controls, previously unmedicated children with ADHD demonstrated significantly smaller total cerebral volumes (overall $F_{3,280}$=6.65; all pairwise comparisons Bonferroni corrected, −5.8%; P=.002) and cerebellar volumes (−6.2%, $F_{1,280}$=8.97, P<.001). Unmedicated children with ADHD also exhibited strikingly smaller total white matter volumes ($F_{2,288}$=11.65) compared with controls (−10.7%, P<.001) and with medicated children with ADHD (−8.9%, P<.001). Volumetric abnormalities persisted with age in total and regional cerebral measures (P=.002) and in the cerebellum (P=.003). Caudate nucleus volumes were initially abnormal for patients with ADHD (P=.05), but diagnostic differences disappeared as caudate volumes decreased for patients and controls during adolescence. Results were comparable for male and female patients on all measures. Frontal and temporal gray matter, caudate, and cerebellar volumes correlated significantly with parent- and clinician-rated severity measures within the ADHD sample (Pearson coefficients between −0.16 and −0.26; all P values were <.05).

Conclusions Developmental trajectories for all structures, except caudate, remain roughly parallel for patients and controls during childhood and adolescence, suggesting that genetic and/or early environmental influences on brain development in ADHD are fixed, nonprogressive, and unrelated to stimulant treatment.

JAMA. 2002;288:1740-1748 www.jama.com

ATTENTION-DEFICIT/HYPERactivity disorder (ADHD), the most common childhood psychiatric disorder, is thought to reflect subtle abnormalities in central nervous system functioning.[1] For this reason, ADHD is being studied increasingly with a variety of brain imaging techniques throughout the life span. Magnetic resonance imaging (MRI) is particularly suitable for the study of pediatric patients, providing high-resolution images without ionizing radiation. Previous MRI neuroimaging studies, most with small samples, have reported smaller anatomic areas and/or volumes in patients with ADHD in regions of the cor-

Figure 2. Predicted Unadjusted Longitudinal Growth Curves for Total Caudate and Cerebellar Volume for Patients With ADHD vs Controls



ADHD indicates attention-deficit/hyperactivity disorder. Data beyond 16 years are for male patients only, because data from female patients did not exist beyond 16 years (effects ascribable to sex were assumed to be the same between ages 16-19 years as for ages 5-16 years, warranted as a single value to select the differences in intercepts [curve heights] for any case).

Table 4. Unadjusted Brain Volumes for Unmedicated and Medicated Patients With ADHD and Controls*

	Mean (SD)					*P* Values (Bonferroni Comparison)		
	Patients With ADHD							
	Unmedicated (n = 49)	Medicated (n = 103)	Controls (n = 139)	F Statistic†	*P* Values†	Unmedicated vs Medicated	Unmedicated vs Controls	Medicated vs Controls
Total cerebral volume	1040.4 (96.9)	1068.4 (124.9)	1104.5 (111.3)	6.65	.001	.58	.002	.03
Total gray matter	704.2 (70.0)	699.3 (80.8)	727.9 (74.3)	4.67	.01	>.99	.21	.01
Total white matter	336.2 (41.9)	369.1 (55.3)	376.6 (49.8)	11.65	<.001	<.001	<.001	.50
Frontal gray matter	216.6 (20.7)	217.6 (26.8)	225.2 (22.5)	4.06	.02	>.99	.10	.05
Parietal gray matter	117.0 (11.4)	116.4 (13.7)	122.0 (12.9)	6.22	.002	>.99	.08	.006
Temporal gray matter	173.2 (15.6)	174.4 (19.7)	181.6 (18.2)	6.32	.002	>.99	.02	.006
Occipital gray matter	63.2 (9.5)	62.1 (9.7)	66.5 (10.5)	6.05	.003	>.99	.17	.003
Frontal white matter	127.1 (16.6)	140.0 (22.2)	141.9 (18.5)	10.59	<.001	<.001	<.001	.84
Parietal white matter	66.5 (7.8)	72.6 (10.8)	74.9 (9.8)	12.86	<.001	.003	<.001	.14
Temporal white matter	69.7 (8.5)	76.6 (11.3)	77.6 (10.6)	10.54	<.001	<.001	<.001	>.99
Occipital white matter	28.6 (4.6)	31.1 (5.8)	32.2 (5.9)	7.39	.001	.06	<.001	.27
Caudate	10.50 (1.07)	10.29 (1.16)	10.75 (0.98)	5.69	.004	.52	.54	.002
Cerebellum	121.8 (11.7)	125.1 (12.4)	129.8 (12.7)	8.97	<.001	.47	<.001	.005

*ADHD indicates attention-deficit/hyperactivity disorder.
†Two-way analysis of variance (group [medicated vs unmedicated vs control] by sex); *df* (2, 288) for all regions. No sex by diagnoses interactions approached significance.

- N = 152 ADHD Pat, 5 – 18 J
- N = 49 unbeh. ADHD Pat.
- N= 139 Kontrollen
- kein Unterschied unbeh vs beh. Pat: Total Vol u graue Subst,
- unbeh vs beh Pat signif weniger weiße Subst (- 8.9%)

Volumetric MRI differences in treatment-naïve vs chronically treated children with ADHD

Steven R. Pliszka, MD; Jack Lancaster, PhD; Mario Liotti, MD, PhD; and Margaret Semrud-Clikeman, PhD

Abstract—*Objective:* To determine if there are differences in the volume of the caudate and anterior cingulate cortex (ACC) between children with attention deficit hyperactivity disorder (ADHD) and controls, and if such differences are related to the subjects' history of stimulant treatment. *Methods:* We performed a case-control study in an academic medical center. Twenty-one healthy controls, 16 children with ADHD, combined type with a history of stimulant treatment, and 14 children with ADHD, combined type treatment naïve, underwent structural MRI. All children with ADHD were medication-free at the time of the MRI. Regional hemispheric volumes (in cm^3) of caudate and anterior cingulate cortex were determined. *Results:* There were significant differences bilaterally on caudate volume for both ADHD groups vs controls, with no difference between the ADHD groups on either side. In contrast, the right ACC was significantly smaller for the ADHD-treatment naïve (ADHD/TN) group compared to the ADHD-treated (ADHD/Rx) and control group. The volume of left ACC approached significance contrast between ADHD/RX and ADHD/TN. There were no differences found between the ADHD/Rx and controls on the ACC volumes bilaterally. *Conclusions:* The results from this study indicate a relationship of previous treatment history with caudate and anterior cingulate volumetric changes in children with attention deficit hyperactivity disorder–combined type.

