Attention Deficit Hyperactivity Disorder Across the Life Span

Friday-Sunday, March 15-17, 2013

The Charles Hotel • Harvard Square

Course Directors

Joseph Biederman, MD
Chief, Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, Massachusetts General Hospital; Professor of Psychiatry, Harvard Medical School

Thomas J. Spencer, MD
Associate Chief, Pediatric Psychopharmacology Research Program, Massachusetts General Hospital; Associate Professor of Psychiatry, Harvard Medical School

Timothy E. Wilens, MD
Director, Substance Abuse Services in Pediatric Psychopharmacology, and Director, Center for Addiction Medicine, Massachusetts General Hospital; Associate Professor of Psychiatry, Harvard Medical School

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WELCOME

Welcome to the Massachusetts General Hospital Psychiatry Academy's Attention Deficit Hyperactivity Disorder (ADHD) Across the Life Span course.

This comprehensive three-day course highlights the latest research findings and their clinical applications for diagnosis, treatment and management of ADHD across the life span. Co-morbidities such as substance use, autism and dyslexia will also be covered.

This course has been designed for psychiatrists, pediatricians, psychologists, general and family practitioners, physician assistants, nurses, social workers, and school-based clinicians.

SYLLABUS/SLIDES

Please note that the slide presentations printed in your syllabus might not coincide with the speakers' presentations for the following reasons:

- Changes were made to the slides after the syllabus was printed
- The speaker excluded proprietary slides from the presentation that was submitted for printing in the syllabus

Please also note that the slides for two talks did not make it into the syllabus as they were not available by the printing deadline.

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Fleetwood Multimedia will be onsite during the conference. Audio recordings of individual lectures are available on CD. You may place your orders at the CD order table outside the Ballroom, Friday through Sunday, between 9:00 AM and 5:00 PM, and Sunday, between 9:00 AM and 2:30 PM. Order forms are also available in your folder.

FACULTY

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Faculty

Pradeep G. Bhide, PhD
Professor, Jim and Betty Ann Rodgers Eminent Scholar Chair of Developmental Neuroscience, and Director, Center for Brain Repair, Department of Biomedical Sciences, Florida State University College of Medicine

Barbara J. Coffey, MD, MS, Director
Tics and Tourette's Clinical and Research Program, Mount Sinai School of Medicine, Professor, Department of Psychiatry; Research Psychiatrist, Nathan Kline Institute for Psychiatric Research

Stephen V. Faraone, PhD
Director, Medical Genetics Research, Director, Child and Adolescent Psychiatry Research; Professor of Psychiatry and Neuroscience and Physiology, SUNY Upstate Medical University

Ronna Fried, EdD
Co-Director Neuropsychology, Pediatric Psychopharmacology, Massachusetts General Hospital; Instructor in Psychology, Harvard Medical School

Paul Hammerness, MD
Scientific Coordinator Pediatric ADHD Research, Pediatric Psychopharmacology and Adult ADHD Research Program, Massachusetts General Hospital; Director, Child and Adolescent Psychiatry Outpatient Service, Newton Wellesley Hospital; Assistant Professor of Psychiatry, Harvard Medical School

Aude Henin, PhD
Director, Cognitive-Behavior Therapy Program, Pediatric Psychopharmacology, Massachusetts General Hospital; Assistant Professor of Psychology, Harvard Medical School

Michael S. Jellinek, MD
Chief Clinical Officer, Partners Healthcare System, Inc.; Professor of Psychiatry and of Pediatrics, Harvard Medical School

Gagan Joshi, MD
Scientific Director, Pervasive Developmental Disorders Program, Pediatric Psychopharmacology Clinical and Research Programs, Massachusetts General Hospital; Instructor in Psychiatry, Harvard Medical School

Jefferson B. Prince, MD
Staff Child Psychiatrist, Massachusetts General Hospital; Director, Child Psychiatry, North Shore Medical Center; Instructor in Psychiatry, Harvard Medical School.

Ronald Schouten, MD, JD
Director, Law & Psychiatry Service, Massachusetts General Hospital; Associate Professor of Psychiatry, Harvard Medical School

Bennett A. Shaywitz, MD
Charles and Helen Schwab Professor in Dyslexia and Learning Development; Yale University School of Medicine; Chief, Pediatric Neurology, and Co-Director, Yale Center for Dyslexia & Creativity

Sally E. Shaywitz, MD
Audrey G. Ratner Professor in Learning Development, Yale University School of Medicine, Co-Director, Yale Center for Dyslexia & Creativity

Craig Surman, MD
Scientific Coordinator, Adult ADHD Research Program, Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD, ADHD Course Director, MGH Psychiatry Residency Program, Massachusetts General Hospital; Instructor in Psychiatry, Harvard Medical School

Eve Valera, PhD
Research Associate, Massachusetts General Hospital; Assistant Professor, Harvard Medical School

Janet Wozniak, MD
Director, Pediatric Bipolar Disorder Clinical and Research Unit, Massachusetts General Hospital; Associate Professor of Psychiatry, Harvard Medical School

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Friday, March 15, 2013

7:00AM – 7:30AM	**Registration and Continental Breakfast**
7:30AM – 7:40AM	**Introduction** Course Directors
7:40AM – 8:40AM	**Definitions and Overview of ADHD** Joseph Biederman, MD
8:40AM – 9:25AM	**Genetics of ADHD** Stephen V. Faraone, PhD
9:25AM – 9:40AM	**Coffee Break**
9:40AM – 10:40AM	**Deficient Emotional Self Regulation in ADHD** Joseph Biederman, MD
10:40AM – 11:15AM	**Population Management of ADHD in the Era of Healthcare Redesign** Michael Jellinek, MD
11:15AM – 12:15PM	**Mechanism of Action of Psychostimulants in Animal Models** Pradeep Bhide, PhD
12:15PM – 1:30PM	**Lunch Break (On Your Own)**
1:30PM – 2:30PM	**Treatment of Pediatric ADHD with Stimulants** Thomas J. Spencer, MD
2:30PM – 3:30PM	**Treatment of Pediatric ADHD with Non-Stimulants** Timothy E. Wilens, MD
3:30PM – 3:45PM	**Coffee Break**
3:45PM – 4:45PM	**Late Onset and Atypical Forms of ADHD** Stephen V. Faraone, PhD
4:45PM – 5:30PM	**Ask the Experts Panel Discussion/Question and Answer** Joseph Biederman, MD, Thomas J. Spencer, MD, Timothy E. Wilens, MD, and Janet Wozniak, MD, Moderator: Jefferson Prince, MD
5:30PM – 6:30PM	**Dinner (On your own)**

Friday, March 15, 2013

6:30PM – 7:30PM

Evening Seminars

1. **Management and assessment of ADHD in college students with ADHD**
Jefferson Prince, MD

2. **Management of the Complex Adult Patient with ADHD**
Craig Surman, MD

Saturday, March 16, 2013

7:30AM – 8:00AM	**Continental Breakfast**
8:00AM – 9:00AM	**ADHD and Mania** Janet Wozniak, MD
9:00AM – 10:00AM	**Comorbidity of ADHD with Substance Abuse and Associated Risk Management Issues,*** Timothy E. Wilens, MD
10:00AM – 10:15AM	Coffee Break
10:15AM – 11:15AM	**CBT & Psychosocial Treatments in ADHD** Aude Henin, PhD
11:15AM – 12:15PM	**ADHD, Tics and Tourette's Disorder** Barbara J. Coffey, MD, MS
12:15PM – 1:45PM	**Lunch Break (On Your Own)**
1:45PM – 2:15PM	**Driving and Working Impairments in ADHD** Ronna Fried, EdD
2:15PM – 2:45PM	**Management of ADHD in the Context of Autism Spectrum Disorders** Gagan Joshi, MD
2:45PM – 3:00PM	**Coffee Break**
3:00PM – 3:45PM	**Neuroimaging of ADHD** Eve Valera, PhD
3:45PM – 4:30PM	**Diagnostic Assessment Approaches to Adult ADHD** Craig Surman, MD
4:30PM – 5:15PM	**Cardiovascular Risk in the Management of ADHD*** Paul Hammerness, MD
5:15PM – 6:30PM	**Dinner (On Your Own)**
6:30PM – 7:30PM	**Evening Seminars**
	1. Perspectives on Proposed Changes for ADHD in DSM-V Craig Surman, MD
	2. Educational Assessment and School Accommodations for Children and Adolescents with ADHD, Ronna Fried, EdD

Sunday, March 17, 2013

7:30AM – 8:00AM	**Continental Breakfast**
8:00AM – 9:00AM	**Neuropsychology of ADHD** Ronna Fried, PhD
9:00AM – 10:00AM	**Adult ADHD** Thomas J. Spencer, MD
10:00AM – 10:15AM	**Coffee Break**
10:15AM – 11:15AM	**Pharmacology of Adults with ADHD** Thomas J. Spencer, MD
11:15AM – 12:15PM	**Neurobiology of Dyslexia** Bennett A. Shaywitz, MD and Sally E. Shaywitz, MD
12:15PM – 1:30PM	**Lunch Break (On Your Own)**
1:30PM – 2:30PM	**Legal Issues in Treating Individuals with ADHD Disorders*** Ronald Schouten, MD, JD
2:30PM	**Adjourn**

* Sessions are eligible for risk management credit

Attention Deficit Hyperactivity Disorder Across the Life Span

FRIDAY MARCH 15, 2013

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Definitions and Overview of ADHD

Joseph Biederman, MD

Current Concepts in The Neurobiology of ADHD Across the Lifecycle

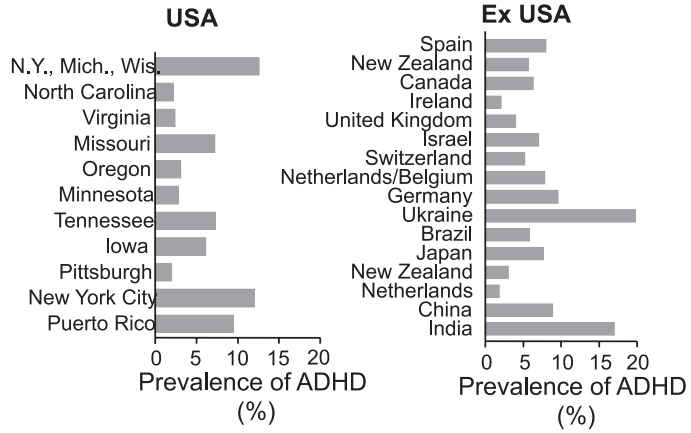
MASSACHUSETTS GENERAL HOSPITAL
HARVARD MEDICAL SCHOOL

Joseph Biederman, M.D.
Professor of Psychiatry,
Massachusetts General Hospital
and Harvard Medical School

Disclosure Statement (2010-2013)

- Research Support
  - APSARD
  - Department of Defense
  - ElMindA
  - Janssen
  - McNeil
  - Shire
  - Vaya Pharma/Enzymotec
- Honoraria
  - MGH Psychiatry Academy (tuition-funded CME courses)
  - The Children's Hospital of Southwest Florida/Lee Memorial Health System (tuition-funded CME course)
  - ADHRS Royalties (paid to the MGH Department of Psychiatry
  - Fundacion Dr. Manuel Camelo, Monterrey Mexico
  - Shionogi & Cipher Pharmaceuticals Inc. (single consultation fees paid to the MGH Department of Psychiatry
  - Spanish Neurological Association
  - Israeli Child Psychiatry Association
  - Cambridge University Press (Chapter Publication)
  - Juste Pharmaceutical Spain (unpaid)

Worldwide Prevalence of ADHD in Children



Faraone SV et al. (2003), World Psychiatry 2(2):104-113

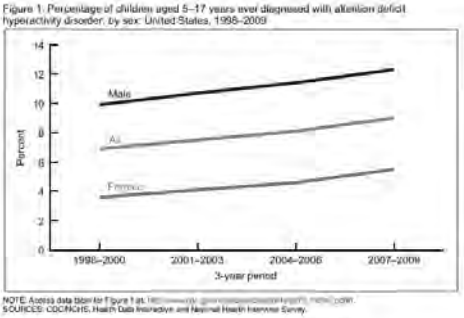
Key findings

Data from the National Health Interview Survey, 1998–2009

- The percentage of children ever diagnosed with attention deficit hyperactivity disorder (ADHD) increased from 7% to 9% from 1998–2000 through 2007–2009.
- ADHD prevalence trends varied by race and ethnicity. Differences between groups narrowed from 1998 through 2009; however, Mexican children had consistently lower ADHD prevalence than other racial or ethnic groups.
- From 1998 through 2009, ADHD prevalence increased to 10% for children with family income less than 100% of the poverty level and to 11% for those with family income between 100% and 199% of the poverty level.
- From 1998 through 2009, ADHD prevalence rose to 10% in the Midwest and South regions of the United States.

The percentage of children ever diagnosed with ADHD increased from 1998 through 2009 among both boys and girls.

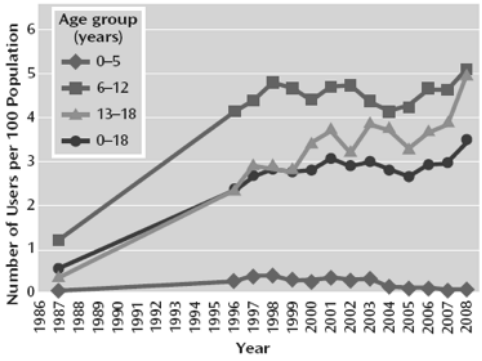
Figure 1. Percentage of children aged 5–17 years ever diagnosed with attention deficit hyperactivity disorder, by sex: United States, 1998–2009



NOTE: Access data table for Figure 1 at: http://www.cdc.gov/nchs/data/databriefs/db70.htm#data_table
SOURCES: CDC/NCHS, Health Data Interactive and National Health Interview Survey.

Akinbami et al. *NCHS Data Brief* No. 70, August 2011

FIGURE 1. Trends in Prevalence of Stimulant Use in the U.S. Population Age 18 and Younger, 1987–2008[a]

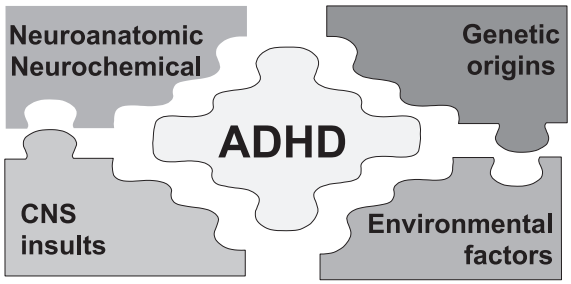


[a] Based on the Medical Expenditure Panel Survey (1996–2008) and the National Medical Expenditure Survey (1987).

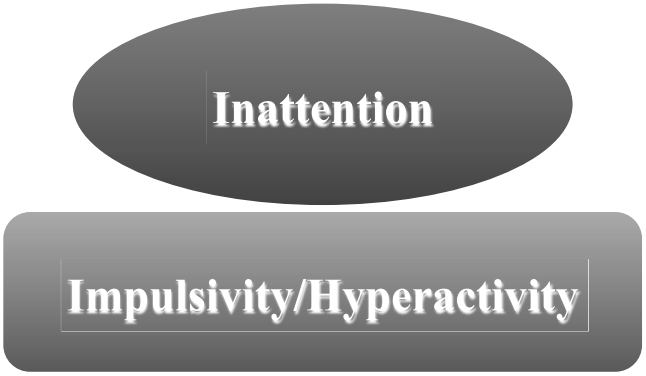
Zuvekas al. *Am J Psychiatry* 2012; 169:160-166

ADHD: Etiology

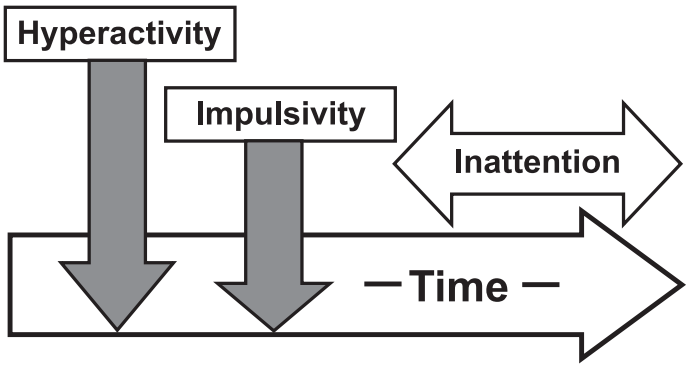
ADHD is a heterogeneous behavioral disorder with multiple possible etiologies



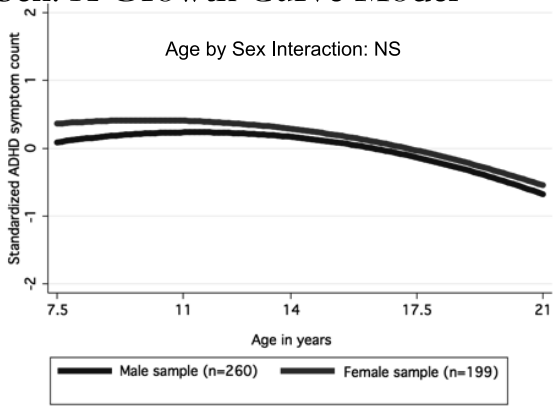
ADHD: Core Symptom Areas



ADHD: Course of the Disorder

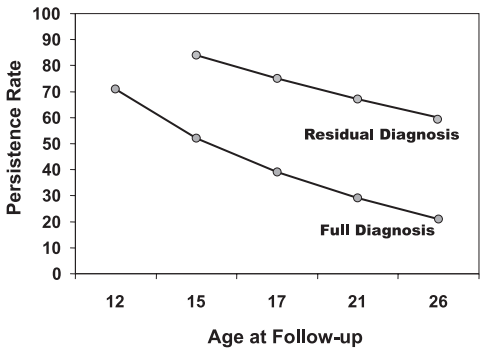


Course of ADHD Symptoms Over Time by Sex: A Growth Curve Model



Biederman et al 2009

Persistence of Full and Residual Diagnoses in Prospective Studies



Loss of full diagnostic status is not equivalent to remission.

Faraone et al. *Psychol Med.* 2006;36:159-165.

The Prevalence and Correlates of Adult ADHD in the United States: Results From the National Comorbidity Survey Replication

Ronald C. Kessler, Ph.D.
Lenard Adler, M.D.
Russell Barkley, Ph.D.
Joseph Biederman, M.D.
C. Keith Conners, Ph.D.
Olga Demler, M.A., M.P.H.
Stephen V. Faraone, Ph.D.
Laurence L. Greenhill, M.D.
Mary J. Howes, Ph.D.
Kristina Secnik, Ph.D.
Thomas Spencer, M.D.
T. Bedirhan Ustun, M.D.
Ellen E. Walters, M.S.
Alan M. Zaslavsky, Ph.D.

Objective: Despite growing interest i adult attention deficit hyperactivity diso der (ADHD), little is known about its prev alence or correlates.

Method: A screen for adult ADHD was in cluded in a probability subsample (N= 3,199) of 18–44-year-old respondents i the National Comorbidity Survey Replica tion, a nationally representative house hold survey that used a lay-administered diagnostic interview to assess a wide range of DSM-IV disorders. Blinded clini cal follow-up interviews of adult ADHD were carried out with 154 respondents, oversampling those with positive screen results. Multiple imputation was used to estimate prevalence and correlates of clinician-assessed adult ADHD.

Results: The estimated prevalence of current adult ADHD was 4.4%. Significant correlates included being male, previously married, unemployed, and non-Hispanic white. Adult ADHD was highly comorbid with many other DSM-IV disorders assessed in the survey and was associated with substantial role impairment. The majority of cases were untreated, although many individuals had obtained treatment for other comorbid mental and substance-related disorders.

Conclusions: Efforts are needed to increase the detection and treatment of adult ADHD. Research is needed to determine whether effective treatment would reduce the onset, persistence, and severity of disorders that co-occur with adult ADHD.

(Am J Psychiatry 2006; 163:716–723)

Persistent Controversy BMJ | 3 april 2010 | Vol 340

HEAD TO HEAD

Is ADHD a valid diagnosis in adults?

Philip Asherson and colleagues argue that the concept of ADHD in adults is valid but **Joanna Moncrieff** and **Sami Timimi** believe that it is supported by little more than aggressive marketing

Philip Asherson, professor of molecular psychiatry and honorary consultant psychiatrist, MRC Social Genetic and Developmental Psychiatry, Institute of Psychiatry, King's College London
philip.asherson@kcl.ac.uk
Makis Adamou, consultant psychiatrist, Service for adults with ADHD, Maudsley Clinic, South West Yorkshire Partnership NHS Foundation Trust, Yorkshire; Bianca Boka, consultant psychiatrist and honorary lecturer, University of Bristol, Bristol Adult ADHD Clinic, Avon and Wiltshire Partnership Mental Health Trust, Bristol; Ulrich Muller, university lecturer and honorary consultant psychiatrist, Adult ADHD Research Clinic, Department of Psychiatry, University of Cambridge and Peterborough NHS Foundation Trust, Addenbrooke's Hospital, Cambridge; Susan Dunn, Mirus founder and chairwoman adult attention-deficit disorder UK (AADD-UK), Adult Attention Deficit Disorder UK (AADD-UK), London, and Bristol; Mark Pitts, clinical nurse specialist, Adult ADHD Service, Maudsley Hospital, South London and Maudsley NHS Foundation Trust, London; Johannes Thome, professor of psychiatry, Swansea Medical School, University of Wales, Swansea; Susan Young, senior lecturer in clinical forensic psychology and consultant clinical and forensic psychologist, Department of Forensic Mental Health Science, Institute of Psychiatry, King's College London

YES Attention deficit hyperactivity disorder (ADHD) is well established in childhood, with 3.6% of children in the United Kingdom being affected.[1] Most regions have child and adolescent mental health or paediatric services for ADHD. Follow-up studies of children with ADHD find that 15% still have the full diagnosis at 25 years, and a further 50% are in partial remission, with some symptoms associated with clinical and psychosocial impairments persisting.[2]

ADHD is a clinical syndrome defined in the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, by high levels of hyperactivity, impulsivity, and inattentive behaviours in early childhood that persist over time, pervade across situations, and lead to notable impairments. ADHD is thought to result from complex interactions between genetic and environmental factors.[3]

Proof of validity

Using the Washington University diagnostic criteria, the National Institute for Health and Clinical Excellence (NICE) reviewed the validity of the system used to diagnose ADHD in children and adults.[4,5]

Symptoms of ADHD are reliably identifiable. The symptoms used to define ADHD are found to cluster together in both clinical and population samples. Studies in such samples also separate ADHD symptoms from conduct problems and neurodevelopmental traits. Twin studies show a distinct pattern of genetic and environmental influences on ADHD compared with conduct problems,[6] and overlapping genetic influences between ADHD and neurodevelopmental disorders such as autism and specific reading difficulties.[7,8] Disorders that commonly, but not invariably, occur in adults with ADHD include antisocial personality, substance misuse, and depression.[9]

Symptoms of ADHD are continuously distributed throughout the population.[9] As with anxiety and depression, most people have symptoms of ADHD at some time. The disorder is diagnosed by

Joanna Moncrieff senior lecturer and honorary consultant psychiatrist, University College London and North East London Mental Health Trust, UCL, Department of Mental Health Sciences, London W1W 7EJ j.moncrieff@ucl.ac.uk
Sami Timimi consultant child and adolescent psychiatrist and

perceptions and variation of diagnosis across sex and class,[3] and serious adverse outcomes being more strongly related to co-occurring problems such as conduct disorder and familial conflict.[4]

ADHD as a Brain Disorder: Neuroimaging Findings

Brain Imaging and ADHD

- Magnetic Resonance Imaging (MRI) Anomalies (N= >25 studies):
  - Asymmetry of the Caudate Nucleus
  - Corpus Callosum size and shape
  - Smaller Right Frontal area
  - Smaller Right Basal Ganglia
  - Cerebellum (vermis)

Developmental Trajectories of Brain Volume Abnormalities in Youth w/ ADHD

- Design: MRI case control study
- N=152 youth w/ ADHD and 139 controls of both genders
- Objective: assess volumetric changes overtime in medicated vs unmedicated youth w/ADHD and controls

Castellanos et al. JAMA. 2002 Oct;288(14):1740-8

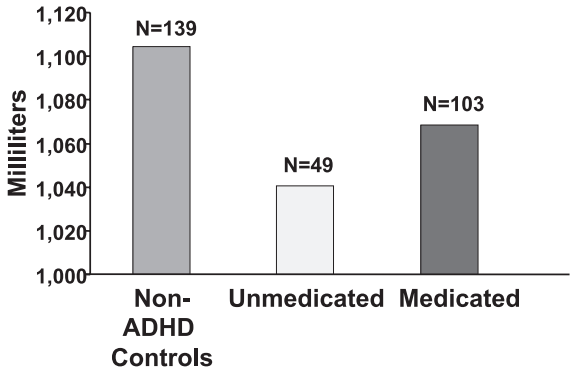
Developmental Trajectories of Brain Volume Abnormalities in Youth w/ ADHD

- Main Findings:
  - Smaller brain volumes in all regions independently of medication status
  - Smaller total cerebral (-3.2%) and cerebellar (-3.5%) volumes
  - Volumetric abnormalities (except caudate) persisted with age
  - No gender differences
  - Volumetric findings correlated with severity of ADHD

Castellanos et al. JAMA. 2002 Oct;288(14):1740-8

Brain Volumes and ADHD

Unadjusted Total Cerebral Brain Volume for Unmedicated and Medicated Children and Adolescents With ADHD and Controls



*p=0.001 by 2-way analysis of variance (group [medicated vs. unmedicated vs. control] by sex); Castellanos FX et al. (2002), JAMA 288(14):1740-1748

Developmental Trajectories of Brain Volume Abnormalities in Youth w/ ADHD

- Conclusions:
  - Genetic and or early environmental influences on brain development in ADHD are fixed, nonprogressive and unrelated to stimulant treatment

Castellanos et al. JAMA. 2002 Oct;288(14):1740-8

AJP in Advance. Published August 24, 2011 (doi: 10.1176/appi.ajp.2011.11020281)

Reviews and Overviews

Mechanisms of Psychiatric Illness

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

Tomohiro Nakao, M.D., Ph.D.
Joaquim Radua, M.D.
Katya Rubia, Ph.D.
David Mataix-Cols, Ph.D.

Objective: Structural neuroimaging studies in attention-deficit hyperactivity disorder (ADHD) have been relatively inconsistent and have mainly been conducted with pediatric samples. Furthermore, there is evidence that stimulant medication may have an effect on brain structure. The authors conducted a meta-analysis of voxel-based morphometry studies in children and adults with ADHD and examined the potential effects of age and stimulant medication on regional gray matter volumes.

Method: The PubMed, ScienceDirect, Web of Knowledge and ScienceDirect databases were searched for articles published between 2001 and 2011. Manual searches were also conducted, and authors of studies were contacted for additional data. Coordinates were extracted from clusters of significant gray matter differences between ADHD patients and healthy comparison subjects. Metaregression methods were used to explore potential age and stimulant medication effects.

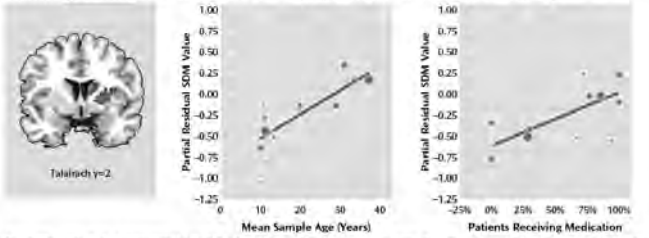
Results: Fourteen data sets comprising 378 patients with ADHD and 344 healthy subjects met inclusion criteria. The ADHD group had global reductions in gray matter volumes, which were robustly localized in the right lentiform nucleus and extended to the caudate nucleus. Both increasing age and percentage of patients taking stimulant medication were found to be independently associated with more normal values in this region. Patients also had slightly greater gray matter volumes in the left posterior cingulate cortex.

Conclusions: These findings confirm that the most prominent and replicable structural abnormalities in ADHD are in the basal ganglia. They furthermore suggest that ADHD patients may progressively catch up with their developmental delay with advancing age and that use of stimulant medication may be associated with normalization of structural abnormalities in ADHD, although longitudinal studies are needed to confirm both observations.

(*Am J Psychiatry* Nakao et al., AiA 1-10)

The most prominent & replicable structural abnormalities in ADHD are in the basal ganglia that normalize with age & stimulant treatment

FIGURE 2. Results of the Metaregression Analysis Showing Independent Associations of Mean Age and Percentage of Patients Receiving Stimulant Medication With More Normal Gray Matter Volumes in the Right Basal Ganglia[a]

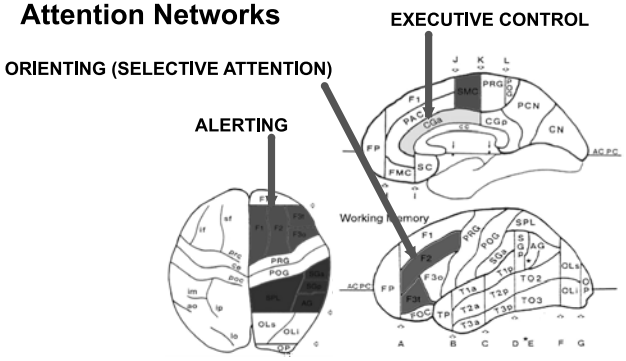


[a] In the graphs, each study is represented as a dot, with dot size reflecting sample size: large dots indicate samples with over 40 patients; medium dots, samples with 20–40 patients; and small dots, samples with under 20 patients. The regression line (metaregression signed differential mapping slope) is presented as a straight line. SDM refers to the signed differential mapping meta-analytic method (www.sdmproject.com).

Nakao et al. *Am J Psychiatry* 2011

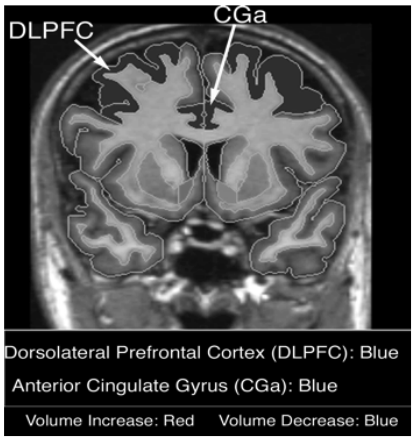
ADHD: Neurobiologic Basis

Attention Networks



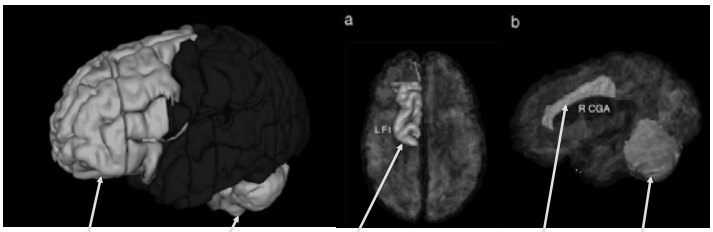
Posner and Raichle. *Images of Mind.* Scientific American Books; 1996.

MRI findings in Adult with ADHD



Seidman et al, *Biological Psychiatry*. 2006; In Press

Volume Reductions in Adult ADHD



Volumetric reductions in light blue (frontal and cerebellar regions)

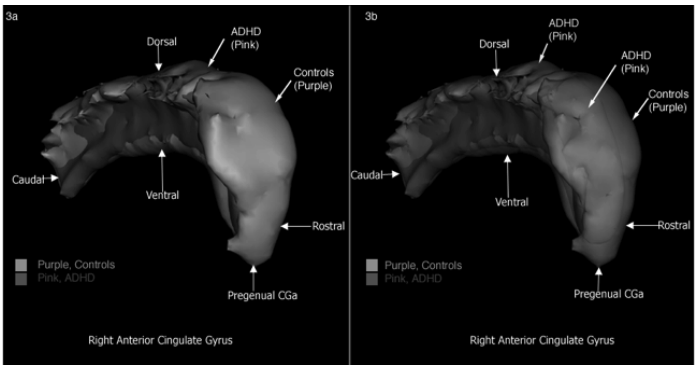
Superior frontal gyrus

Anterior cingulate gyrus

Cerebellar cortex

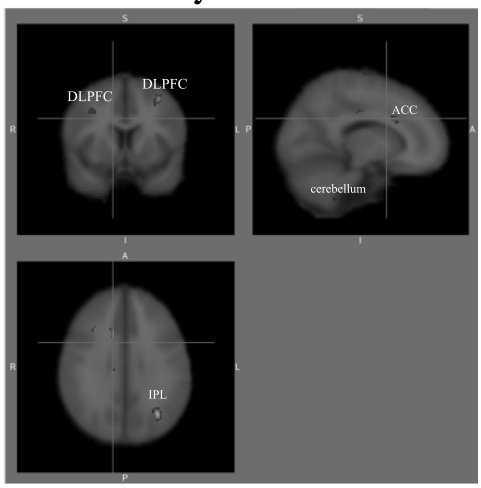
Biederman, Makris, Valera et al. *Psychol Med.* In Press.

Smaller Dorsal and Rostral ACC in ADHD



Seidman et al, *Biological Psychiatry*. 2006; 60: 1071-1080

VBM Analysis Seidman et al Biol Psych 2011



SPM5-VBM, Sample1
Control Group (N=18) >ADHD Group (N=24)
at uncorrected p-value <= 0.05

Coronal section shows bilateral DLPFC structural-volume decrease in the ADHD group

Midsagittal section shows right ACC and cerebellar structural-volume decrease in the ADHD group

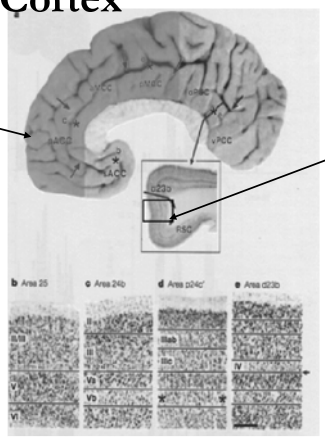
Axial section shows left inferior parietal lobule (IPL) structural-volume decrease in the ADHD group

R=right - L=left
A=anterior - P=posterior
S=superior - I=inferior

Cerebral Cortex

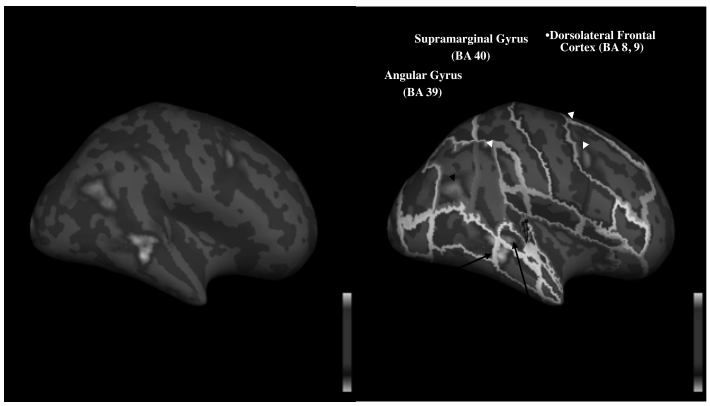
Cortical Volume

Cortical Thickness



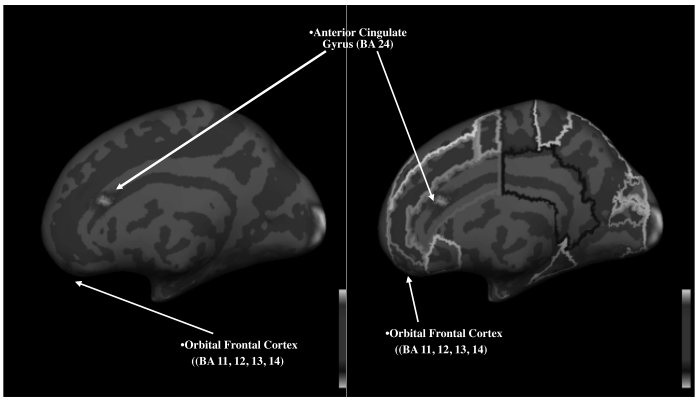
Vogt, 2005

Cortical Thickness Aanalysis in Aduldt with ADHD



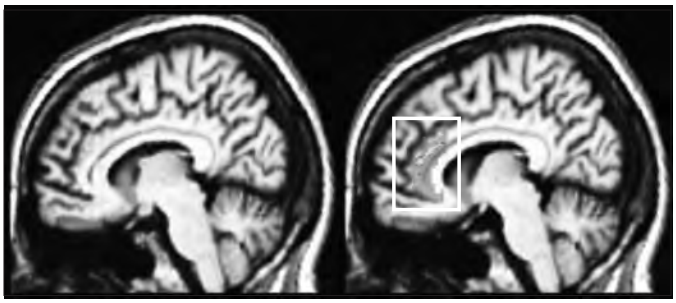
Makris et al. *Cerebral Cortex* June 2007; 17:1364-1375

Cortical Thickness Aanalysis in Aduldt with ADHD



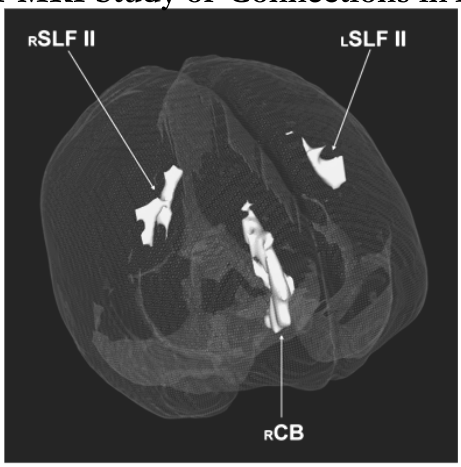
Makris et al. *Cerebral Cortex* June 2007; 17:1364-1375

A DTI-MRI Study of Connections in ADHD



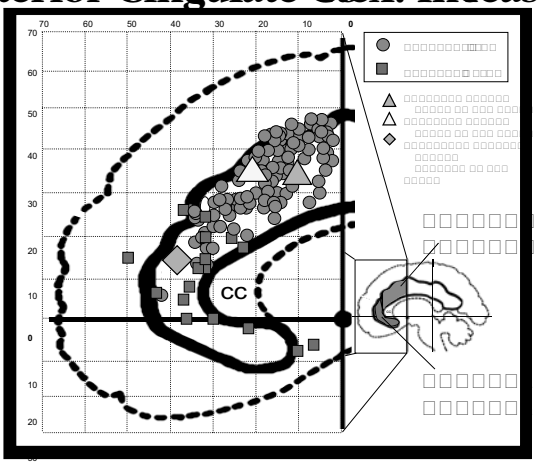
Reproduced from Makris N, et al. *Cerebral Cortex*. 2007; doi:10.1093/cercor/bhm156.