NEUROLOGY 2006;67:1023–1027

- N=16 Pat Stimulantien-beh. (≥ 1 J., mean: 4.9 J.)
- N= 14 Pat medik.-naiv
- N=21 ges Kontrollen; ≤ 13 J.
- alle: ohne Medik bei MRI
- signif Vol Reduktion Pat vs Kontr: N caud bilateral
- signif TN < Rx: re ant Cing (R ACC)
- kein Unterschied: Rx u Kontr, ACC bilateral

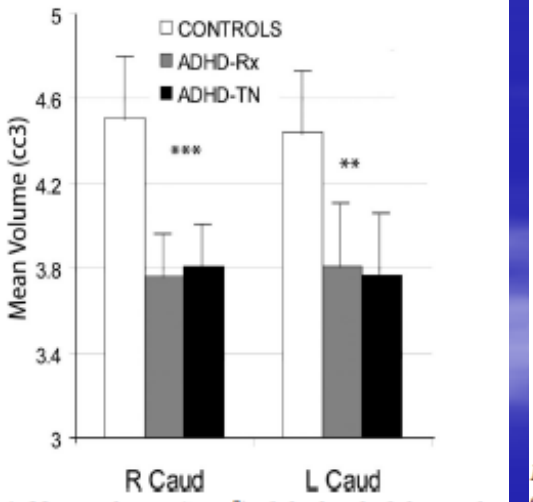


*Figure 1. Mean volumes (in cc^3) of the head of the caudate nucleus for the three groups. R Caud = right caudate head; ADHD Rx = children with attention deficit hyperactivity disorder (ADHD) with chronic treatment; ADHD TN = children with ADHD never treated. ***$p < 0.0001$; **$p < 0.001$.*

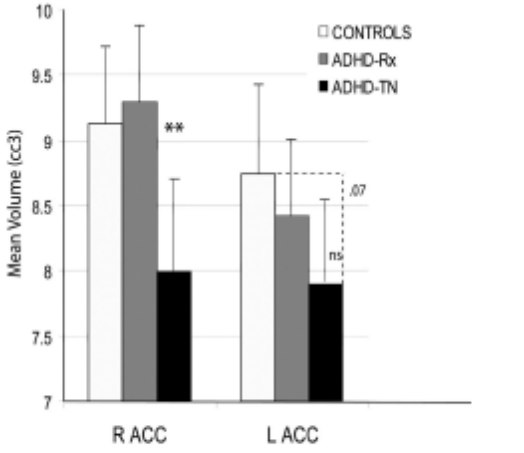


*Figure 2. Mean volumes (in cc^3) of the anterior cingulate cortex in the three groups. R ACC = right anterior cingulate cortex; L ACC = left cingulate cortex (L ACC); ADHD Rx = children with attention deficit hyperactivity disorder (ADHD) with chronic treatment; ADHD TN = children with ADHD never treated. **$p < 0.001$.*

Disc.:
„..speculate .. stimulants .. may lead to increased formations of connections within the ACC and .. increase in volume.
… It may be that improved communication between the frontal lobes and ACC .. is facilitated by administration of medication.“

MPH Behandlung assoziiert mit ‚Normalisierung‘ des ACC Volumens (Gruppenvgl.)

(nach K. Konrad, 10/2008)

Langzeiteffekte von MPH (funktionell; fMRT)

Ähnliche Veränderungen (gegenüber Gesunden) in fronto-striatalen Bahnen bei vorbehandelten wie bei medikamenten-naiven Patienten:

Konrad et al., 2006,

Pliszka et al., 2006,

Rubia et al. 2005,

Smith et al. 2006

„Abnorme Aktivierungsmuster bei ADHD sind zentral für die Erkrankung, nicht Folge der (medikamentösen) Behandlung“

(nach K. Konrad, 10/2008)

Neuroimaging

Effekte von MPH (funktionell; akut, div.)

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Neurobiology

Selective effects of methylphenidate in attention deficit hyperactivity disorder: A functional magnetic resonance study

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f MRT

- N=10 Jungen mit ADHD, ≥ 10 J. ,
  7.5–30 mg MPH (übl. Dosis)
- N= 6 Kontrollen: 10 mg MPH Einmalgabe
- fMRTs ≥ 1 Wo Abstand (on, off MPH);
- Response-inhibition tasks
- Pat vs C: > Aktiv frontal (response-contr.),
  < striatal (stimulus-contr., Fig !)
- MPH: Verbess (Leistung) für bd Grp bei 1. Aufg, nur bei Pat in der 2. Aufg
- MPH: Aktiv frontral bd Grp, striatal Pat, Reduktion in Kontr (Fig !)
- *„MPH affects striatal activation differently..“*
  „… drug-related modulation region-specific and task-specific…“