A DTI-MRI Study of Connections in ADHD



Makris et al. *Cerebral Cortex* 2008 in press

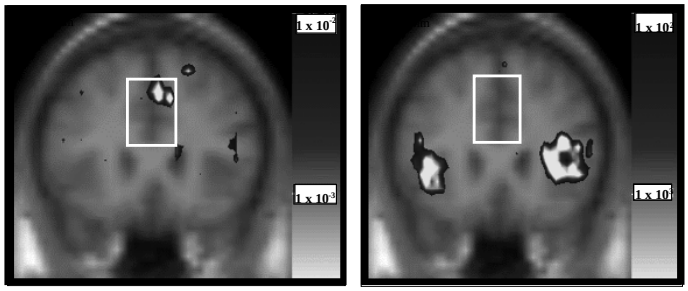
Anterior Cingulate Cortex: Increases



Bush, Luu & Posner (2000) *Trends in Cognitive Sciences* 4:215-222

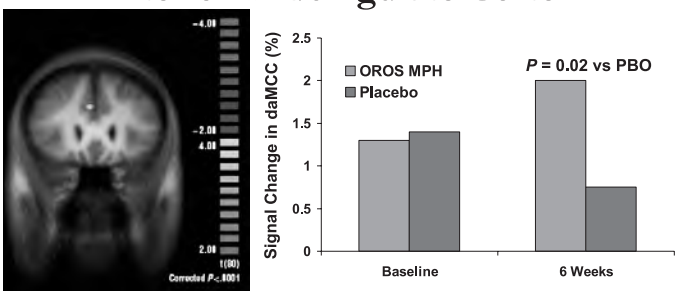
Dorsal Anterior Cingulate Cortex (Cognitive Division) Fails to Activate in ADHD

Normal Controls ADHD



MGH-NMR Center & Harvard- MIT CITP Bush et al, *Biological Psychiatry* 1999

Methylphenidate Activates Dorsal Anterior Midcingulate Cortex



- fMRI at baseline and again at week 6
- OROS MPH group showed higher daMCC activation at 6 weeks vs placebo
- N=21 adults with ADHD; dosing to 1.3 mg/kg/day OROS MPH or placebo

Bush et al. *Arch Gen Psychiatry.* 2008:65:102-114.

Contents lists available at SciVerse ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Brief report

Atomoxetine increases fronto-parietal functional MRI activation in attention-deficit/hyperactivity disorder: A pilot study

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ARTICLE INFO

Article history:
Received 28 July 2011
Received in revised form
22 August 2012
Accepted 16 September 2012

Keywords:
Neuroimaging
Psychopharmacology
Neuroimaging

ABSTRACT

We hypothesized that atomoxetine (ATMX) would produce similar brain effects in attention-deficit/hyperactivity disorder (ADHD) as those of methylphenidate (MPH). Eleven ADHD adults performed the Multi-Source Interference Task (MSIT) during functional magnetic resonance imaging (fMRI) at baseline and after 6weeks of ATMX treatment. ATMX was associated with increased fMRI activation of dorsolateral prefrontal cortex, parietal cortex and cerebellum but not dorsal anterior midcingulate cortex (daMCC). These results suggest that ATMX and MPH have similar but not identical brain effects.

Bush et al. *Psychiatry Research: Neuroimaging* 2012

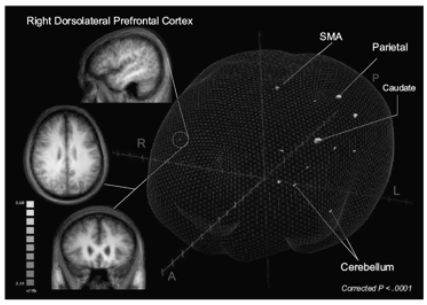
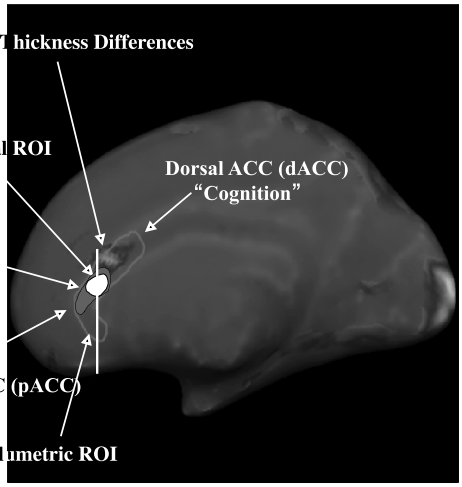
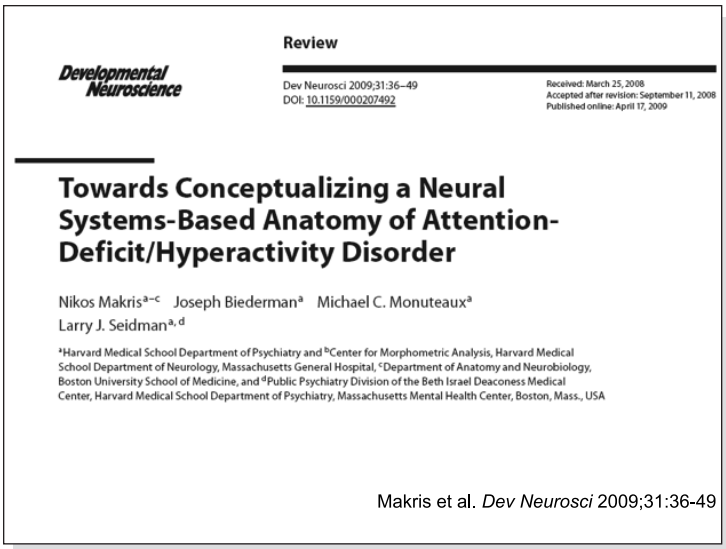


Fig. 1. Atomoxetine produces higher fMRI activation at 6 weeks. Six weeks of ATMX significantly increased activation of right DLPFC, parietal cortex, supplementary motor cortex, caudate, cerebellum and other brain regions, but not within daMCC (cf. Table 2). The regional activations depicted passed a multi-step masked random effects repeated measures ANOVA GLM analysis, showing *both* (1) significant activation during a voxelwise mask representing all voxels showing $MSIT_{Interference} > MSIT_{Control}$ activity for all 32 subjects (ATMX, MPH, and Placebo) and (2) significantly higher $MSIT_{Interference}$ fMRI activation at 6 weeks of ATMX treatment than at baseline. The above figure at right depicts the resulting GLM statistical map data superimposed on a pseudo-3D wire mesh brain representation (R=right, L=left, A=anterior, P=posterior). At left are shown 3 orthogonal (sagittal, axial and coronal) views of the right DLPFC activation (x/y/z=45/22/28). A stringent cluster constraint was used throughout resulting in corrected regional thresholds of $P < 1 \times 10^{-4}$.

Bush et al. *Psychiatry Research: Neuroimaging* 2012





Review

Developmental Neuroscience

Dev Neurosci 2009;31:36–49
DOI: 10.1159/000207492

Received: March 25, 2008
Accepted after revision: September 11, 2008
Published online: April 17, 2009

Towards Conceptualizing a Neural Systems-Based Anatomy of Attention-Deficit/Hyperactivity Disorder

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Larry J. Seidman[a, d]

[a]Harvard Medical School Department of Psychiatry and [b]Center for Morphometric Analysis, Harvard Medical School Department of Neurology, Massachusetts General Hospital, [c]Department of Anatomy and Neurobiology, Boston University School of Medicine, and [d]Public Psychiatry Division of the Beth Israel Deaconess Medical Center, Harvard Medical School Department of Psychiatry, Massachusetts Mental Health Center, Boston, Mass., USA

Makris et al. *Dev Neurosci* 2009;31:36-49

Resting-State Functional Connectivity in a Longitudinal Sample of ADHD Children Grown Up

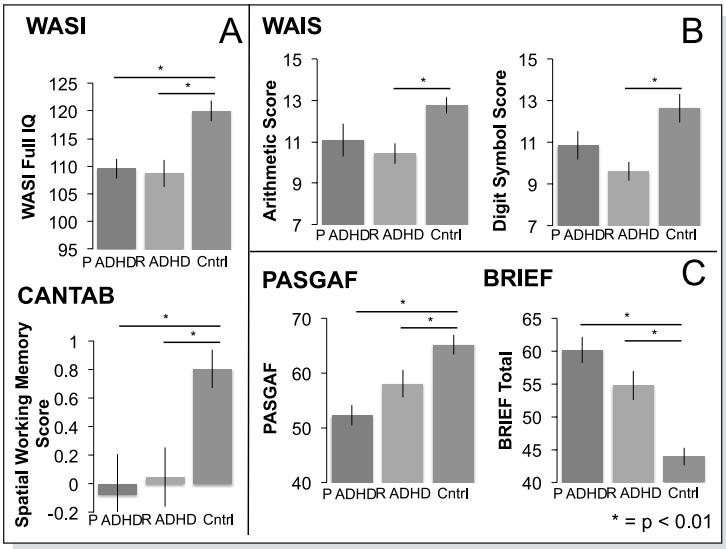
Default Mode Network (DMN)

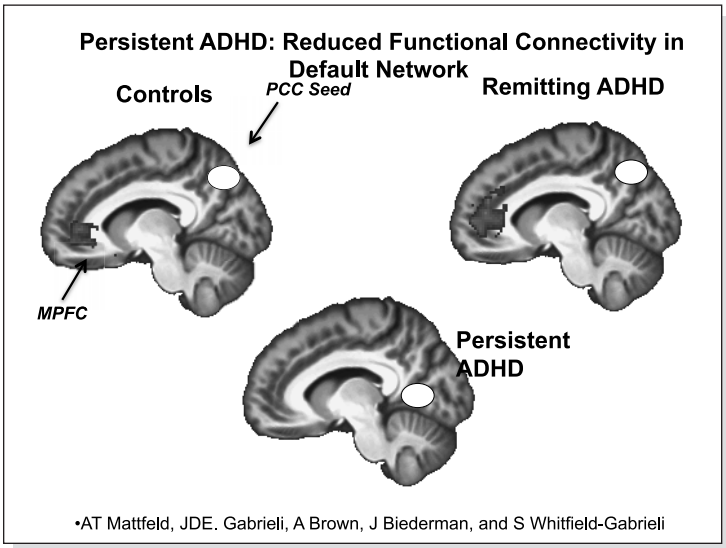
- DMN or task-negative network (**TNN**) is a network of brain regions that are active when the individual is not focused on the outside world and the brain is at wakeful rest
- During goal-oriented activity, the DMN is deactivated and another network, the task-positive network (**TPN**) is activated
- Negative correlations exist between **TPN** & **TNN.** They are "intrinsically **anticorrelated**"
- Resting-state functional connectivity MR**I** (fcMR**I**) detects temporal correlations in spontaneous blood oxygen level–dependent (BOLD) signal oscillations while subjects rest quietly in the scanner and reflects structural connectivity of brain networks

Methods

- fcMRI
- The PCC seed was defined by the Castellanos et al. in a sample of ADHD adults
- Longitudinally sample with confirmed childhood diagnosis of ADHD, who did (**Persistent ADHD**, N = 14) or did not (**Remitted ADHD**, N = 22) maintain diagnostic status at F-U in adult years
- Controls (N = 17) who did not have ADHD in either childhood or adulthood

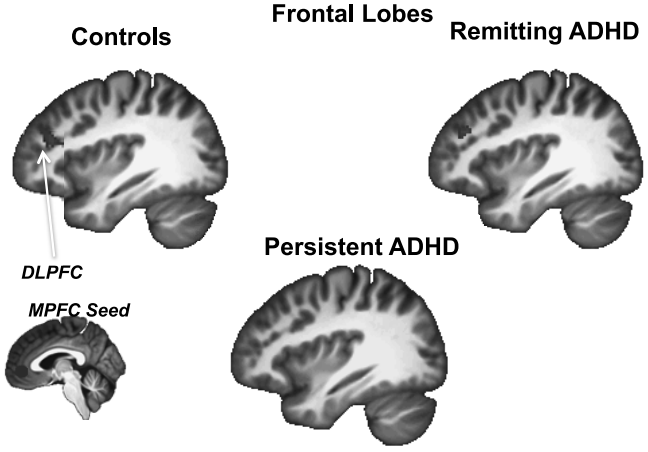
•AT Mattfeld, JDE. Gabrieli, J Biederman, and S Whitfield-Gabrieli





•AT Mattfeld, JDE. Gabrieli, A Brown, J Biederman, and S Whitfield-Gabrieli

Persistent ADHD: Reduced Functional Connectivity in Frontal Lobes



•AT Mattfeld, JDE. Gabrieli, A Brown, J Biederman, and S Whitfield-Gabrieli

Resting-State Functional Connectivity in a Longitudinal Study of ADHD Children Grown Up Reflects Diagnostic Status

- Significant ***decreases*** in connectivity between the PCC and MPFC
- Significant ***decreases*** in anticorrelations between MPFC and DLPC in Persistent ADHD vs. both Controls and Remitted ADHD
- There were no differences between Control and remitted ADHD

•AT Mattfeld, JDE. Gabrieli, A Brown, J Biederman, and S Whitfield-Gabrieli

Neural Basis of Persistent ADHD

Persistent ADHD alter intrinsic functional organization of the brain

Findings supports the idea that adult ADHD diagnosis reflects a true brain difference (vs. controls & vs. remitting ADHD)

MPH Normalizes Resting-State Brain Dysfunction in Boys with ADHD

- Acute doses of MPH normalized all fronto-parieto-cerebellar dysfunctions in boys with ADHD during the resting state

Neuropsychopharmacology preview online January 22, 2013

ORIGINAL ARTICLE

Brain Gray Matter Deficits at 33-Year Follow-up in Adults With Attention-Deficit/Hyperactivity Disorder Established in Childhood

Erika Proal, PhD; Philip T. Reiss, PhD; Rachel G. Klein, PhD; Salvatore Mannuzza, PhD; Kristin Gotimer, MPH; Maria A. Ramos-Olazagasti, PhD; Jason P. Lerch, PhD; Yong He, PhD; Alex Zijdenbos, PhD; Clare Kelly, PhD; Michael P. Milham, MD, PhD; F. Xavier Castellanos, MD

Context: Volumetric studies have reported relatively decreased cortical thickness and gray matter volumes in adults with attention-deficit/hyperactivity disorder (ADHD) whose childhood status was retrospectively recalled. We present, to our knowledge, the first prospective study combining cortical thickness and voxel-based morphometry in adults diagnosed as having ADHD in childhood.

Objectives: To test whether adults with combined-type childhood ADHD exhibit cortical thinning and decreased gray matter in regions hypothesized to be related to ADHD and to test whether anatomic deficiencies are associated with a current ADHD diagnosis, including persistent vs remitting ADHD.

Design: Cross-sectional analysis embedded in a 33-year prospective follow-up at a mean age of 41.2 years.

Setting: Research outpatient center.

Participants: We recruited probands with ADHD from a cohort of 207 white boys aged 6 to 12 years. Male comparison participants (n = 178) were free of ADHD in childhood. We obtained magnetic resonance images in 89 probands and 80 comparison participants (29.3% and 44.9% of the original samples, respectively).

Main Outcome Measures: Whole-brain voxel-based morphometry and vertexwise cortical thickness analyses.

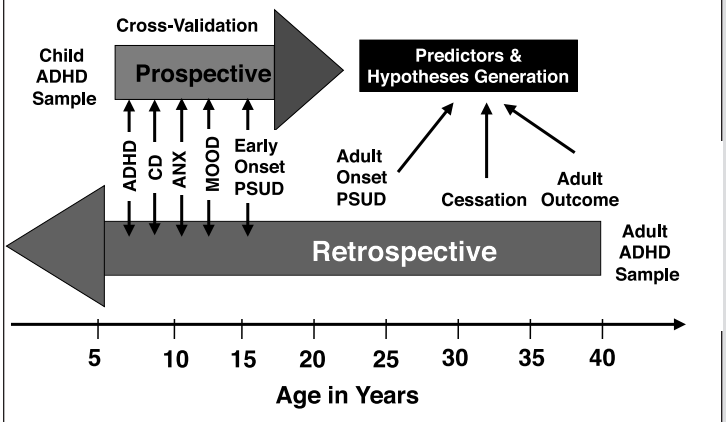
Results: The cortex was significantly thinner in ADHD probands than in comparison participants in the dorsal attentional network and limbic areas (false discovery rate < 0.05, corrected). In addition, gray matter was significantly decreased in probands in the right caudate, right thalamus, and bilateral cerebellar hemispheres. Probands with persistent ADHD (n = 17) did not differ significantly from those with remitting ADHD (n = 26) (false discovery rate < 0.05). At uncorrected $P < .05$, individuals with remitting ADHD had thicker cortex relative to those with persistent ADHD in the medial occipital cortex, insula, parahippocampus, and prefrontal regions.

Conclusions: Anatomic gray matter reductions are observable in adults with childhood ADHD, regardless of the current diagnosis. The most affected regions underpin top-down control of attention and regulation of emotion and motivation. Exploratory analyses suggest that diagnostic remission may result from compensatory normalization of prefrontal, cerebellar, and thalamic circuitry.

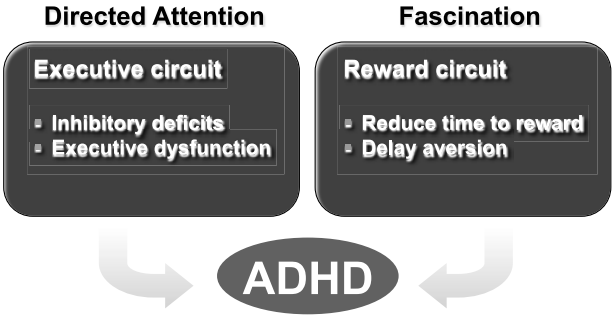
Arch Gen Psychiatry. 2011;68(11):1123-1134

Proal et al. *Arch Gen Psychiatry* 2011;68:1122-1134

Prospective and Retrospective Methodology



Toward a Dual Pathway Model



Sonuga-Barke. *Neurosci Biobehav Rev.* 2003;27:593.

CLINICAL FOCUS: ADHD, DEPRESSION, AND NEUROLOGICAL DISORDERS

Toward Defining Deficient Emotional Self-Regulation in Children with Attention-Deficit/ Hyperactivity Disorder Using the Child Behavior Checklist: A Controlled Study

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Stephen V. Faraone, PhD[2]
Craig B. H. Surman, MD[3]
Carter Petty, MA[3]
Allison Clarke, BA[3]
Holly Batchelder, BS[3]
Janet Woznaik, MD[3]
Joseph Biederman, MD[3]

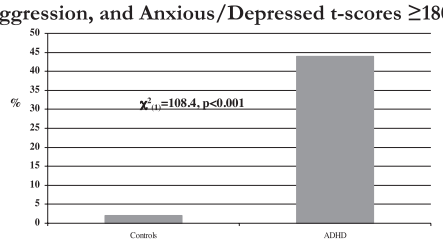
Abstract

Objective: Deficient emotional self-regulation (DESR) is characterized by deficits in self-regulating the physiological arousal caused by strong emotions. We examined whether a unique profile of the Child Behavior Checklist (CBCL) would help identify DESR in children with attention-deficit/hyperactivity disorder (ADHD). **Methods:** Subjects included 147 children with ADHD and 224 children without ADHD. We defined DESR if a child had an aggregate cut-off score of > 180 but < 210 on the Anxiety/Depression, Aggression, and Attention scales of the CBCL (CBCL-DESR). This profile was selected because of: 1) its conceptual congruence with the clinical concept of DESR; and 2) because its extreme (> 210) form has been previously associated with severe forms of mood and behavioral dysregulation in children with ADHD. All subjects were comprehensively assessed with structured diagnostic interviews and a wide range of functional measures. **Results:** Forty-five percent of children with ADHD had a positive CBCL-DESR profile versus 8% of controls ($P < 0.001$). The CBCL-DESR profile was associated with elevated rates of anxiety and disruptive behavior disorders, as well as significantly more impairments in emotional and interpersonal functioning. **Conclusions:** The CBCL-DESR profile helped identify a subgroup of children with ADHD who had a psychopathological and functional profile consistent with the clinical concept of DESR.

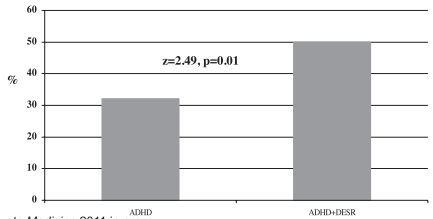
Keywords: attention-deficit/hyperactivity disorder; affective symptoms; severity of illness index; youth; emotional self-regulation

Spencer et al. *Postgraduate Medicine* 2011 in press

Rates of Deficient Emotional Self-Regulation (DESR, sum of CBCL Attention, Aggression, and Anxious/Depressed t-scores ≥180 and <210)

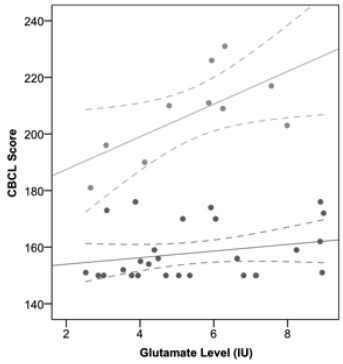


Percent of subjects with ADHD-associated severe impairment



Spencer et al. *Postgraduate Medicine* 2011 in press

CBCL scores vs Glutamate levels



Wozniak et al 2012

Solid lines represent the linear fits to the low score group data (blue) and high score group data (green). Dashed lines represent 95% confidence intervals.

ADHD
Imaging Studies Summary

- Neuroimaging studies confirm that brain abnormalities in fronto-subcortical networks are associated with ADHD
- But neuroimaging techniques are not valid tools for ADHD diagnosis; imaging measures are not sensitive or specific enough to be used for diagnostic purposes

ADHD as a Neurobiological Disorder: Catecholamine Dysregulation

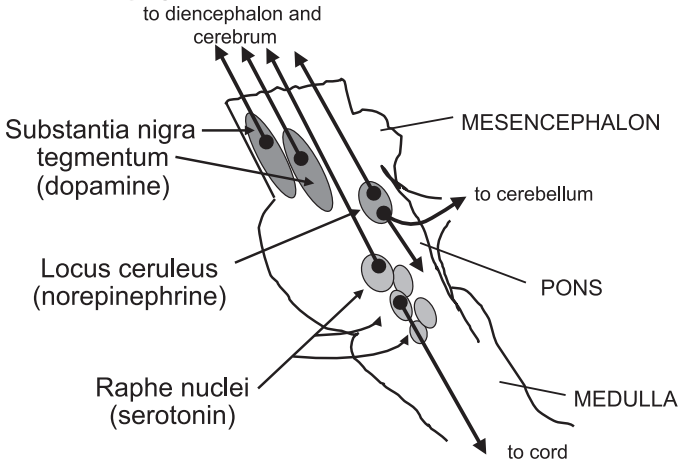
Frontosubcortical Networks and Catecholamines

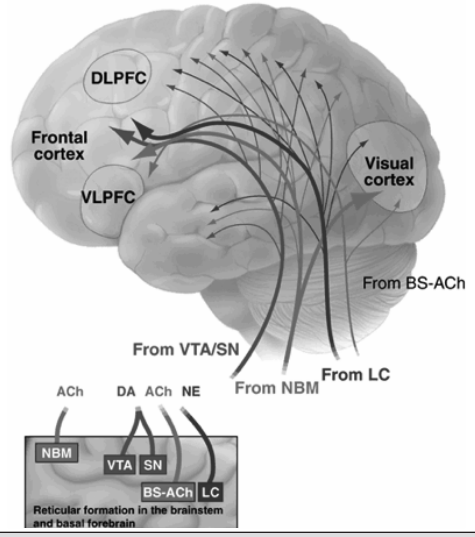
- Dopaminergic and noradrenergic dysregulation abnormalities in fronto subcortical pathways
- Medications that are effective in ADHD are either dopaminergic or noradrenergic

Zametkin. *J Am Acad Child Adolesc Psychiatry.* 1987;26(5):676-686

Zametkin. *J Am Acad Child Adolesc Psychiatry.* 1987;26(5):676-686.

Brain Stem





ADHD as a Neurobiological Disorder: Genetic Findings

ADHD: Genetics

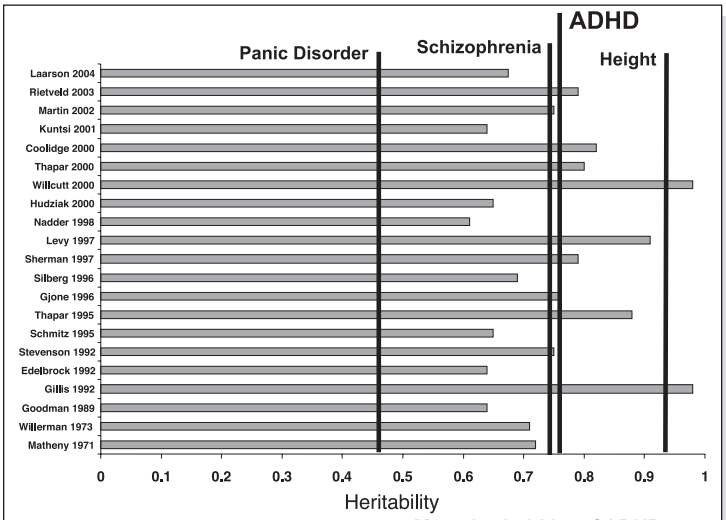
Twin Studies

Family Studies

Genetic Basis of ADHD

Adoption Studies

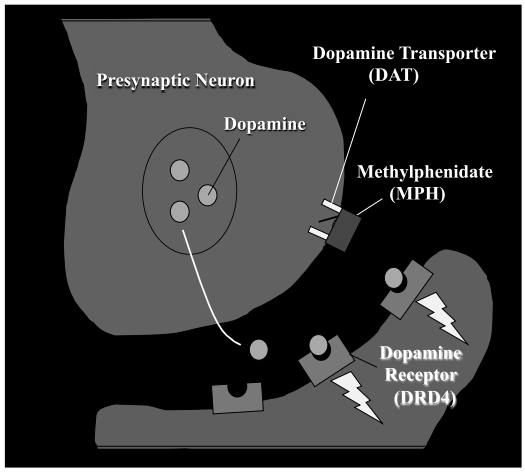
Molecular Genetics



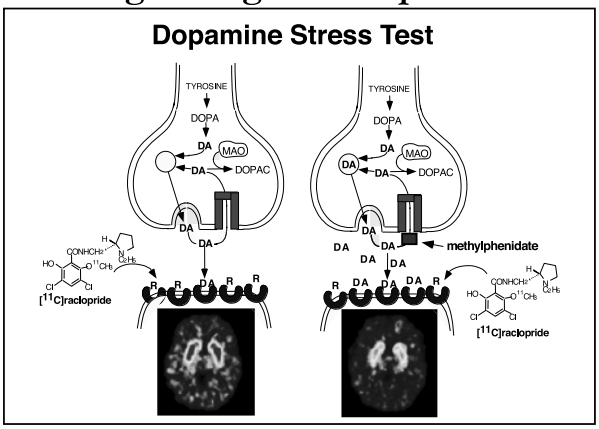
Faraone et al. *Biol Psychiatry*. 2005;57:1313-23.

Mean heritability of ADHD = .75

The Dopamine Story...

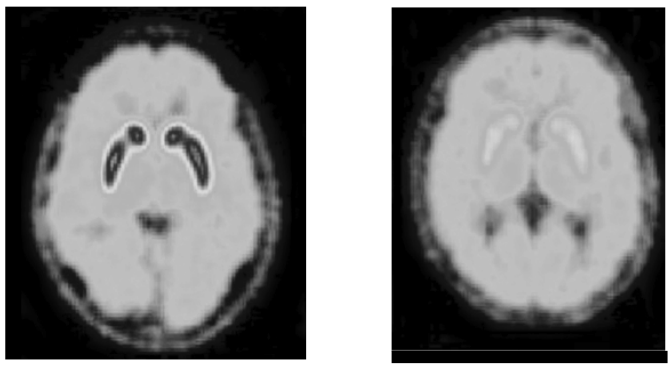


Measuring Changes in Dopamine



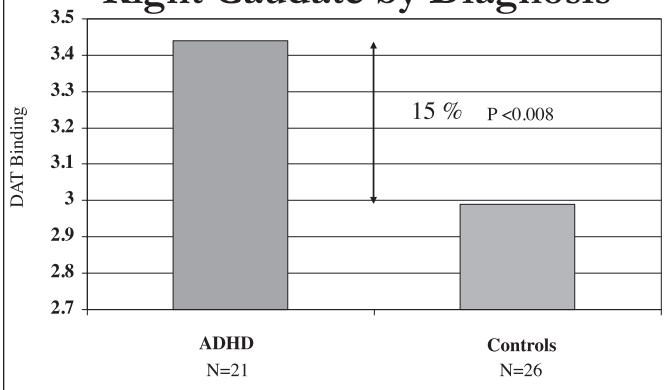
Volkow, Swanson. Am J Psychiatry. 2003 Nov;160(11):1909-18

DAT PET Imaging (Altropane) with and without oral MPH



Baseline | After Oral MPH

DAT Binding (age-corrected) in Right Caudate by Diagnosis



Spencer et al Biol Psychiatry 2007

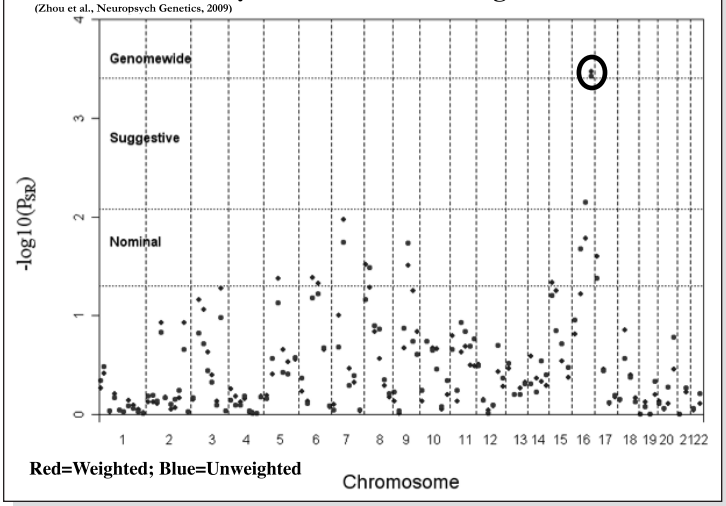
GSMA Meta-Analysis of 7 ADHD Linkage Studies

(Zhou et al., Neuropsych Genetics, 2009)

- All available linkage studies were used
- 2,084 total subjects analyzed
- Analyses done with Genome Scan Meta Analysis (GMSA) method

GSMA Meta-Analysis of 7 ADHD Linkage Studies

(Zhou et al., Neuropsych Genetics, 2009)

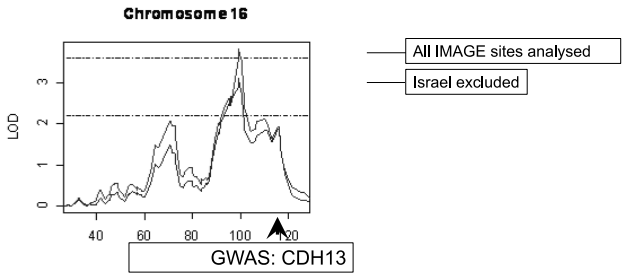


Red=Weighted; Blue=Unweighted

Genome-wide association scan of Attention Deficit Hyperactivity Disorder (ADHD)

Linkage analysis in IMAGE

Asherson et al, Mol. Psychiatry 2008; 13(5):514-521

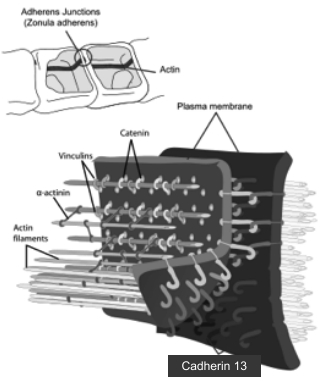


Lasky-Su et al, Am. J. Med. Genet. B, in press

CDH13 encodes Cadherin 13

Genome-wide association scan of Attention Deficit Hyperactivity Disorder (ADHD)

- **Member of protein family**
- **Plays a role in cell adhesion, cell-cell contacts and cell-migration**
- **Found in GWAS in Nicotine dependence**



Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: a genome-wide analysis

Large rare CNVs in chromosome 16p13.11 (prevuously found in Autism and schizophrenia

Summary

Background Large, rare chromosomal deletions and duplications known as copy number variants (CNVs) have been implicated in neurodevelopmental disorders similar to attention-deficit hyperactivity disorder (ADHD). We aimed to establish whether burden of CNVs was increased in ADHD, and to investigate whether identified CNVs were enriched for loci previously identified in autism and schizophrenia.

Methods We undertook a genome-wide analysis of CNVs in 416 children with ADHD and 1156 unrelated ethnically matched controls from the 1958 British Birth Cohort. Children of white UK origin, aged 5–17 years, who met diagnostic criteria for ADHD or hyperkinetic disorder, but not schizophrenia and autism, were recruited from community child psychiatry and paediatric outpatient clinics. Single nucleotide polymorphisms (SNPs) were genotyped in the ADHD and control groups with two arrays; CNV analysis was limited to SNPs common to both arrays and included only samples with high-quality data. CNVs in the ADHD group were validated with real-time quantitative genomic hybridisation. We assessed the genome-wide burden of large (>500 kb), rare (<1% population frequency) CNVs according to the average number of CNVs per sample with significance assessed via permutation. Locus-specific tests of association were undertaken for best regions defined for all identified CNVs and for 20 loci implicated in autism or schizophrenia. Findings were replicated in 625 Icelandic patients with ADHD and 35 243 Icelandic controls.

Findings Data for full analyses were available for 366 children with ADHD and 1047 controls. 57 large, rare CNVs were identified in children with ADHD and 23 in controls, showing a significantly increased rate of CNVs in ADHD (0·156 vs 0·022; p=8·9×10⁻⁹). This increased rate of CNVs was particularly high in those with intellectual disability (0·424; p=2·0×10⁻⁶), although there was also a significant excess in cases with no such disability (0·125; p=0·0077). An excess of chromosome 16p13.11 duplications was noted in the ADHD group (p=0·0003 after correction for multiple testing), a finding that was replicated in the Icelandic sample (p=0·031). CNVs identified in our ADHD cohort were significantly enriched for loci previously reported in both autism (p=0·0095) and schizophrenia (p=0·039).

Interpretation Our findings provide genetic evidence of an increased rate of large CNVs in individuals with ADHD and suggest that ADHD is not purely a social construct.

Funding Action Research; Baily Thomas Charitable Trust; Wellcome Trust; UK Medical Research Council; European Union.

Williams et al. *Lancet* 2010; 376 (9750): 1401-8.

Article

Genome-Wide Analysis of Copy Number Variants in Attention Deficit Hyperactivity Disorder: The Role of Rare Variants and Duplications at 15q13.3

Nigel M. Williams, Ph.D.
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Sandra Loo, Ph.D.
Stanley Nelson, M.D.
Corina Shtir, Ph.D.
Philip Asherson, M.R.C.Psych., Ph.D.
Andreas Reif, M.D.
Klaus-Peter Lesch, M.D.
Stephen V. Faraone, Ph.D.

Large rare CNVs in ADHD implicating duplications of 15q13.3 as a novel risk factor for ADHD with a frequency of 0.6% in the population

Williams et al. *Am J Psychiatry* 2012; 169:195-204

Genome Wide Copy Number Variation Study Associates Metabotropic Glutamate Receptor Gene Networks with Attention Deficit Hyperactivity Disorder

Elia et al. *Nature Genetics* 2011 in press

Attention-Deficit, Hyperactivity Disorder (ADHD) is a common, heritable neuropsychiatric disorder of unknown etiology. We performed a whole-genome copy number variation (CNV) study on 1,013 ADHD cases and 4,105 healthy children of European ancestry, using 550,000 SNPs. Significant findings were evaluated in multiple independent cohorts, totaling 2,493 ADHD cases and 9,222 controls of European ancestry, using matched platforms. CNVs impacting metabotropic glutamate receptor genes were enriched across all cohorts (P=2.1x10^{-9}). *GRM5* deletions (glutamate receptor, metabotropic 5) occurred in ten cases and one control (P=1.36x10^{-6}). *GRM7* deletions occurred in six cases and *GRM8* in eight cases and zero controls. *GRM1* was duplicated in eight cases. Observed variants were experimentally validated using qPCR. Gene network analysis demonstrated that genes interacting with GRM genes are enriched for CNVs in ~10% of cases (P=4.38x10^{-10}), corrected for control occurrence. We have uncovered rare recurrent CNVs that are overrepresented in multiple ADHD cohorts impacting glutamatergic neurotransmission genes.

Rare (10% of cases) recurrent CNVs that are over represented in ADHD Implicationg glutaminergic neuro transmission

RESEARCH

CNS Neuroscience & Therapeutics

Brain Biochemical Effects of Methylphenidate Treatment Using Proton Magnetic Spectroscopy in Youth with Attention-Deficit Hyperactivity Disorder: A Controlled Pilot Study

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2 Center for Comparative Neuroimaging, University of Massachusetts Medical School, Cambridge, MA, USA

Keywords
ADHD, Methylphenidate, Spectroscopy.

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doi: 10.1111/j.1755-5949.2010.00221.x

SUMMARY

Introduction: This study conducted spectroscopic analyses using proton (1H) Magnetic Resonance Spectroscopy (at 4 Tesla) in a sample of adolescents with Attention Deficit Hyperactivity Disorder (ADHD), before and after treatment with extended release methylphenidate (OROS MPH), as compared to a sample of healthy comparisons. **Aims:** The main aim of this study is to use 1H MRS to measure differences in brain biochemistry between adolescents with and without ADHD, and to assess changes in cerebral biochemistry, before and after stimulant treatment in ADHD youth. **Results:** Subjects with ADHD were medically healthy adolescents treated in an open label fashion with OROS MPH (mean dose: 54 mg/day; 0.90 mg/kg/day). Subjects with ADHD were scanned before and after OROS MPH treatment. Healthy comparators were scanned once. Magnetic resonance (MR) spectroscopy studies were performed on a 4.0 T Varian Unity/Inova MR scanner; proton spectra were acquired from the Anterior Cingulate Cortex (ACC). Data were analyzed using MANOVA and repeated measurement ANOVA. Higher metabolite ratios (glutamate/creatine, Inositol /Creatine, Glutamine/myo-inositol, Glutamate + Glutamine/myo-inositol) were observed in the ACC in untreated ADHD subjects as compared to controls, and in treated ADHD youth; these group differences did not reach the *a priori* threshold for statistical significance. **Conclusions:** These preliminary findings suggest the presence of glutamatergic abnormalities in adolescents with ADHD, which may normalize with MPH treatment. Larger sample, controlled studies are needed to confirm these preliminary findings.

Hammerness et al. *CNS Neuroscience & Therapeutics* 2010

High loading of polygenic risk for ADHD in those with comorbid aggression

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Abstract

Objective: Although ADHD is highly heritable, genome-wide association studies (GWAS) have not yet demonstrated that common genetic variants contribute to risk. There is evidence that conduct disorder/aggression in those with ADHD is an index of higher genetic loading as well as clinical severity. We set out to investigate whether common genetic variants, when considered *en masse* as polygenic scores for ADHD, are especially enriched in those with comorbid conduct disorder (CD).

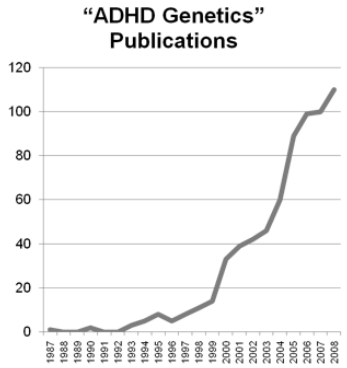
Method: Polygenic scores derived from a published ADHD GWAS meta-analysis were calculated in an independent ADHD sample (N=452 children). Multivariate logistic regression analyses were employed to compare polygenic scores in the ADHD group and controls and test for higher scores in those with ADHD and comorbid CD vs. controls and vs. those without comorbid CD. Association with symptom scores was tested using linear regression analysis.

Results: Polygenic risk for ADHD, as derived from the meta-analysis was higher in the independent ADHD sample than in controls (p=0.0005). The polygenic score was significantly higher in ADHD cases with CD compared to those without CD (p=0.0006). Furthermore, ADHD polygenic score showed significant association with comorbid CD symptoms. This relationship was explained by the aggression items (β=0.139, t=2.981, p=0.004).