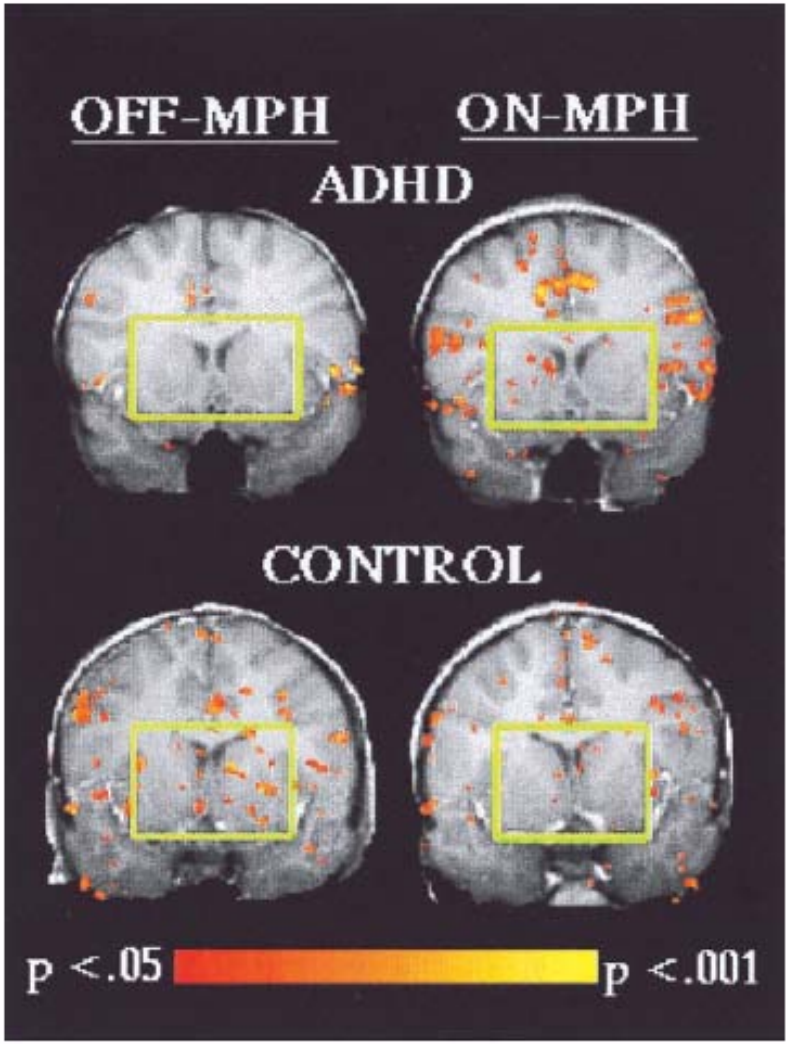

FIG. 6. Activation during response inhibition on the stimulus-controlled task in a coronal slice located 12 mm anterior to the anterior commissure for an ADHD and a control child. Green squares highlight the opposite effect of MPH in the head of the caudate and putamen in the ADHD and control child.

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NeuroImage 42 (2008) 96–41

Increased cerebral perfusion in adult attention deficit hyperactivity disorder is normalised by stimulant treatment: A non-invasive MRI pilot study

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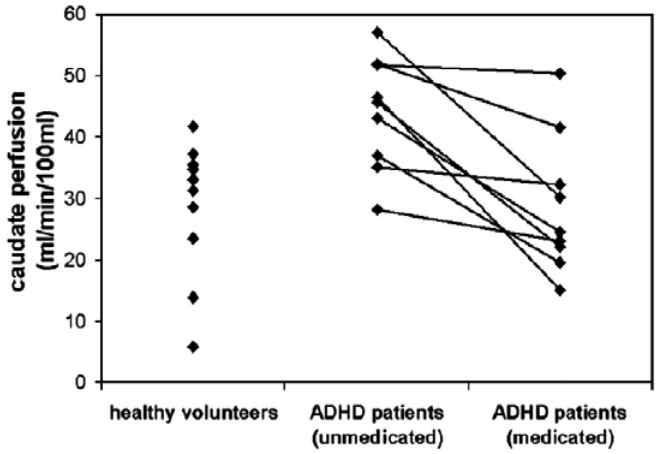

Fig. 3. Distribution of perfusion values extracted from the caudate nucleus cluster showing reduced perfusion following treatment in the ADHD group. Perfusion in the same cluster for the control group is shown for comparison. The unmedicated ADHD group demonstrated a 51% increase in perfusion in this region compared to controls; after medication these perfusion values were normalised (−1% relative to controls).

- N=9 erw. ADHD Pat
- alle Responder auf Stimulantien
- Beh ≥ 1 Mo
- MRT (CASL), 1 Scan n. Abs. ≥ 1 Wo
- 11 Kontrollen
- No task ! Relax!

- Perfusion erhöht für Pat: li N caud, frontale u parietale Regionen
- MPH: Reduktion in N caud u front Reg (‚Normalisierung')

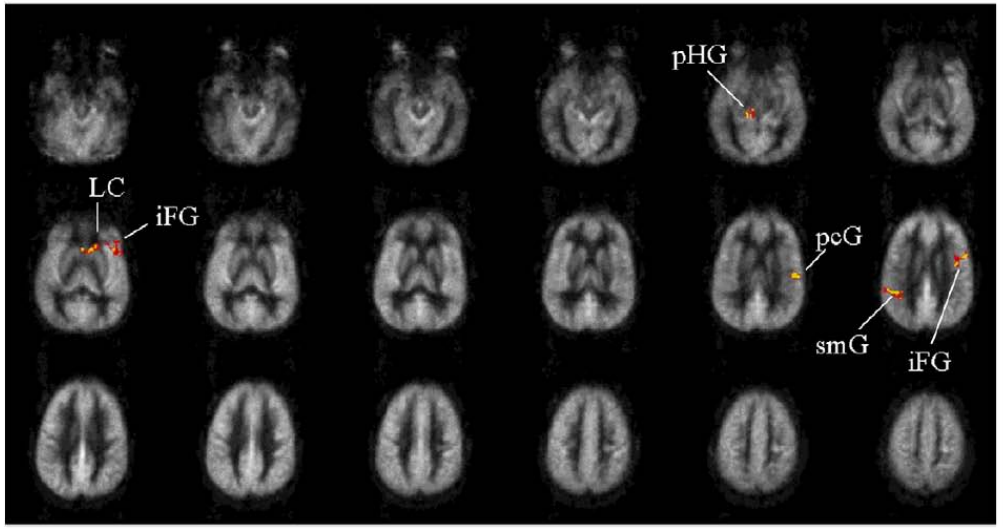

Fig. 2. Significant clusters from the paired comparison between ADHD patients on and off treatment with methylphenidate. Red regions denote clusters where the perfusion decreased with medication (off>on). Significance level: $p<0.005$, corrected. Significant clusters are in the left caudate (LC), inferior frontal gyrus (iFG), parahippocampal gyrus (pHG), post-central gyrus (pcG), and supra-marginal gyrus (smG). Images are shown in radiological orientation.

5976 • The Journal of Neuroscience, June 4, 2008 • 28(23):5976–5982

Behavioral/Systems/Cognitive

Methylphenidate Has Differential Effects on Blood Oxygenation Level-Dependent Signal Related to Cognitive Subprocesses of Reversal Learning

Chris M. Dodds,[1,2] Ulrich Müller,[1,2,3] Luke Clark,[1,2] Anouk van Loon,[1,4] Roshan Cools,[1,5] and Trevor W. Robbins[1,2]
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Complete understanding of the neural mechanisms by which stimulants such as methylphenidate ameliorate attention deficit hyperactivity disorder is lacking. Theories of catecholamine function predict that the neural effects of stimulant drugs will vary according to task requirements. We used event-related, pharmacological functional magnetic resonance imaging to investigate the effects of 60 mg of methylphenidate, alone and in combination with 400 mg of sulpiride, on blood oxygenation level-dependent (BOLD) signal in a group of 20 healthy participants during probabilistic reversal learning, in a placebo-controlled design. In a whole-brain analysis, methylphenidate attenuated BOLD signal in the ventral striatum during response switching after negative feedback but modulated activity in the prefrontal cortex when subjects maintained their current response set. The results show that the precise neural site of modulation by methylphenidate depends on the nature of the cognitive subprocess recruited.

Key words: methylphenidate; dopamine; striatum; prefrontal cortex; reversal learning; fMRI

- N = 20 Gesunde f MRT
- Plc-kontrolliert,
- Einmalgabe 60 mg MPH,
  mit u. ohne Sulpirid, 400mg
- Task: Reversal learning
- MPH: Abschwächung re Putamen (Switching), Fig !
  Zunahme präfront Kortex (Maintenance)
- signif Interaktion MPH/Aufgabenbedingung
- regionale und Aufgabenspezifität

‚modulated' = increased

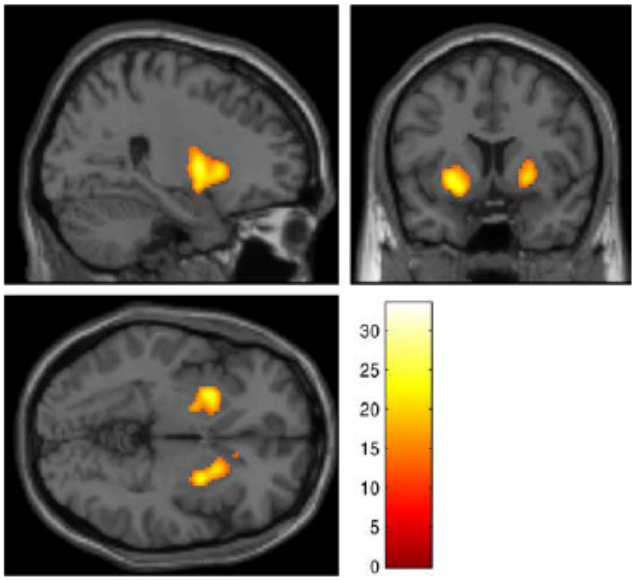


Figure 3. Whole-brain SPM showing areas in which there was a significant interaction between methylphenidate and condition in the random-effects contrast final reversal errors — nonswitch errors, superimposed on the MNI template brain. Methylphenidate reduced switch-related activity bilaterally in the ventral putamen, with small peaks also in the right cuneus and right precentral gyrus. In this figure, higher-intensity values represent a greater methylphenidate-induced decrease in BOLD response. The figure displays all significantly activated clusters below a threshold of p < 0.05, FWE corrected, containing at least 20 voxels. Color scale represents magnitude of F values. The right putamen was also activated at the more conservative threshold of $p < 0.05$, FWE corrected.

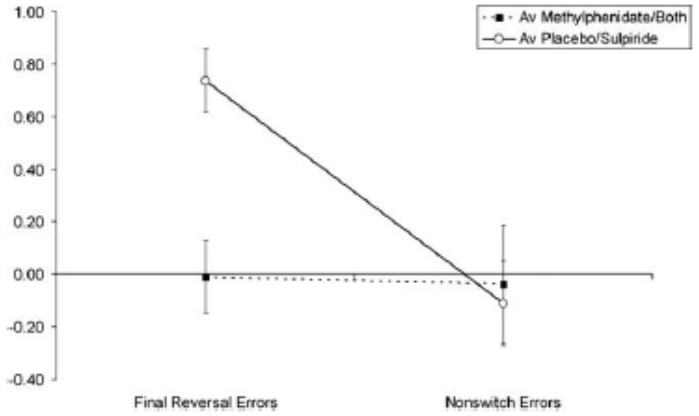


Figure 4. Mean parameter estimates for final reversal errors and nonswitch errors in the right putamen. For each subject, beta values were extracted from a region of interest (ROI) based on the activated cluster from the second-level contrast, which showed a main effect of methylphenidate on BOLD signal in the contrast final reversal errors — nonswitch errors. This region is shown in Figure 3. Beta values were then averaged across the three task sessions and across all subjects to obtain a mean beta value for each event in each drug condition. These values were then averaged across the methylphenidate and combined drug conditions and across the sulpiride and placebo drug conditions to show the main effect of methylphenidate on switch-related BOLD signal. ROI definition and beta value extraction were performed with the ROI toolbox Marsbar (Brett et al., 2002). Error bars represent SEM.

Article

Evidence That Methylphenidate Enhances the Saliency of a Mathematical Task by Increasing Dopamine in the Human Brain

Nora D. Volkow, M.D.
Gene-Jack Wang, M.D.
Joanna S. Fowler, Ph.D.
Frank Telang, M.D.
Laurence Maynard, M.D.
Jean Logan, Ph.D.
Samuel J. Gatley, Ph.D.
Naomi Pappas, M.S.
Christopher Wong, M.S.
Paul Vaska, Ph.D.
Wei Zhu, Ph.D.
James M. Swanson, Ph.D.

Objective: Methylphenidate is the most commonly prescribed drug for attention deficit hyperactivity disorder (ADHD), yet its therapeutic mechanisms are poorly understood. The objective of this study was to assess if methylphenidate, by increasing dopamine (neurotransmitter involved in motivation) in brain, would enhance the saliency of an academic task, making it more interesting.

Method: Healthy subjects (N=16) underwent positron emission tomography with [^{11}C]raclopride (dopamine D_2 receptor radioligand that competes with endogenous dopamine for binding) to assess the effects of oral methylphenidate (20 mg) on extracellular dopamine in the striatum. The authors compared the effects of methylphenidate during an academic task (solving mathematical problems with monetary reinforcement) and a neutral task (passively viewing cards with no remuneration). In parallel, the effects of methylphenidate on the interest that the academic task elicited were also evaluated.

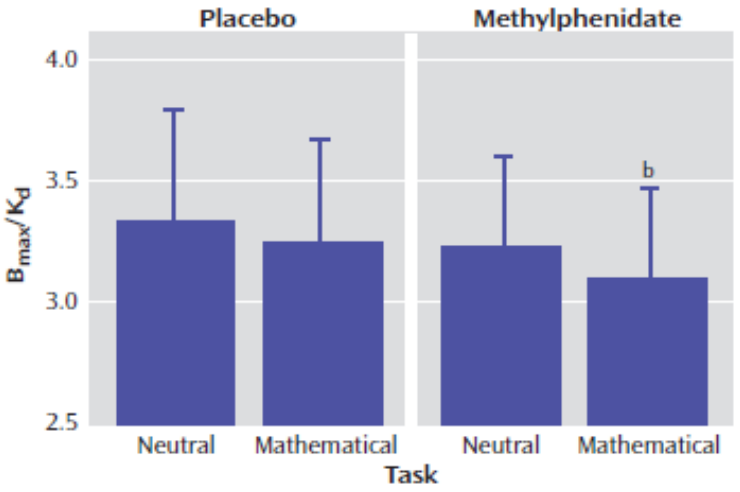
Results: Methylphenidate, when coupled with the mathematical task, significantly increased extracellular dopamine, but this did not occur when coupled with the neutral task. The mathematical task did not increase dopamine when coupled with placebo. Subjective reports about interest and motivation in the mathematical task were greater with methylphenidate than with placebo and were associated with dopamine increases.