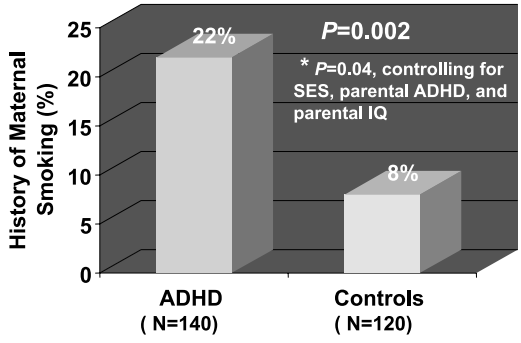
Conclusions: Common genetic variation appears relevant to ADHD, especially those with comorbid CD/aggression. The findings suggest that the previously published negative ADHD GWAS meta-analysis does contain associations to common variants, support for which falls below accepted genome-wide significance levels. The findings also highlight that aggression in ADHD indexes genetic as well as clinical severity.

ADHD Genetics

- The literature is predominated by candidate gene studies
- Genome-wide association studies are emerging
- CNV studies are emerging
- These studies will lead to greater progress as they do not assume we know more than we do about the etiology of ADHD



Maternal Smoking During Pregnancy: Results in Children

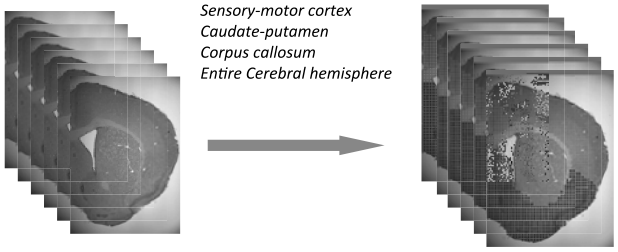


Milberger et al. *Am J Psychiatry* 1996;153:1138.

Prenatal Nicotine Exposure

Effects on brain structure

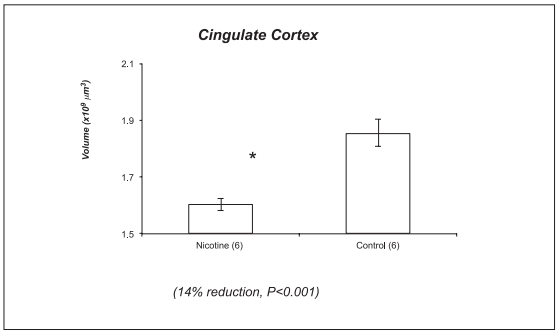
Stereological
Analysis of volume
of the cingulate cortex
Sensory-motor cortex
Caudate-putamen
Corpus callosum
Entire Cerebral hemisphere



Bhide et al 2009

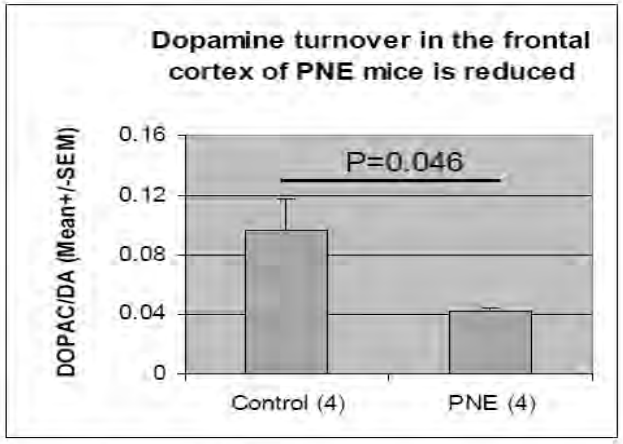
Prenatal Nicotine Exposure

Effects on brain structure



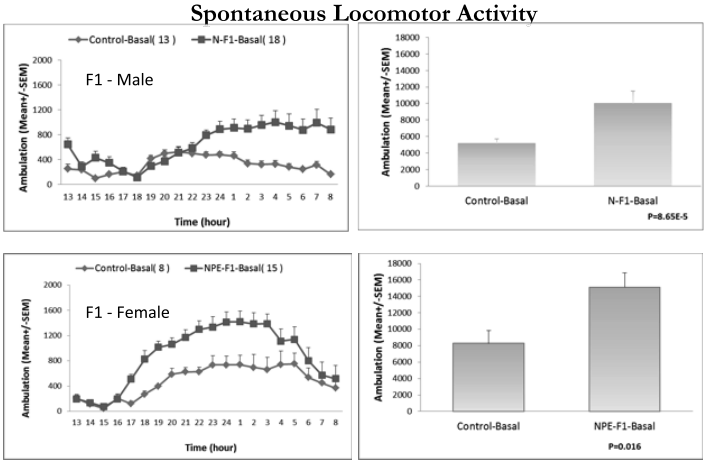
Prenatal nicotine exposure reduces the volume of the cingulate cortex

Bhide et al 2009



Jinmin Zhu, unpublished

Prenatal Exposure (PNE (F1) Mice Have Increased Spontaneous Locomotor Activity



9410 • The Journal of Neuroscience, July 4, 2012 • 32(27):9410–9418

Development/Plasticity/Repair

Prenatal Nicotine Exposure Mouse Model Showing Hyperactivity, Reduced Cingulate Cortex Volume, Reduced Dopamine Turnover, and Responsiveness to Oral Methylphenidate Treatment

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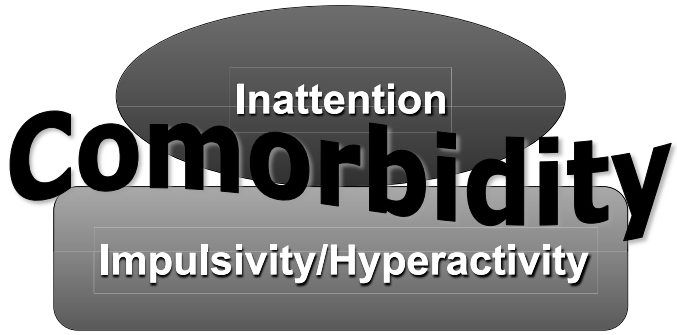
[1]Department of Biomedical Sciences, Florida State University College of Medicine, Tallahassee, Florida 32311, and Department of Neurology, and [3]Pediatric Psychopharmacology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts 02114

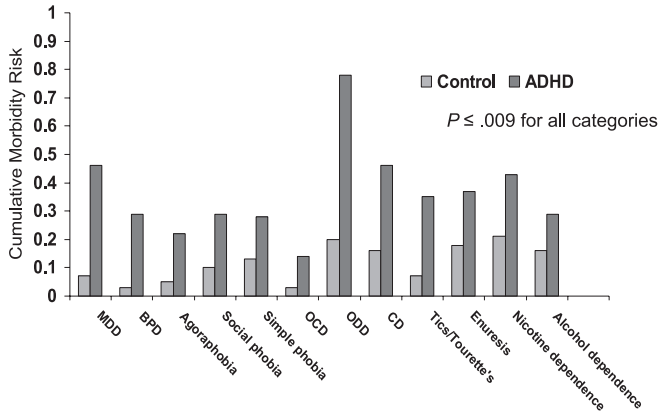
Cigarette smoking, nicotine replacement therapy, and smokeless tobacco use during pregnancy are associated with cognitive disabilities later in life in children exposed prenatally to nicotine. The disabilities include attention deficit hyperactivity disorder (ADHD) and conduct disorder. However, the structural and neurochemical bases of these cognitive deficits remain unclear. Using a mouse model we show that prenatal nicotine exposure produces hyperactivity, selective decreases in cingulate cortical volume, and radial thickness, as well as decreased dopamine turnover in the frontal cortex. The hyperactivity occurs in both male and female offspring and peaks during the "active" or dark phase of the light/dark cycle. These features of the mouse model closely parallel the human ADHD phenotype, whether or not the ADHD is associated with prenatal nicotine exposure. A single oral, but not intraperitoneal, administration of a therapeutic equivalent dose (0.75 mg/kg) of methylphenidate decreases the hyperactivity and increases the dopamine turnover in the frontal cortex of the prenatally nicotine exposed mice, once again paralleling the therapeutic effects of this compound in ADHD subjects. Collectively, our data suggest that the prenatal nicotine exposure mouse model has striking parallels to the ADHD phenotype not only in behavioral, neuroanatomical, and neurochemical features, but also with respect to responsiveness of the behavioral phenotype to methylphenidate treatment. The behavioral, neurochemical, and anatomical biomarkers in the mouse model could be valuable for evaluating new therapies for ADHD and mechanistic investigations into its etiology.

Zhu et al. J Neuroscience 2012; 32(27):9410-9418

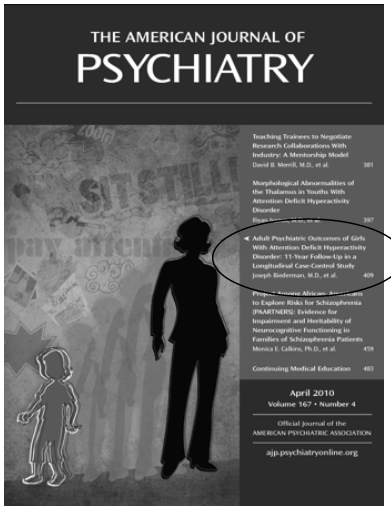
ADHD
Diagnostic Considerations



Cumulative Morbidity Risks for Psychiatric Disorders in ADHD and Control Probands

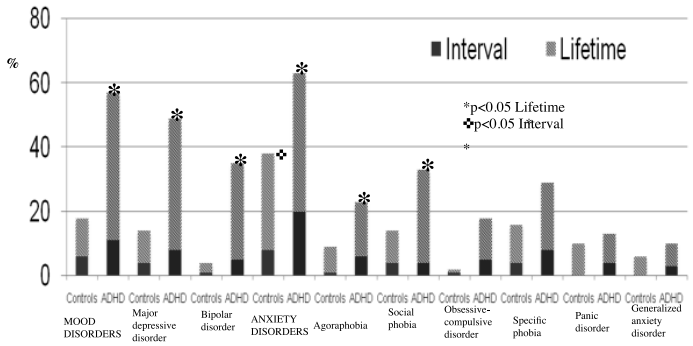


Biederman et al. *Psychological Medicine*, 2006, 36, 167–179.



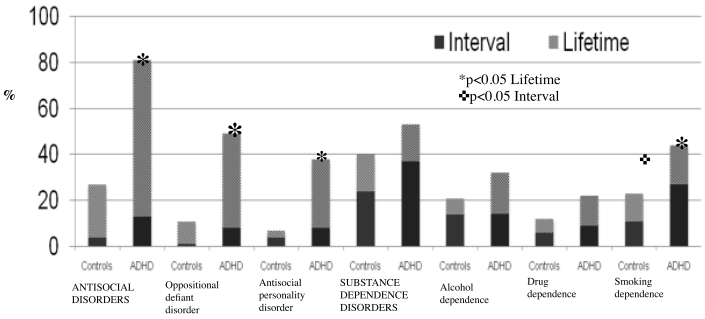
Biederman et al.
AJP. April 2010

Rates of Lifetime vs. Interval Disorders in ADHD Subjects vs. Controls at the 16 Yr F-U: Mood and Anxiety Disorders



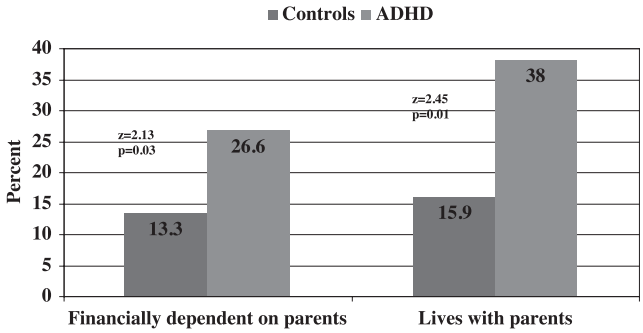
Biederman et al. 2012 In Press

Rates of Lifetime and Interval Disorders in ADHD Subjects vs. Controls at the 16 Yr F-U: Antisocial and Substance Dependence Disorders



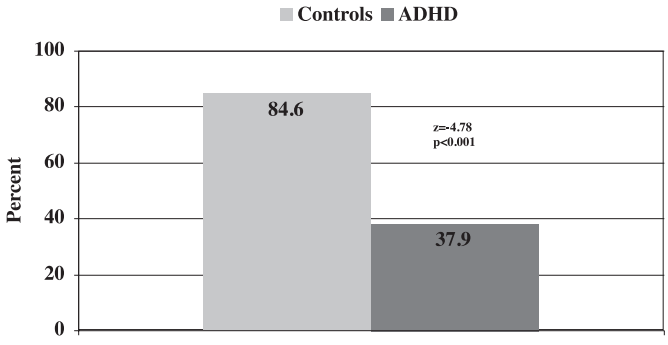
Biederman et al. 2012 In Press

Parental Support at the 16 year F-U



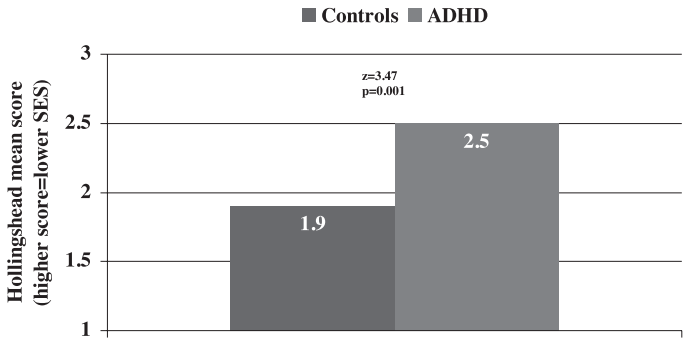
Biederman et al. 2012 In Press

College Graduate at the 16-Year Follow-Up



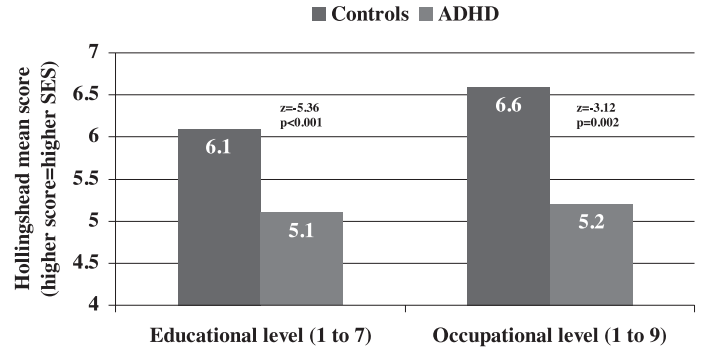
Biederman et al. 2012 In Press

Overall SES at the 16-Year Follow-Up



Biederman et al. 2012 In Press

Educational and Occupational Level at the 16-Year Follow-Up



Biederman et al. 2012 In Press

Adult Outcome of Attention-Deficit/Hyperactivity Disorder: A Controlled 16-Year Follow-Up Study

Joseph Biederman, MD; Carter R. Petty, MA; K. Yvonne Woodworth, BA; Alexandra Lomedico, BA; Laran L. Hyder, BA; and Stephen V. Faraone, PhD

ABSTRACT

Objective: To estimate the risks for psychopathology and functional impairments in adulthood among a longitudinal sample of youth with and without attention-deficit/hyperactivity disorder (ADHD) diagnosed in childhood.

Method: This was a case-controlled, 16-year (15–19 years) prospective follow-up study of ADHD: 140 boys with and 120 without *DSM-III-R* ADHD were recruited from pediatric and psychiatric settings. The main outcome measures were structured diagnostic interviews and measures of psychosocial, educational, and neuropsychological functioning. Data were collected from 1988 to 2006.

Results: At the 16-year follow-up, subjects with ADHD continued to significantly differ from controls in lifetime rates of antisocial, mood, anxiety, and addictive disorders, but with the exception of a higher interval prevalence of anxiety disorders (20% vs 8%; $z = 2.32$, $P = .02$) and smoking dependence (27% vs 11%; $z = 2.30$, $P = .02$), the incidence of individual disorders in the 6-year interval between the current and prior follow-up did not differ significantly from controls. At follow-up, the ADHD subjects compared with controls were significantly ($P < .05$) more impaired in psychosocial, educational, and

Among follow-up studies of children with attention-deficit/hyperactivity disorder (ADHD),[1–5] very few have assessed adult outcomes (Table 1). Moreover, the overwhelming majority of long-term follow-up studies of adults who had ADHD as children (eg, mean age >25 years) ascertained samples of children with "hyperactivity" and had a limited focus on antisocial and addictive disorders in adulthood (Table 1).[6–9] Fergusson et al.[10] conducted the only adult outcome of adolescents diagnosed with *DSM-III* ADHD criteria (Table 1). However, because most prior long-term follow-up studies were not long enough, more work is needed to better connect the prospective pediatric literature with that of retrospective adult ADHD.

This issue is particularly relevant in the context of associated psychiatric disorders. Studies of adult ADHD clearly document that ADHD is associated with high levels of functional impairment.[11–15] However, because adult ADHD is also associated with high rates of other psychiatric disorders,[16–18] questions remain as to whether the morbidity and dysfunction associated with ADHD are due to ADHD itself or its associated psychiatric disorders.

The retrospective and cross-sectional findings in the literature on adult ADHD document a large discrepancy between the high lifetime and the low current rates of others psychiatric disorders,[19] along with high levels of current impairment in multiple domains. This pattern of findings suggests that the functional impairments of ADHD adults are not due to associated disorders but to ADHD itself. However, the discrepancy between lifetime and current disorders observable in prospective samples has not been adequately investigated. Prior longitudinal studies have also not disentangled the contributions of ADHD and other active psychopathology to functional impairments in adulthood. Clarifying these issues will lead to an improved

Biederman et al. *J Clin Psychiatry* 2012;73(3):941.

ARTICLES

Do Stimulants Protect Against Psychiatric Disorders in Youth With ADHD? A 10-Year Follow-up Study

abstract

OBJECTIVE: Little is known about the effect of stimulant treatment in youth with attention-deficit/hyperactivity disorder (ADHD) on the subsequent development of comorbid psychiatric disorders. We tested the association between stimulant treatment and the subsequent development of psychiatric comorbidity in a longitudinal sample of patients with ADHD.

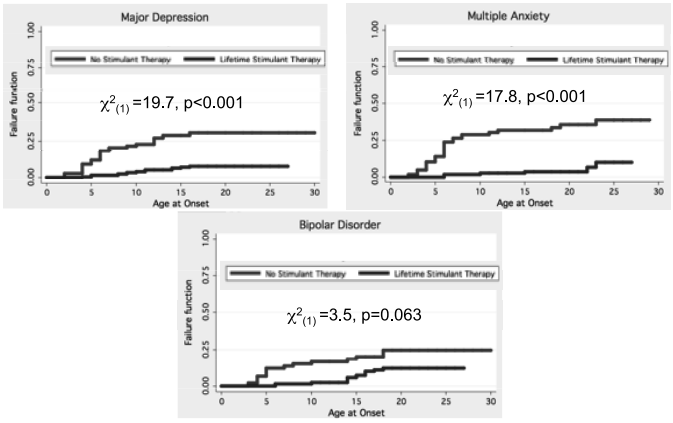
METHODS: We conducted a case-control, 10-year prospective follow-up study into young-adult years of youth with ADHD. At baseline, we assessed consecutively referred white male children with ($n = 140$) and without ($n = 120$) ADHD, aged 6 to 18 years. At the 10-year follow-up, 112 (80%) and 105 (88%) of the children in the ADHD and control groups, respectively, were reassessed (mean age: 22 years). We examined the association between stimulant treatment in childhood and adolescence and subsequent comorbid disorders and grade retention by using proportional hazards survival models.

RESULTS: Of the 112 participants with ADHD, 82 (73%) were previously treated with stimulants. Participants with ADHD who were treated with stimulants were significantly less likely to subsequently develop depressive and anxiety disorders and disruptive behavior and less likely to repeat a grade compared with participants with ADHD who were not treated.