Conclusions: The significant association between methylphenidate-induced dopamine increases and the interest and motivation for the task confirms the prediction that methylphenidate enhances the saliency of an event by increasing dopamine. The enhanced interest for the task could increase attention and improve performance and could be one of the mechanisms underlying methylphenidate's therapeutic effects. These findings support educational strategies that make schoolwork more interesting as nonpharmacological interventions to treat ADHD.

(Am J Psychiatry 2004; 161:1173–1180)

- **PET**, Racloprid (D2 Ligand)
- N=16 Gesunde, 20 mg MPH, Plc, Einzelgaben
- Tasks: neutral (Karten), mathem. (mit Belohnung, 50 $)
- Effekte:
- Racloprid Bindung am geringsten bei mathem Aufg/MPH (mehr extrazell DA); Striatum
  - *„context-dependency,*
  - *interest, motivation; ..increase attention, improve performance (?)*
  - *..support educational strategies that make schoolwork more interesting as non-pharm interventions to treat ADHD.“*

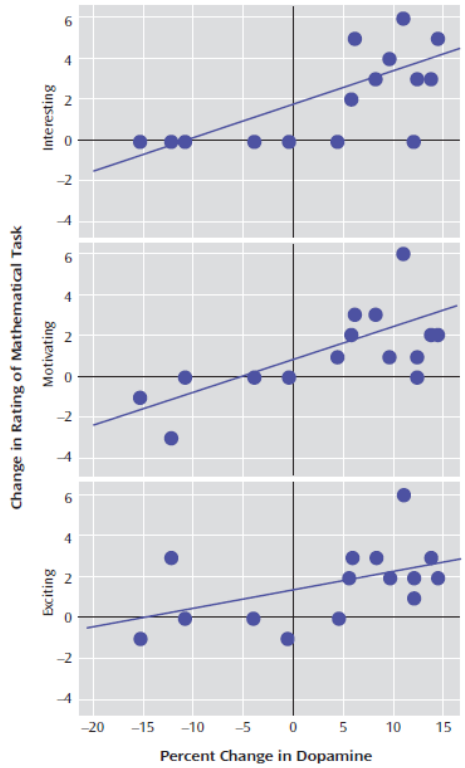
FIGURE 2. Methylphenidate-Induced Changes in Dopamine Transporter Binding Potential (B_{max}/K_d) in the Striatum of 16 Healthy Subjects Performing a Math Task With a Monetary Reward or a Noncompensated Neutral Task[a]



[a] Following oral administration of methylphenidate (20 mg) or placebo, subjects underwent positron emission tomography scans while solving mathematical problems with monetary reinforcement (math task) or passively viewing pictures of scenery with no renumeration (neutral task). Bars represent standard deviations of the mean values.

[b] Significantly different from the placebo/neutral task condition (which was considered the baseline), per post hoc paired t test ($p \leq 0.05$).

FIGURE 3. Relationship Between the Changes in Extracellular Brain Dopamine During a Math Task With a Monetary Reward and Changes in Descriptor Ratings of the Math Task Following Administration of Methylphenidate in 16 Healthy Subjects[a]



[a] Changes were determined by comparing values after oral methylphenidate (20 mg) with values after placebo.

p = 0.003

p = 0.004

p = 0.05

Dopaminergic dysfunction in attention deficit hyperactivity disorder (ADHD), differences between pharmacologically treated and never treated young adults: A 3,4-dihdroxy-6-[^{18}F]fluorophenyl-L-alanine PET study

Andrea G. Ludolph,[a] Jan Kassubek,[b] Klaus Schmeck,[c] Cornelia Glaser,[a] Arthur Wunderlich,[d] Andreas K. Buck,[e] Sven N. Reske,[e] Joerg M. Fegert,[a] and Felix M. Mottaghy[e,f,*]

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[c]*Department of Child and Adolescent Psychiatry, University of Basel, Switzerland*
[d]*Department of Radiology, University of Ulm, Germany*
[e]*Department of Nuclear Medicine, University of Ulm, Germany*
[f]*Department of Nuclear Medicine, University Hospital KU Leuven, Belgium*

NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 41 (2008) 718–727

- FDOPA **PET** study
- 20 männl. erw. ADHD Pat
- 12 MPH behandelt, 8 nie behandelt
- 18 Kontrollen
- MPH abgesetzt 1 Wo vor Untersuchung
- ADHD Pat vs C, lower Ki bilateral Putamen, Amygdala, re ant Cingulum
- Unbeh Pat vs C, lower Ki: li Putamen, re Amygdala, re dorsal Mittelhirn
- Beh Pat vs C, lower Ki: Striatum u Amygdala bds, re dorsal Mittelhirn
- *„.. Untreated .. dopamine dysfunction ..partly due to compensatory mechanisms.*

Ludolph et al., 2008; *treated vs. untreated pats*

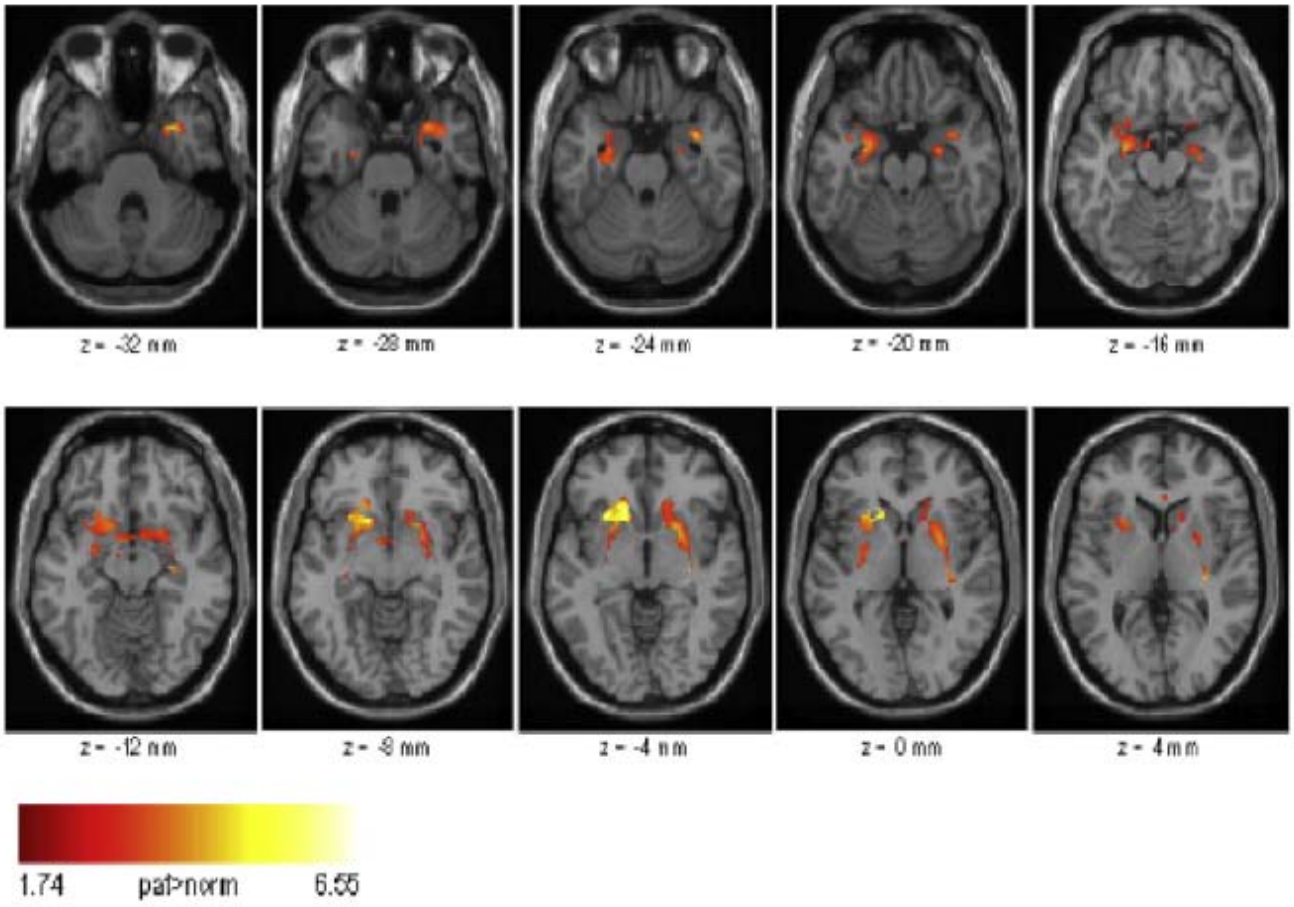

Fig. 4. Treated vs. untreated patients. The comparison 'treated patients > than untreated patients' revealed no significant results. However, in the comparison 'treated patients < than untreated patients', the bilateral putamen and bilateral amygdala showed a significantly decreased K_i in treated ADHD patients. Treatment might have augmented pre-existing compensatory processes.

- **ADHD treated pats.: signif decreased Ki in putamen and amygdala bilaterally (vs untreated pats);**

- ***„MPH seems to down-regulate DA turnover; .. might have augmented pre-existing compensatory processes,***
- ***This effect one component in the MOA of MPH in ADHD treatment?“***

Dopamintransporter – Struktur, Funktion und Bedeutung für die ADHS

Klaus-Henning Krause[1], Johanna Krause[2]

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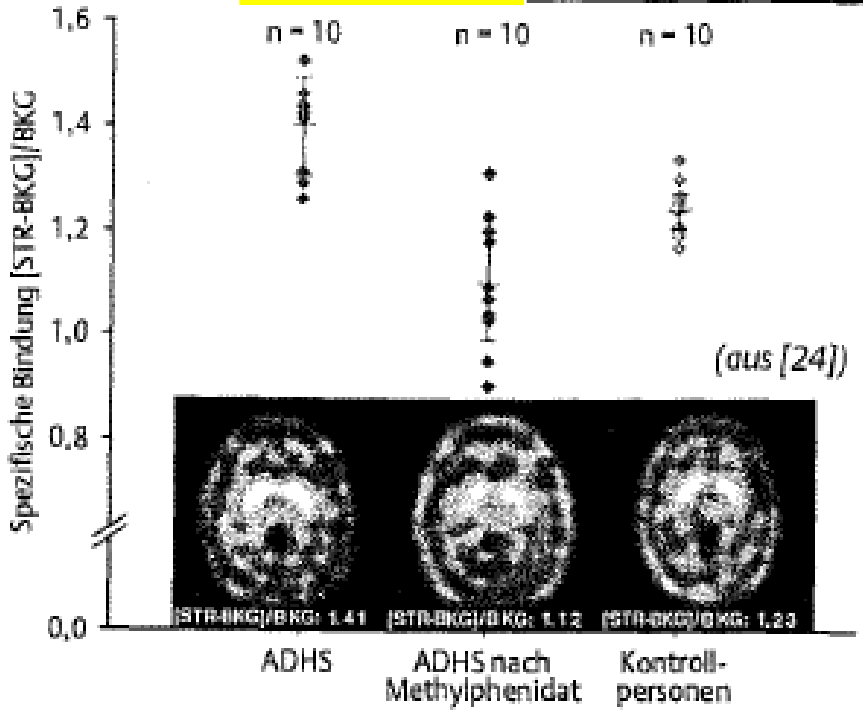
[2] *Praxis für Psychiatrie und Psychotherapie, Ottobrunn*

psycho*neuro* 2006; 32 (4): 209–214

SPECT

- N = 10 erw. ADHD Pat
- N = 10 Kontrollen
- MPH: 15 mg/d
- ADHD Pat: 17 % Erhöhung der Verf

Abb. 6 Striatäre DAT-Verfügbarkeit im TRODAT1-SPECT



Erwachsene Patienten mit ADHS vor Einleitung einer Therapie mit Methylphenidat und nach Einnahme von 3 x 5 mg Methylphenidat pro Tag im Vergleich zu gleichaltrigen Kontrollen. STR = Dichte im Striatum, BKG = Dichte im Background (Zerebellum)