CONCLUSIONS: We found evidence that stimulant treatment decreases the risk for subsequent comorbid psychiatric disorders and academic failure in youth with ADHD. *Pediatrics* 2009;124:71–78

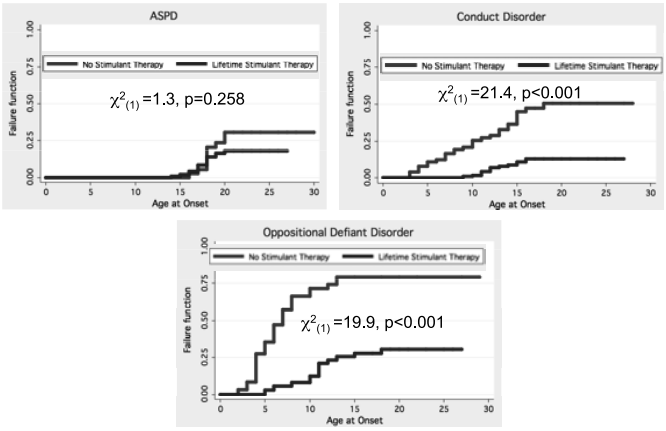
Biederman et al. *Pediatrics* 2009 Jul;124(1):71-8.

Protective Effect of Stimulants on Comorbidity



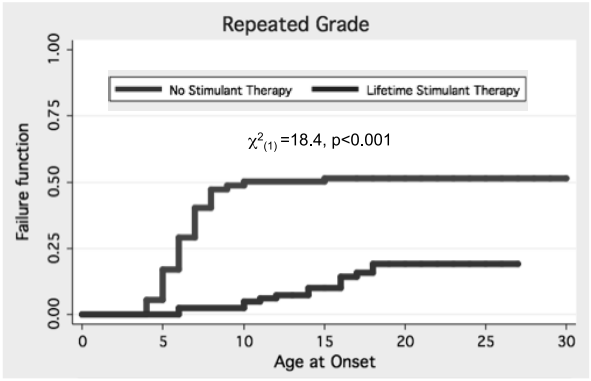
Biederman et al. *Pediatrics* in press 2009

Protective Effect of Stimulants on Comorbidity



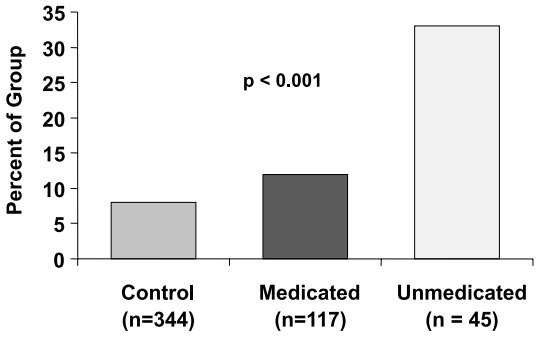
Biederman et al. *Pediatrics* in press 2009

Protective Effect of Stimulants

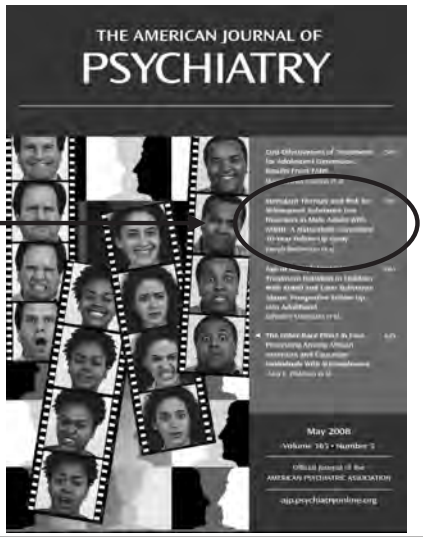


Biederman et al. *Pediatrics* in press 2009

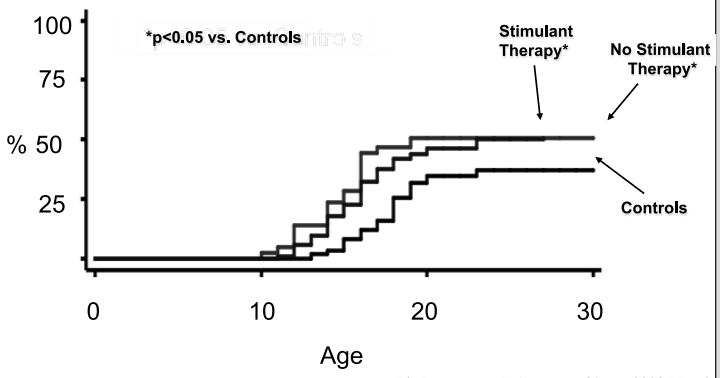
SUD in ADHD Youth Growing Up: Overall Rate of Substance Use Disorder



Biederman, Wilens, Mick et al., Pediatric 1999



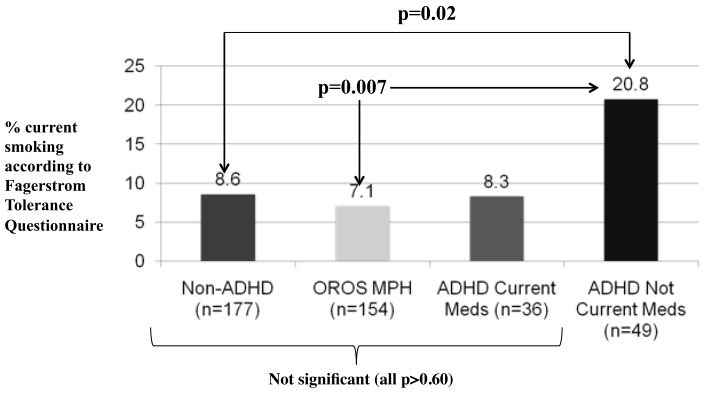
Stimulant Therapy and Subsequent Risk for Substance Dependence Disorders



Biederman et al. *Am J Psychiatry*. 2008 Mar 3

Prospective Study of OROS MPH vs. non-ADHD and ADHD Comparators on Rates of Smoking

Omnibus test, chi-squared(1)=8.44, p=0.04



Hammerness and Biederman, 2011

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Do Stimulants Reduce the Risk for Cigarette Smoking in Youth with Attention-Deficit Hyperactivity Disorder? A Prospective, Long-Term, Open-Label Study of Extended-Release Methylphenidate

Paul Hammerness, MD[1], Gagan Joshi, MD[1], Robert Doyle, MD[1], Anna Georgiopoulos, MD[1], Daniel Geller, MD[1], Thomas Spencer, MD[1], Carter R. Petty, MA[1], Stephen V. Faraone, PhD[2], and Joseph Biederman, MD[1]

Objective Although attention-deficit hyperactivity disorder (ADHD) is a well-known risk factor for cigarette smoking, prospective studies aimed at reducing smoking risk in this population are critically needed.
Study design This was a 2-year, prospective, open-label clinical trial of extended-release methylphenidate for smoking prevention in adolescents with ADHD (n = 154). Smoking outcomes were assessed with the Fagerstrom Tolerance Questionnaire. Comparisons were made using data from a historical, naturalistic sample of ADHD (n = 103) and non-ADHD comparators (n = 188) of similar age and sex assessed with the same assessment battery as that used in subjects participating in the clinical trial.
Results The smoking rate at endpoint (mean, 10 months of methylphenidate treatment) was low in the clinical trial subjects and not significantly different from that in the non-ADHD comparators or the ADHD comparators receiving stimulants naturalistically (7.1% vs 8.0% vs 10.9%; $P > .20$). In contrast, the smoking rate was significantly lower in the clinical trial subjects than in the naturalistic sample of ADHD comparators who were not receiving stimulant treatment (7.1% vs 19.6%; $P = .009$ [not significant], adjusting for comorbid conduct disorder and alcohol and drug abuse).
Conclusion Although considered preliminary until replicated in future randomized clinical trials, the findings from this single-site, open-label study suggest that stimulant treatment may contribute to a decreased risk for smoking in adolescents with ADHD. If confirmed, this finding would have significant clinical and public health impacts. (*J Pediatr 2012;■:■-■*).

Hammerness et al. *J Pediatr* 2012

Cigarette smoking as a risk factor for other substance misuse: 10-year study of individuals with and without attention-deficit hyperactivity disorder

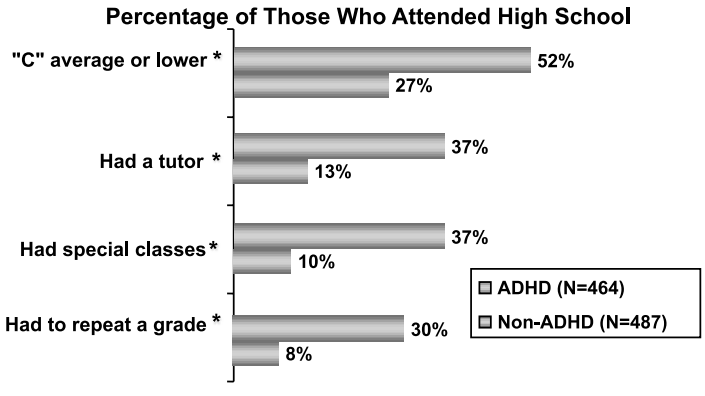
BJPsych

Biederman et al. 2012 *Br J Psychiatry*

Functional Impairments

Results of A Survey of 1000 Subjects with and without ADHD

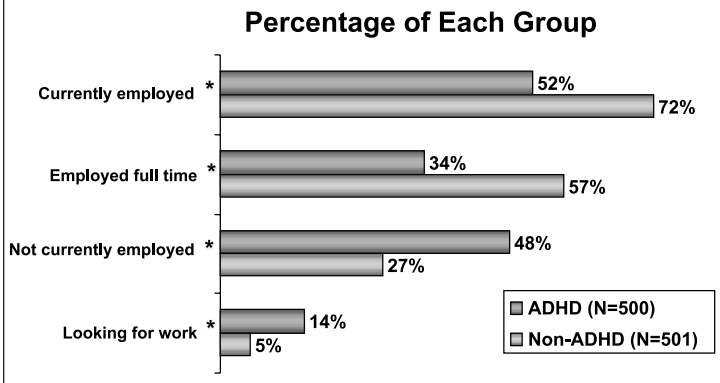
Educational Impairment in High School



* $p \leq .001$

Biederman et al. *J Clin Psychiatry*. 2006 Apr; 67(4):524-40

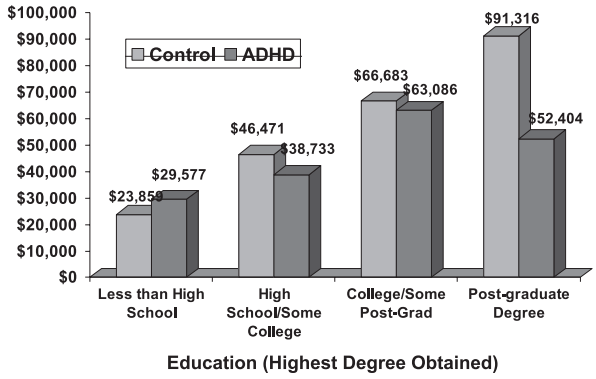
Current Employment Status



* $p \leq .001$

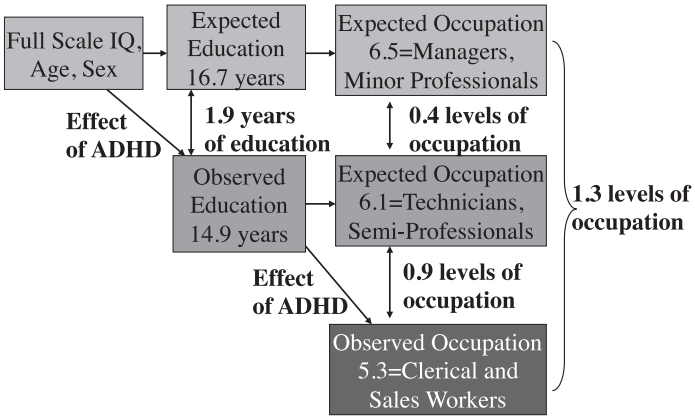
Biederman et al. *J Clin Psychiatry*. 2006 Apr; 67(4):524-40

Average Household Income by Education Level Attained

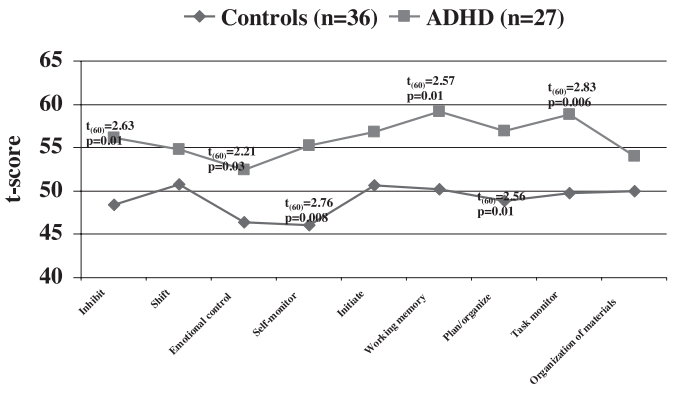


Biederman and Faraone. *Medscape General Medicine* 2006; 8:12.

Expected and Observed Years of Education and Occupational Status in Adults with ADHD

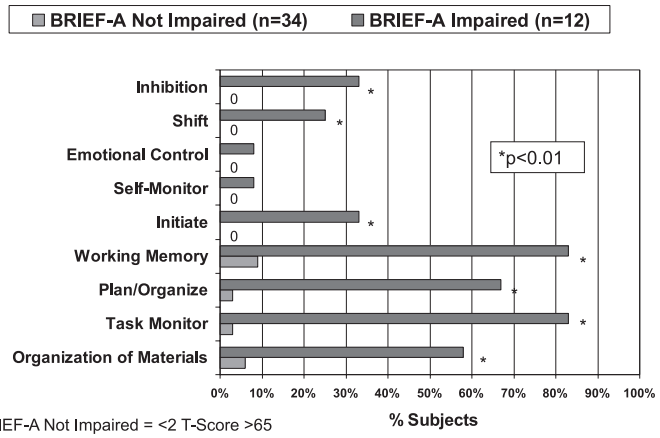


BRIEF T-scores (Past Month)



Biederman et al. 2012 In Press

Residual BRIEF-A Impairments in OROS-MPH Clinical Responders (ADHD Symptoms)

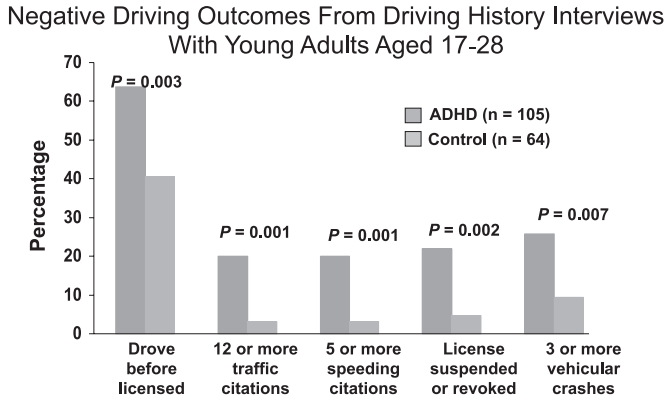


BRIEF-A Not Impaired = <2 T-Score >65

BRIEF-A Impaired = ≥2 T-Score >65

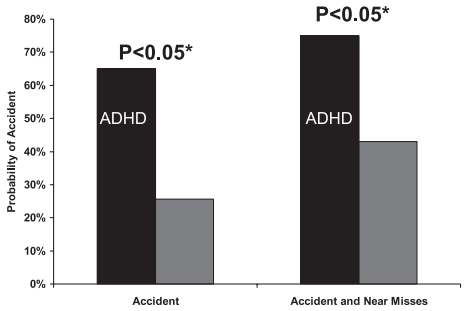
Biederman et al. *Eur Neuropsychopharm* 2011

Traffic Accidents and Violations



Barkley et al. *J Int Neuropsychol Soc.* 2002;8:655-672.

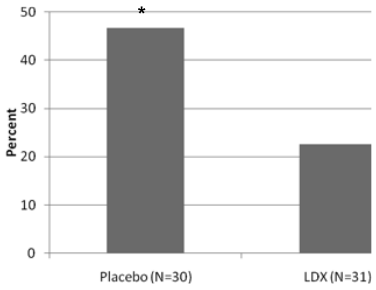
Accidents and Near Misses



*Indicates P<0.05 after controlling for gender, age, time of day and the age*ADHD interaction

(Reimer et al., submitted)

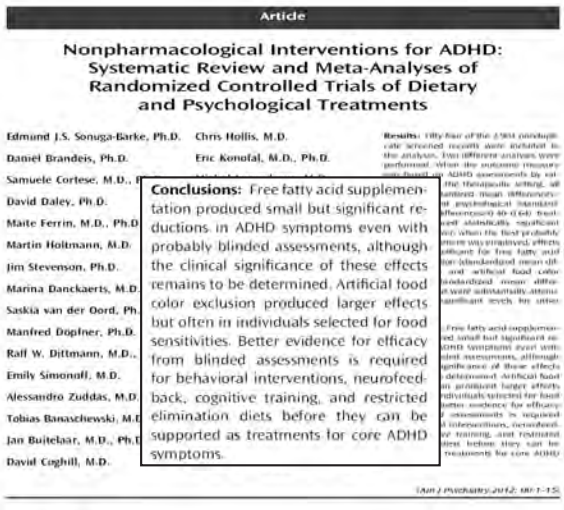
Percent of Subjects Involved in Collisions During Surprise Events



LDX = lisdexamfetamine dimesylate

- During the five surprise events, drivers in the medication group were 67% less likely to have a collision than drivers in the placebo group

Biederman et al. 2011 submitted



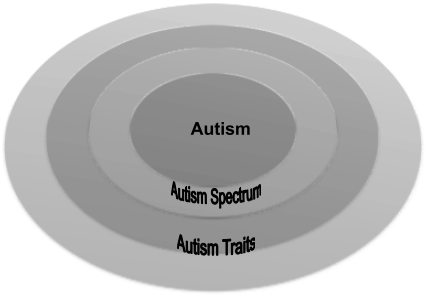
Article

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

Edmund J.S. Sonuga-Barke, Ph.D. Chris Hollis, M.D.
Daniel Brandeis, Ph.D. Eric Konofal, M.D., Ph.D.
Samuele Cortese, M.D.,
David Daley, Ph.D.
Maite Ferrin, M.D., Ph.D.
Martin Holtmann, M.D.
Jim Stevenson, Ph.D.
Marina Danckaerts, M.D.
Saskia van der Oord, Ph.
Manfred Döpfner, Ph.D.
Ralf W. Dittmann, M.D.,
Emily Simonoff, M.D.
Alessandro Zuddas, M.D.
Tobias Banaschewski, M.D.
Jan Buitelaar, M.D., Ph.D.
David Coghill, M.D.

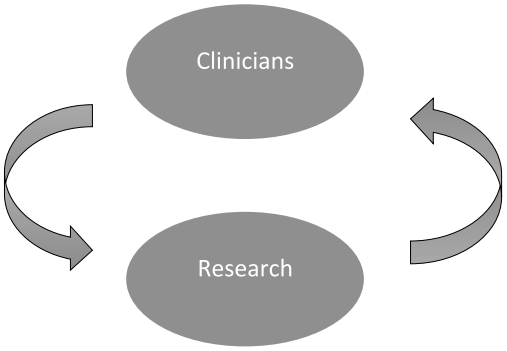
Conclusions: Free fatty acid supplementation produced small but significant reductions in ADHD symptoms even with probably blinded assessments, although the clinical significance of these effects remains to be determined. Artificial food color exclusion produced larger effects but often in individuals selected for food sensitivities. Better evidence for efficacy from blinded assessments is required for behavioral interventions, neurofeedback, cognitive training, and restricted elimination diets before they can be supported as treatments for core ADHD symptoms.