Dopamintransporter – Struktur, Funktion und Bedeutung für die ADHS

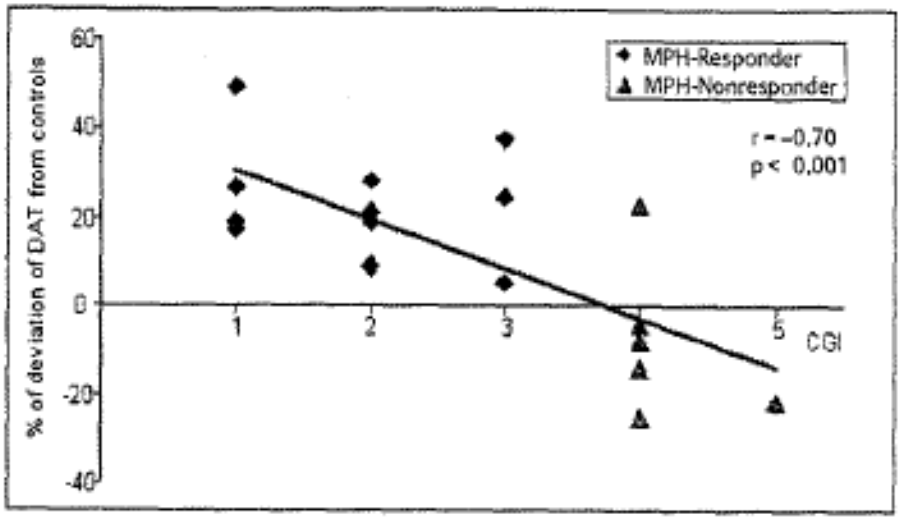
Klaus-Henning Krause[1], Johanna Krause[2]

[1] Friedrich-Baur-Institut, Ludwig-Maximilians-Universität, München
[2] Praxis für Psychiatrie und Psychotherapie, Ottobrunn

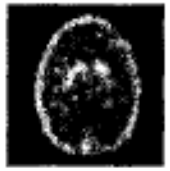
psychoneuro 2006; 32 (4): 209–214

- N = 18 erw. ADHD Pat
- 10 Wo Behandlung
- SPECT; DAT Verfügbarkeit vor (!) Beh gemessen
- CGI-I: 1 = very much improved

Abb. 8 Therapeutisches Ansprechen auf Methylphenidat




hohe DAT


niedrige DAT

Abhängigkeit von der striatären DAT-Verfügbarkeit (ausgedrückt als Prozentsatz der Abweichung von den Normalwerten der jeweiligen altersentsprechenden Kontrollgruppe) vor Therapie bei 18 erwachsenen Patienten mit ADHS ohne Nikotinabusus, beurteilt nach 10wöchiger Behandlung mit Methylphenidat (CGI = Clinical Global Improvement) *(modifiziert nach [23])*

psychoneuro 2006; 32 (4)

„ .. Pat mit ADHS, die primär keine Erhöhung der DAT aufweisen, auf eine Behandlung mit MPH i.d.R. nicht positiv reagieren.“

„ Eigene Untersuchungen .. nicht auf eine Veränderung der DAT-Verfügbarkeit in Abhängigkeit .. des 9- bzw. 10 Allels hin.“

Dopamine Transporter Gene, Response to Methylphenidate and Cerebral Blood Flow in Attention-Deficit/Hyperactivity Disorder: A Pilot Study

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[2]*Department of Genetics, Federal University of Rio Grande do Sul, Brazil*

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KEY WORDS ADHD; DAT1 gene; SPECT; methylphenidate

ABSTRACT The homozygosity of the 10-repeat allele at dopamine transporter gene (DAT1) seems to be associated with a poor response to methylphenidate (MPH) in children with attention-deficit/hyperactivity disorder (ADHD). This pilot study aimed to simultaneously assess polymorphisms at DAT1, response to MPH, and neuroimaging. Only ADHD children with at least a moderate response to MPH were included. Significantly higher regional cerebral blood flows assessed by single photon emission computerized tomography (SPECT) were detected in medial frontal and left basal ganglia areas in children with homozygosity for the 10-repeat allele at DAT1 gene ($n = 4$) than in children without this genotype ($n = 4$) ($P < 0.05$). These findings provide a preliminary connection between pharmacogenetics and neurobiological investigations on stimulant treatment of ADHD. **Synapse 48:87–89, 2003.**

- N=4, ADHD Pat, 10-10 R Genotyp (8-12 J)
- N= 4, ohne diesen G.
- alle Pat. ≥ mittl. Response
- MPH, 4 Tage lang, 0.7 mg/kg/d
- SPECT Untersuchung (Tc-ECD)
- Signif höherer Blutfluss bei 10-10 Homozyg.: medio-frontal und li Basalganglien

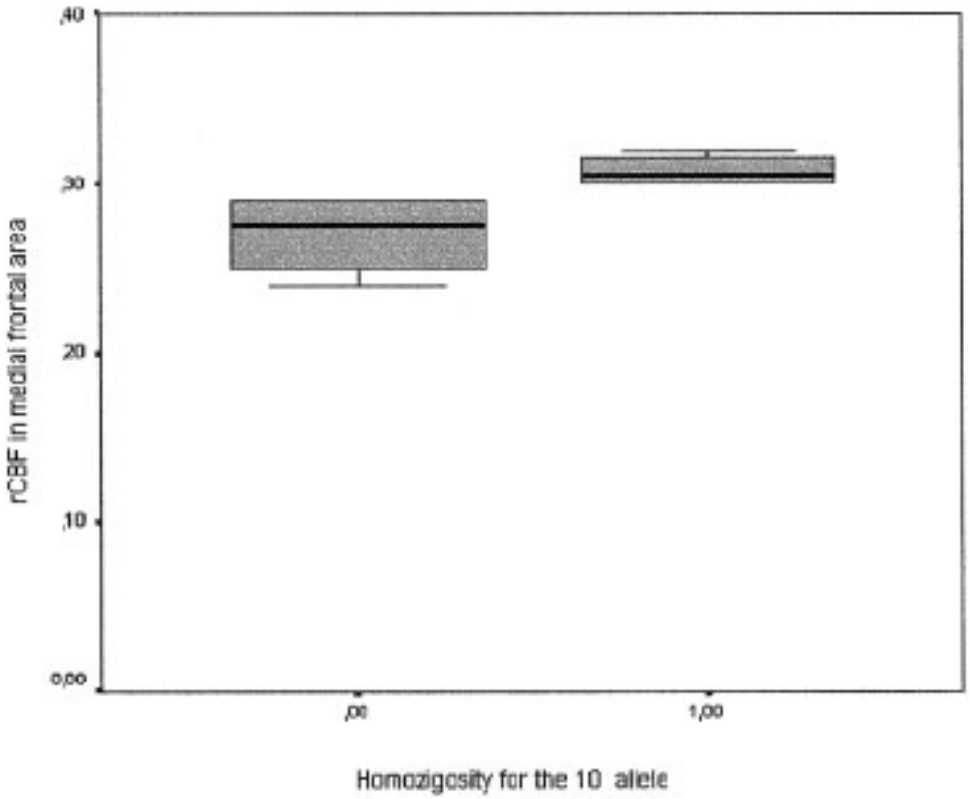

Fig. 1. Regional cerebral blood flow (rCBF) in ADHD children. 0 = group without homozygosity for the 10 repeat allele at DAT1 ($n = 4$); 1 = group with the 10/10 alleles ($n = 4$).

AACAP Symposium, Oct 2008, Chicago, Abstract volume

TREAT ADHD

13.3 COMMON AND UNIQUE EFFECTS OF METHYLPHENIDATE AND ATOMOXETINE IN THE TREATMENT OF ADHD

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Objectives: To review similarities and differences in the nature of response to methylphenidate (MPH) and atomoxetine (ATX), and illustrate that these medications have both common and unique effects. **Methods:** Data from animal studies, human neuroimaging studies, and large composite clinical trials are reviewed. **Results:** MPH is somewhat more effective than ATX. However, many subjects respond well to both medications, and there is preferential response in approximately one third of subjects treated with both medications. This is consistent with findings from animal and human neuroimaging studies which indicate both common and unique mechanisms of action. Recently completed analyses from a large, composite pediatric data set suggest that many subjects respond very well (> 40% decrease in ADHD Rating Scale score) to ATX, but an almost equal number do not (< 25% change score), with a relatively small number of subjects falling in between. This is in contrast to the more typical linear response often seen with stimulants. Among ATX responders (> 40% change score) improvement in ADHD RS (Rating Scale) ratings of > 25% is observed within 2 – 4 weeks, so extended treatment is not required. **Conclusions:** MPH and ATX share many common effects, however, there are also several unique effects that relate to differences in mechanisms of action, and the nature and temporal characteristics of response.

STIM ADHD

55th Annual Meeting, AACAP
Symposium 13 *(open)*
Special Pharmacotherapy Considerations in the Treatment of Pediatric ADHD
Thursday, October 30, 2008: 8:00 AM-11:00 AM

Comparator fMRI Study of Methylphenidate and Atomoxetine: Summary of Findings

- MPH and ATX both increase activation in key regions within attention circuitry
  - Both medications affect anterior and posterior attention networks
    - MPH produces relatively selective activation of striatum, even after 6 weeks of treatment
    - ATX has relatively more robust and possibly selective effects in several cortical regions, most clearly pACC

- Interpretation of findings
  - Profiles of treatment-related activation conform to mechanisms of medication effects delineated in animal studies and seen during baseline performance of the go/no-go task
  - Predominance of common effects are consistent with findings indicating that many subjects respond to either medication
  - Increased activation is not related to repeat scanning
    - Minimal change in error profiles with both treatments, so differences in activation pre to post are not accounted for by task performance
    - Different patterns of activation for the 2 medications also argues against a non-specific effect of time

Newcorn, Schulz, Fan, AACAP Annual Meeting, Oct, 2008, *Unpublished data*

Zusammenfassung/Schlussfolgerungen I

Bspl. von

Medikations‘effekten‘ auf funktionelle und strukturelle Veränderungen bei ADHS

(Pathogenese = Krankheitsentstehung und - entwicklung),

Behandlung assoziiert mit:

- Klinik: DA-erge und Nor-adrenerge Substanzen: ähnl. Effekten auf Kernsymptomatik von ADHS, ggf. Differenzen in der ES
- Schlaf: differentielle Effekten
- Neurophysiologie: ‚Normalisierung‘/Erhöhung der P3a
- Neuropsychologie: Verbesserung kognitiver Testergebnisse (Stroop, CPT)
- Absetzen: Verschlechterung exekutiver Funktionen (CANTAB)
- Pharmakogenetik: 10-10 R Allel (DAT) assoziiert mit schlechterer klin. Response

Zusammenfassung/Schlussfolgerungen II

Bspl. von

Medikations‘effekten‘ auf funktionelle und strukturelle Veränderungen bei ADHS
(Pathogenese = Krankheitsentstehung und - entwicklung),

Behandlung assoziiert mit:

Neuroimaging (Langzeit)

- Kein Hinweis für abnorme Hirnentwicklung (Volumen) (Castellanos et al.)
- Volumen des ACC (‚Normalisierung‘) (Pliszka et al.)
- Medik.-naive und behandelte Pat ähnl. fronto-striatale Veränderungen (funktionell)

Neuroimaging (akut, div.)

- Aktivierung im Striatum: ADHD Pat. erhöht, Gesunde reduziert (Vaidya et al.)
- N. caudatus Perfusion (‚Normalisierung‘/Erniedrigung) (O‘Gorman et al.)
- Regionale Effekte von Art der Aufgabe abhängig (Volkow et al.; Dodds et al.)
- Kontextabhängigkeit, Motivation/Interesse (assoziiert mit erhöhter Aufmerksamkeit?) (Volkow et al.)
- Augmentation vorbestehender kompensatorischer Prozesse (Ludolph et al.)

- DAT: Verfügbarkeit (‚Normalisierung‘/Erniedrigung)
- hohe Verfügbarkeit assoziiert mit guter klin. Wirksamkeit (Krause et al.)
- DAT: 10/10 repeat Allel Pat: höheren reg. Blutfluss (Rohde et al.)

- Atx/MPH Vgl.: ähnliche u. differentielle Effekte (Newcorn et al.)

Zusammenfassung/Schlussfolgerungen III

Diese Bspl. geben Hinweise, dass:

- **Medikation assoziiert mit Effekten, die die bei ADHD beobachteten Symptome und Veränderungen in verschieden – u. a. neurobiologischen - Domänen reduzieren/‘normalisieren‘,**
- **damit – offenbar – mit für ADHD relevanten pathogenetischen Prozesse interagiert; Ursachen/Kausalität damit vermutlich nicht/nur partiell aufgehellt**
- **Zusammenhänge erscheinen komplex/multivariat und zunächst nur auf Gruppenebene darstellbar**
- **(fehlende) Korrelationen zwischen den Domänen (z. B. Klinik/GAF/Kognition/Genetik)**
- **Noch rel. wenige/einzelne Untersuchungen; - Metaanalysen – Multivariate Ansätze mehr ‚Erklärung‘?**
- **Klare Parameter für prognostische Aussagen hinsichtlich klinischer Response im Einzelfall fehlen weiterhin**

Kommentar erscheint weiter gültig:

„ *In .. ADHD .. a need for investigating individual variation in treatment response and elucidating the underlying mechanisms as a step toward personalization of care.“*

(B. Vitiello, NIMH, Am J Psychiatry, 165, 666-7, 2008)

und auch:

„ *Clearly, more work to disentangle these issues is warranted.“ (Wilens et al. Pediatrics, 111, 179-185, 2003)

Vielen Dank für Ihre Aufmerksamkeit !