From Autism to Autistic Traits



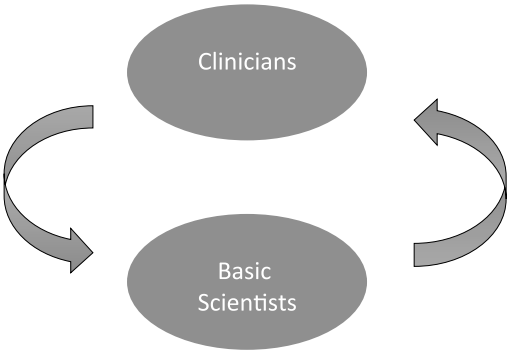
Clinical and Research Programs in Pediatric Psychopharmacology

Clinical-Scientific Collaboration to Advance Discovery



Imaging, Genetics, Animal Models

Clinical-Scientific Collaboration to Advance Discovery



Imaging, Genetics, Animal Models

Summary

- ADHD is a neurobehavioral disorder with a:
  - Complex etiology
  - Neurobiologic basis
  - Strong genetic component
- ADHD
  - Affects millions of people of both genders
  - Persists through adolescence and adulthood in a high percentage of cases
  - Can have negative impact on multiple areas of functioning

Genetics of ADHD

Stephen V. Faraone, PhD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

Genetics of ADHD

Stephen V. Faraone, Ph.D.

Professor, Departments of Psychiatry and of Neuroscience and Physiology
SUNY Upstate Medical University

Disclosures of Potential Conflicts

Source	Research Funding	Advisor/ Consultant	Employee	Speakers' Bureau	Books, Intellectual Property	In-kind Services (example: travel)	Stock or Equity	Honorarium or expenses for this presentation or meeting
NIH	X							
Guilford Press					X			
Akili Interactive Labs		X						
Phoenix Group		X						
Oxford Univ. Press					X			

Reporting period is past 2 years .

What is the Value of Genetic Data?

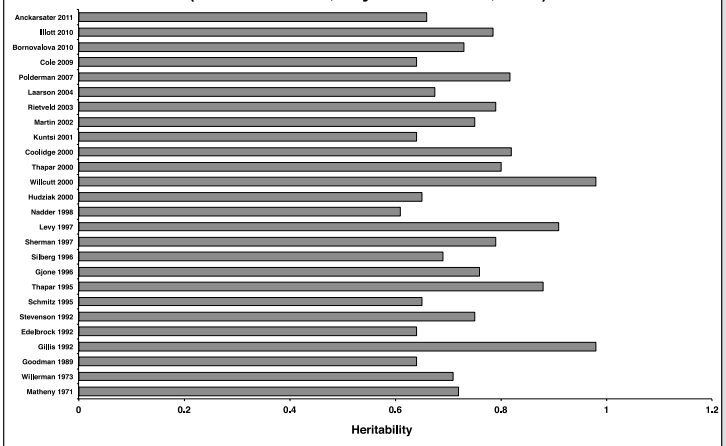
- Improve the construct validity of ADHD
- Understand ADHD as a disorder of families
- Clarify etiology of the disorder
- Provide new targets for drug development.
  - ADHD medications are not completely effective and have side effects
  - Gene discovery will implicate new chemical networks in the brain.
  - These new networks will provide new targets for drug discovery

ADHD Genetics: The Past

- Is ADHD heritable?
- What is the mode of transmission?
  - A few major genes?
  - Many polygenes?
- Do common DNA variants cause ADHD?
  - Candidate gene studies
  - Genomewide linkage studies
  - Pharmacogenetic candidate gene studies

Heritability of ADHD in Youth

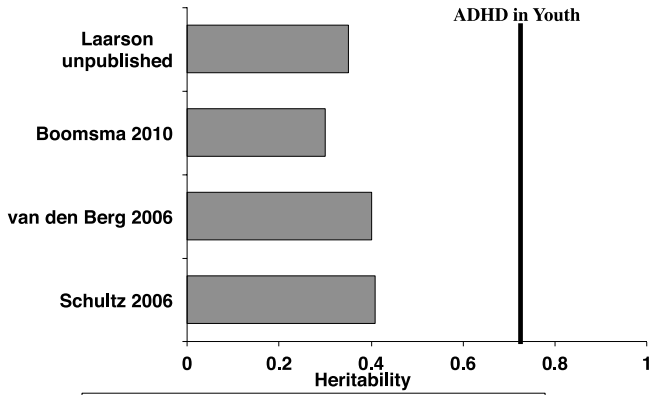
(Faraone & Mick, Psych Clin N. Am, 2010)



Mean Heritability of ADHD in Youth=.75

Heritability of ADHD in Adults

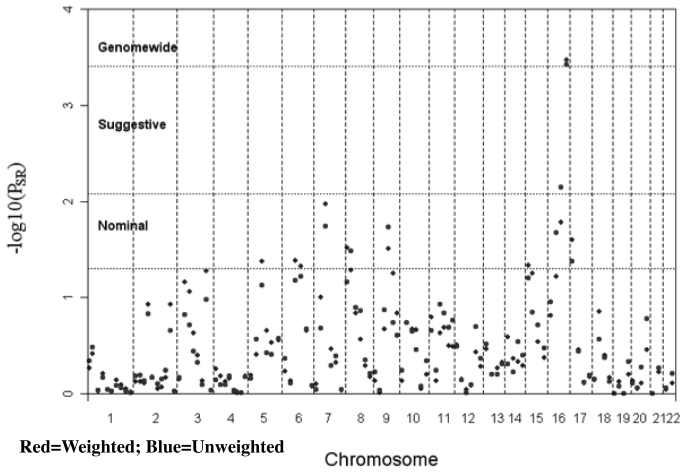
(Franke et al., submitted)



Mean Heritability of ADHD in Adults=.37

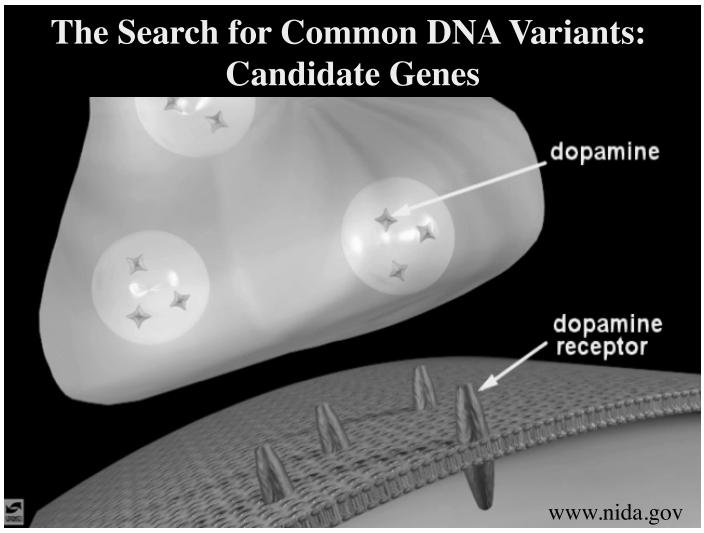
Meta-Analysis of 7 ADHD Linkage Studies

(Zhou et al., Neuropsych Genetics, 2009)

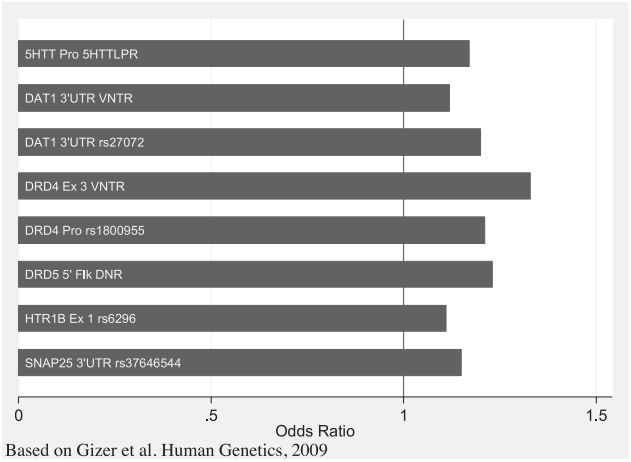


Red=Weighted; Blue=Unweighted

The Search for Common DNA Variants: Candidate Genes



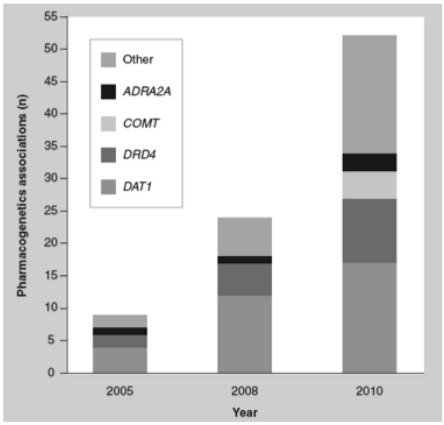
Candidate Gene Variants with Statistically Significant Association to ADHD in Meta Analysis



Based on Gizer et al. Human Genetics, 2009

Ten Years of Pharmacogenetic Candidate Gene Research

(Kieling et al., 2010)



ADHD Genetics: The Present

- Genome-wide association studies (GWAS) of common variants
- GWAS of rare variants
  - Copy Number Variants (CNVs) from GWAS studies
    - Rare duplications and deletions
  - Unlike SNPs from GWAS, functional rare variants are likely to directly affect gene function

The Search for Common DNA Variants: Genomewide Association Studies (GWAS)

- **Linkage analyses have found little.**
- **Candidate gene studies limited to known biological pathways.**
- **GWAS holds the promise of discovering new pathways.**
- **Because the entire genome is examined, the threshold for statistical significance is very stringent: p<.00000005**

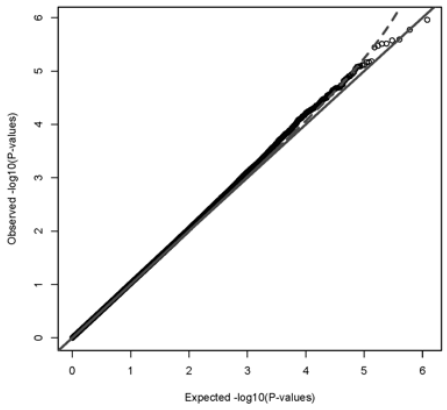
ADHD GWAS Samples

(Neale et al., JAACAP, 2010)

Samples	Cases	Controls	Trios	SNPs
CHOP	-	-	423	469,283
IMAGE 1	-	-	909	438,784
IMAGE 2	896	2,455	-	294,811
PUWMA	-	-	732	645,995
Total	896	2,455	2,064	1,206,462

Quantile-Quantile Plot of Meta-Analysis Results

(Neale et al., JAACAP, 2010)

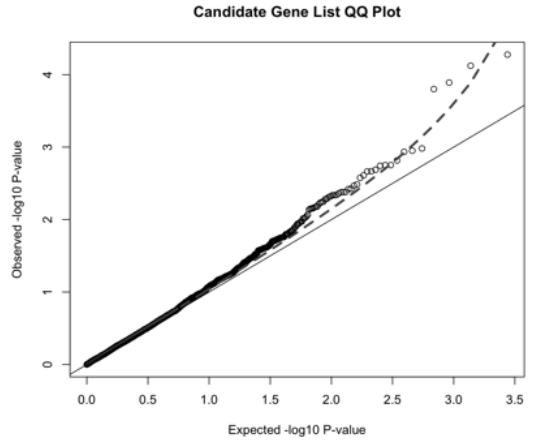


Candidate Genes for ADHD

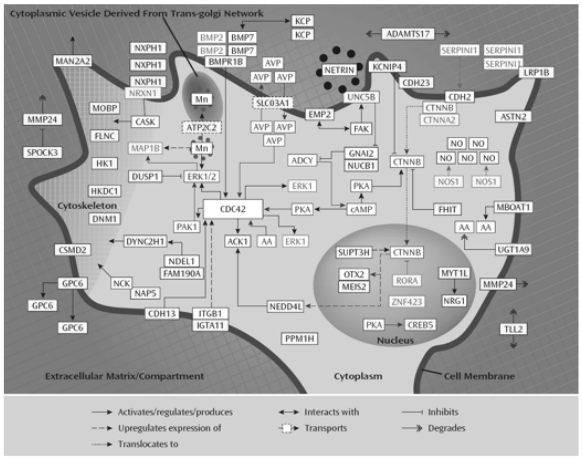
SNAP25, DRD4, SLC6A3, HTR1B, SLC6A4, DBH, NR4A2, PER2, SLC6A1, DRD3, SLC9A9, HES1, ADRA2C, ADRB2, ADRA1B, DRD1, HTR1E, DDC, STX1A, ADRA1A, NFIL3, ADRA2A, ADRB1, SLC18A2, TPH1, BDNF, FADS1, FADS2, ADRBK1, ARRB1, DRD2, HTR3B, TPH2, SYT1, HTR2A, SLC6A2, ARRB2, PER1, PNMT, CHRNA4, COMT, ADRBK2, CSNK1E, MAOA, MAOB, and HTR2C

Quantile-Quantile Candidate Gene Plot

(Neale et al., JAACAP, 2010)

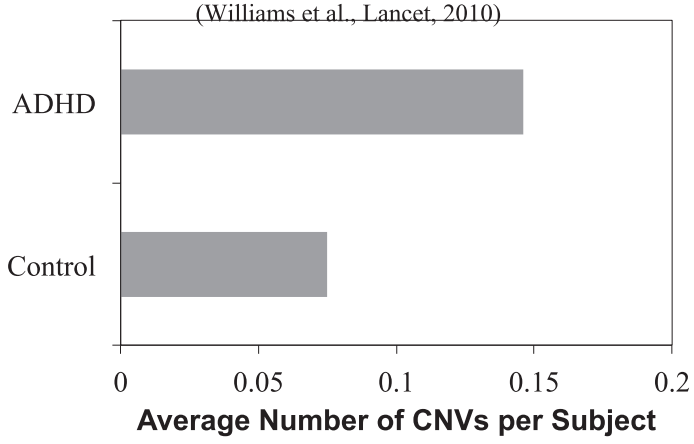


Pathway Analysis of GWAS Implicates Neurite Outgrowth in ADHD (Poelmans et al. AJP, 2011)

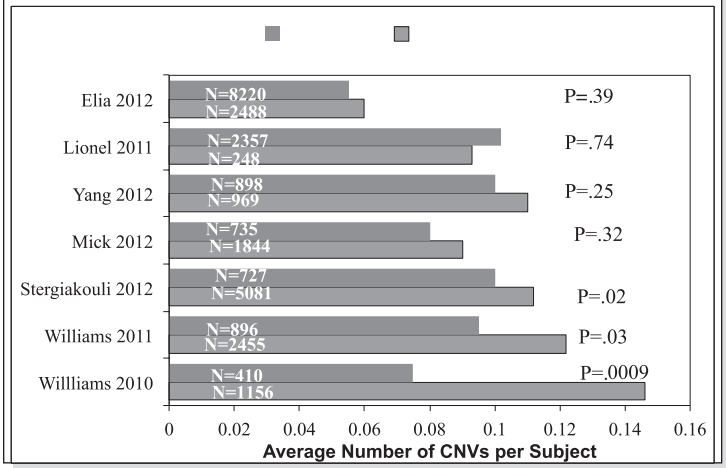


Increased Burden of Rare CNVs among ADHD Patients

(Williams et al., Lancet, 2010)



Replication?: Burden of Large (>500kb) Rare CNVs in ADHD



GWAS of Response to Methylphenidate in 187 Children with ADHD

(Mick et al, NPG, 2008)

72% male (N=135)

9.2±2.0y (6-12 y)

White, non-Latino (N=105, 56%)

White, Latino (N=34, 18%),

African American (N=26, 14%)

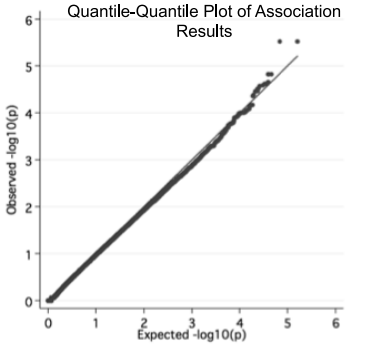
Other (N=22, 12%).

89% (N=166) completed the study

Baseline ADHD-RS = 42.3±7.8.

Endpoint ADHD-RS = 15.4±11.8

Change Score = –26.9±11.2.



We did not observe any strong deviation from the expected distribution of p-values at the extreme tail of the statistical tests of the single SNPs. The plot also shows no evidence for biased inflation of the test statistic or population stratification artifacts.

Study funded by Shire grant to S.Faraone

GWAS of Response to Methylphenidate in 187 Children with ADHD

(Mick et al, NPG, 2008)

Association results for SNPs at p<0.0001 associated with known genes

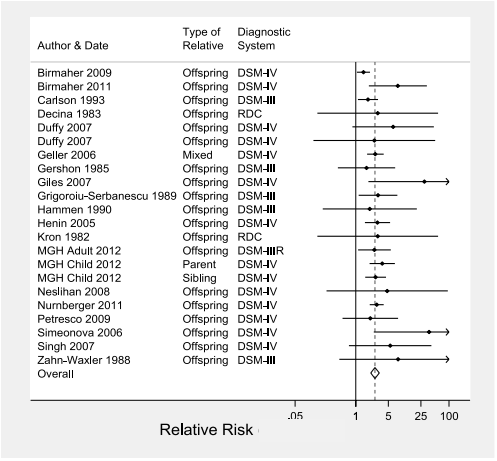
CHR	refSNP ID	Position (base pairs)	Gene	A1	MAF	HWE p-value	Chi-square	p-value
17	rs2157697	9968291	GAS7	G	0.336	0.8	20.5	0.000015
4	rs2594278	88080483	LOC728530	G	0.268	0.5	19.6	0.000024
3	rs3792452	7641784	GRM7*	G	0.183	0.6	18.8	0.000026
21	rs1065758	37230781	HLCS	G	0.118	0.5	18.4	0.000027
10	rs12360508	23260889	ARMC3	A	0.154	0.4	18.6	0.00003
16	rs16959263	12346351	SNX29	G	0.059	0.1	18.3	0.0000675
20	rs17755054	42245512	JPH2	C	0.188	0.6	15.9	0.0000894

*** A metabotropic glutamate receptor gene (GRM7) known to be involved in inhibitory G protein coupled signaling, whereby it reduces cyclic AMP levels, similar to the effects of the type 2 class of dopamine receptors**

Cross Disorder Studies of ADHD

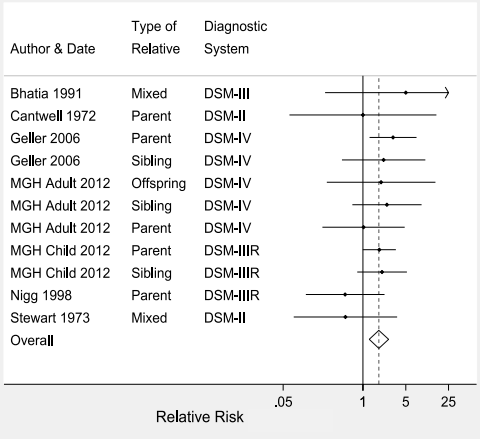
- Psychiatric comorbidity is common
- There is overlap among psychiatric disorders in neuropsychological impairments and neuroimaging abnormalities
- Familial co-aggregation of disorders is common
- Pooling across disorders may be sensible to create the very large samples needed for gene discovery.

Meta-Analysis: ADHD in Relatives of Bipolar Probands
(Faraone et al., Am. J Psychiatry, 2012)



N= 4301 relatives of BP-I probands and 1937 relatives of controls

Meta-Analysis: Bipolar Disorder in relatives of ADHD Probands
(Faraone et al., Am. J Psychiatry, 2012)



N=1877 relatives of ADHD probands and 1601 relatives of controls

Psychiatric Genomics Consortium

- Participants:
  - 200+ members
  - 70 institutions
  - 20 countries
- GWAS Data:
  - 49 Datasets, ~60,000 subjects, ~34 billion genotypes
  - Bipolar disorder, schizophrenia, major depression autism, ADHD
- May expand to:
  - New data types: Exome chip and sequencing data
  - New Disorders: OCD, Tourette's, Anorexia Nervosa, Alzheimer's

Sample Sizes for Five Psychiatric Disorders

(PGC, Lancet, In Press)

Disorder	N Studies	N cases	N controls	N
ADHD *	4	2,787	2,635	**5,440**
AUT *	8	4,949	5,314	**10,263**
SCZ	17	9,379	7,736	**17,115**
BPD	11	6,990	4,820	**11,810**
MDD	9	9,227	7,383	**16,610**
Total	**49**	**33,332**	**27,888**	**61,238**

* Majority family based, broken into pseudocases / pseudocontrols

Susceptibility Genes Discovered by Cross Disorder GWAS

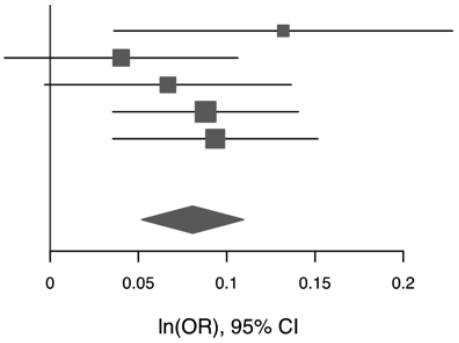
(PGC, Lancet, In Press)

- ITIH3: inter-alpha (globulin) inhibitor H3
- CACNB2: calcium channel, voltage-dependent, beta 2 subunit
- CACNA1C: calcium channel, voltage-dependent, L type, alpha 1C subunit
- NEURL: neuralized homolog
- FPR2: formyl peptide receptor 2

CACNB2 Results for Each Disorder

(PGC, Lancet, In Press)

ADHD
ASD
Bipolar
Depression
Schizophrenia

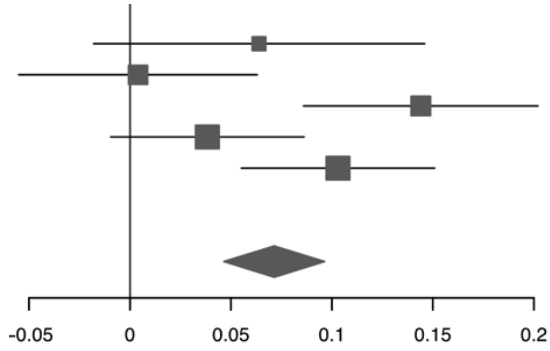


Combined $p=4.29 \times 10^{-8}$

CACNA1C Results for Each Disorder

(PGC, Lancet, In Press)

ADHD
ASD
Bipolar
Depression
Schizophrenia

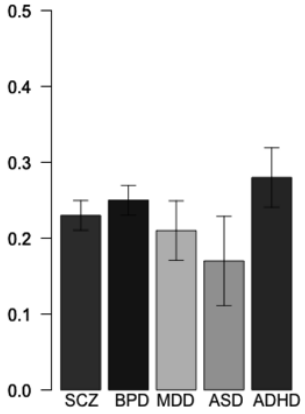


Combined 1.87×10^{-8}

SNP Heritabilities for Five Disorders

(Wray et al., submitted)

Each disorder has a significant polygenic component comprised of common SNP variation



Correlation in SNP Heritability Across Cultures

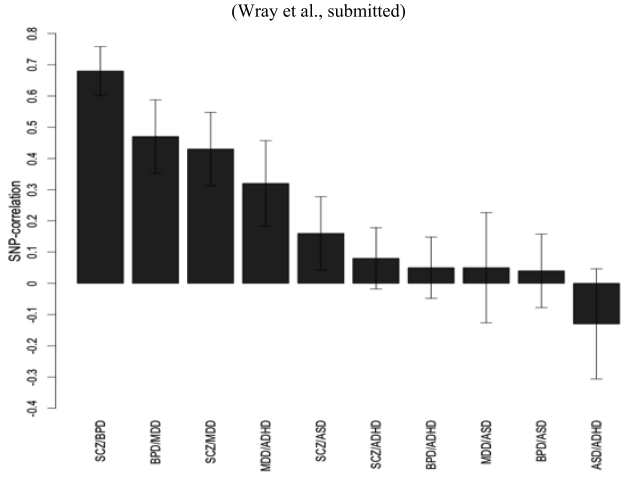
(Wray et al., in progress)

Correlation of US and European ADHD samples = .89

Correlation of Caucasian and Chinese samples = .46

Polygenic Component Correlations for Five Disorders

(Wray et al., submitted)



Lessons from PGC Cross-Disorder Studies

- Small effects of common risk variants: Odds Ratios < 1.4
- Many common risk variants combine to form a polygenic risk continuum that has specific components for ADHD and components in common with other disorders
- Huge samples needed to detect common variants

ADHD Genetics: The Future

- Functional Studies of DNA variants
  - Animal models, cell culture
  - Imaging genomics
- Genes and environment
  - Epigenetics
  - Gene environment interaction?
- Genetic testing for ADHD?

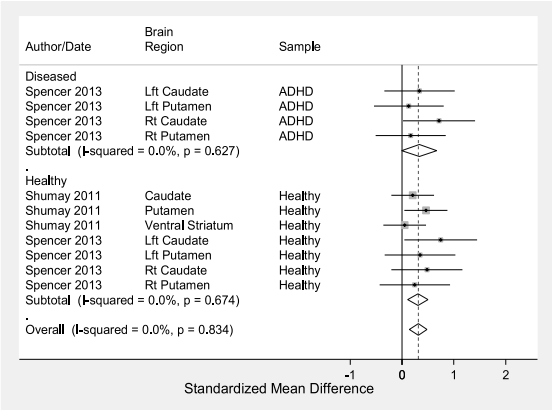
Functional Effects of Dopamine Transporter (DAT) Genotypes on in vivo DAT Functioning

(Faraone et al., submitted for publication)

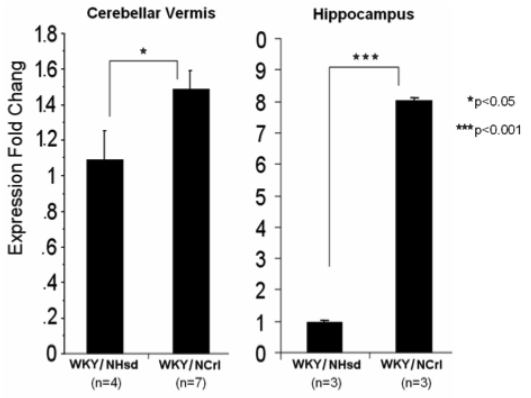
- 9R allele of a a 40-base pair (bp) variable number of tandem repeats (VNTR) polymorphism associated with adult ADHD (Franke et al., 2008)
- Meta-analysis shows increased in vivo DAT availability in humans (Fusar-Poli et al., 2010).

Meta-analysis of Positron Emission Tomography Studies: Association of DAT 9R allele with in vivo DAT Functioning

(Faraone et al., submitted for publication)



Upregulation of Slc9a9 expression in WKY/NCrl rats brain



Zhang-James et al., Neuropsychiatric Genetics, 2011

SLC9A9 novel SNPs in Inattentive ADHD Rat

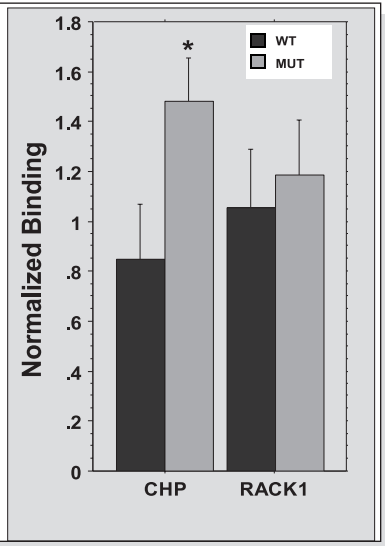
(Zhang-James et al., Neuropsychiatric Genetics, 2011)

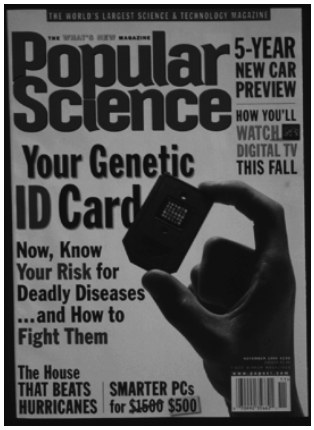
	SHR	WKY/NHsd	WKY/NCrl	genomic location
Intron 2	A	A	G	chr8:99751724
Exon 14	T	T	G	chr8:100135287 synonymous (Gly)
Intron 14	A	A	G	chr8:100135447
Exon 16	T	T	G	chr8:100231157 (V-->G)
	A	A	G	chr8:100231223 (K-->R)

- 511aa: Val→Gly
- 533aa: Lys→Arg

ADD-Rat *SLC9A9* mutation enhances interaction of SLC9A9 protein with CHP protein

(Zhang-James et al., Neuropsychiatric Genetics, 2011)





Molecular Genetics and Diagnosis

Science, Vol 319, Jan, 2008

Players in the Psychiatric Gene-Testing Business

Company	Test available	Disease	Type of test	Number of genes
NeuroMark	mid–2008	Major depression	Risk of suicidality from antidepressants	4
Psynomics	now	Bipolar disorder	Diagnosis and response to antidepressants	2*
SureGene	mid–2009	Schizophrenia	Risk of psychosis and response to antipsychotics	6

* Psynomics plans to add five more genes early this year.

Science, Vol 319, Jan, 2008

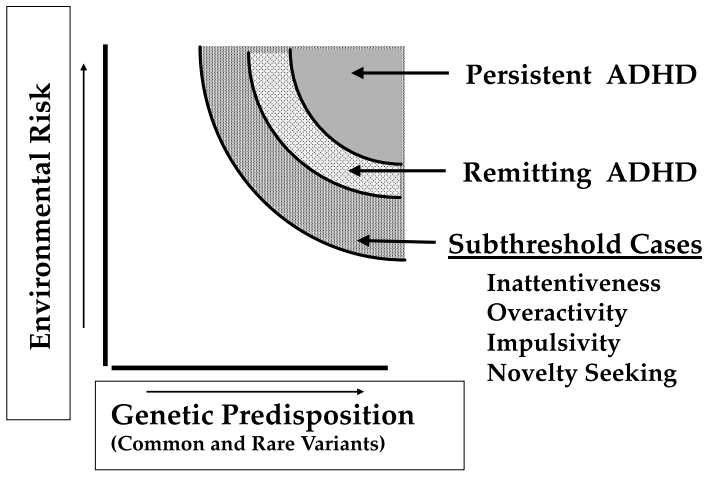
Summary: Genetics of ADHD

- Twin studies show that genes influence susceptibility to ADHD
- Many, many DNA variants are implicated
  - Confirmed common variants have yet to be discovered
  - Several rare variants (CNVs) have been found
- Functional genetic, pharmacogenetic & epigenetic studies beginning to bear fruit
- There is no genetic test for ADHD or drug response to ADHD medications

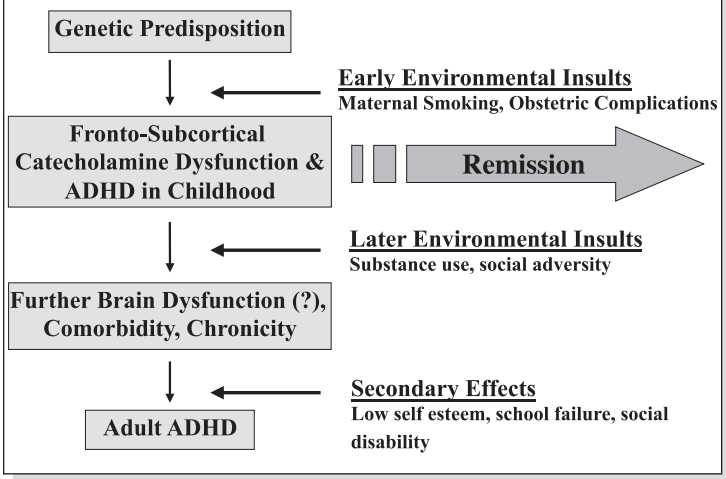
Summary: An Evolving View ADHD's Etiology

- Nature vs. Nurture → ADHD is complex disorder
- Heritability → Specific genes and DNA variants
- Environment → Exposures, timing, epigenetics
- Descriptive Statistical Evidence → Mechanism

The Complex Etiology of ADHD



Developmental Pathophysiology of ADHD



Thanks for Listening!

Deficient Emotional Self Regulation in ADHD

Joseph Biederman, MD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

Deficient Emotional Self Regulation in ADHD

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Harvard Medical School

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Massachusetts General Hospital
Harvard Medical School

Disclosure Statement (2010-2013)

- Research Support
  - APSARD
  - Department of Defense
  - ElMindA
  - Janssen
  - McNeil
  - Shire
  - Vaya Pharma/Enzymotec
- Honoraria
  - MGH Psychiatry Academy (tuition-funded CME courses)
  - The Children's Hospital of Southwest Florida/Lee Memorial Health System (tuition-funded CME course)
  - ADHRS Royalties (paid to the MGH Department of Psychiatry
  - Fundacion Dr. Manuel Camelo, Monterrey Mexico
  - Shionogi & Cipher Pharmaceuticals Inc. (single consultation fees paid to the MGH Department of Psychiatry
  - Spanish Neurological Association
  - Israeli Child Psychiatry Association
  - Cambridge University Press (Chapter Publication)
  - Juste Pharmaceutical Spain (unpaid)

A Brief History of Emotions & ADHD

(Barkley, JARD, 2010)

- Crichton (1798): anger that borders on insanity
- Still (1903): morbid exaggeration of emotional excitability
- Laufer et al. (1957): unpredictable and explosive behavior and low frustration tolerance
- 1960s: MBD syndrome includes "emotional lability"

A Brief History of Emotions & ADHD

(Barkley, JARD, 2010)

- Stewart (1970) child is easily upset
- Cantwell (1975): temper tantrums…low frustration tolerance and a tendency to become overexcited.
- Loney (1980) a short and highly flammable fuse
- Wender (1981) labile mood, temper outbursts, stress intolerance
- Barkley (2010) deficient emotional self-regulation

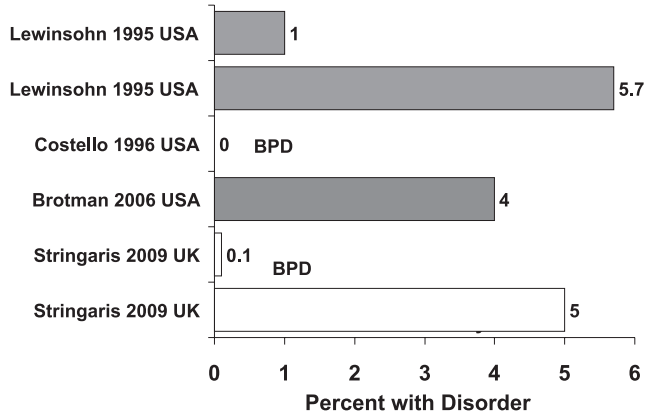
History of Deficits in Emotional Regulation in ADHD

- **DSM II, III, IIIR,IV, IV TR: Associated traits**
  - "low frustration tolerance"
  - "temper outbursts"
  - "mood lability"
  - (DSM-IV TR, APA, 2000)
- **Utah Criteria for Adult ADHD: Core traits**
  - "affective lability"
  - "hot temper"
  - "stress intolerance"
  - (Wender, 1970s)

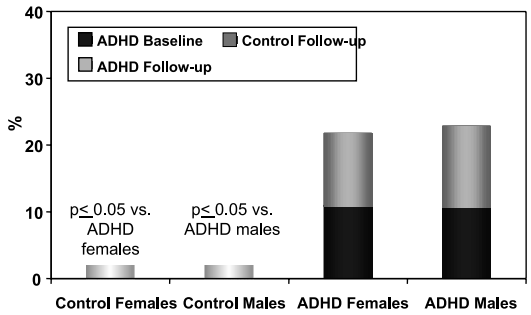
Types of Subsyndromal Mood Disturbance *Potentially* Confused with Bipolar Disorder

- Severe Mood Disturbance (Leibenluft et al., AJP 2003)
- Temper Dysregulation Disorder (DSM V proposal)
- ODD emotional items (DSM IV)
- Emotional Lability (many authors)
- Emotionality (Stringaris et al., JAACAP, 2010)
- Irritability (many uses)
- Deficient Emotional Self-Regulation (Barkley, JARD, 2010)

Bipolar Disorder and Broader Definitions of Mood Disturbance

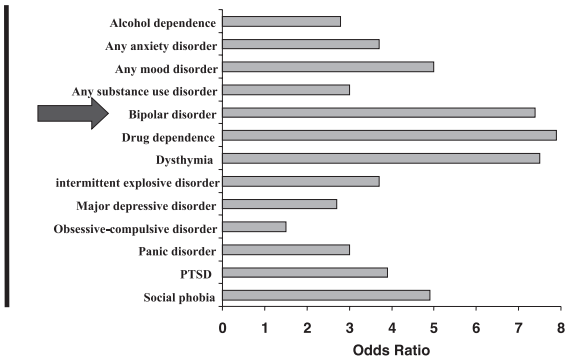


Bipolar Disorder in Girls and Boys With and Without ADHD



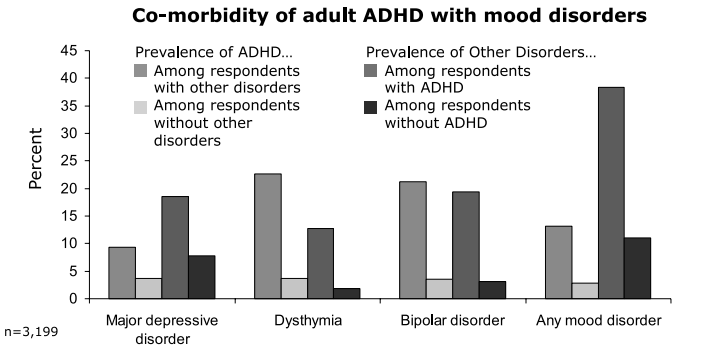
Biederman et al. *Psychological Medicine*. 2006; 36: 167-179.
Biederman et al. *Biological Psychiatry.* 2006; 60: 1098-1105.

Patterns of Comorbidity in ADHD Adults



Kessler et at. *Am J Psychiatry*. 2006; 163:4

Co-morbidity of Adult ADHD with Mood Disorders



Kessler RC *et al.* The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. Am J Psychiatry. 2006 Apr;163(4):716-23.

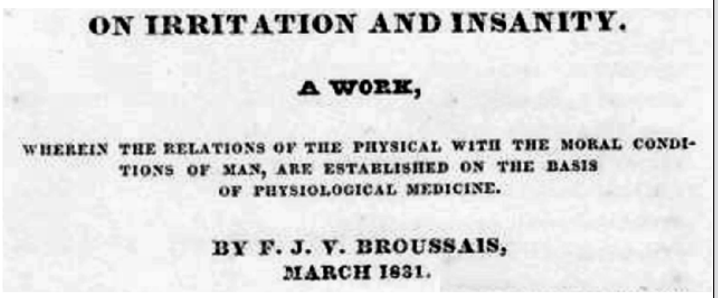
Are All Forms of Irritability the Same?

Heterogeneity of Irritability

Furious mania

(von Krafft-Ebing, Textbook of Insanity, 1905)

- Angry excitement
- Shouting and bawling
- Angry howling and fury
- Constant spitting
- Obscene scolding of nurses
- Irritable exaltation
- Destructive outbreaks



ON IRRITATION AND INSANITY.

A WORK,

WHEREIN THE RELATIONS OF THE PHYSICAL WITH THE MORAL CONDITIONS OF MAN, ARE ESTABLISHED ON THE BASIS OF PHYSIOLOGICAL MEDICINE.

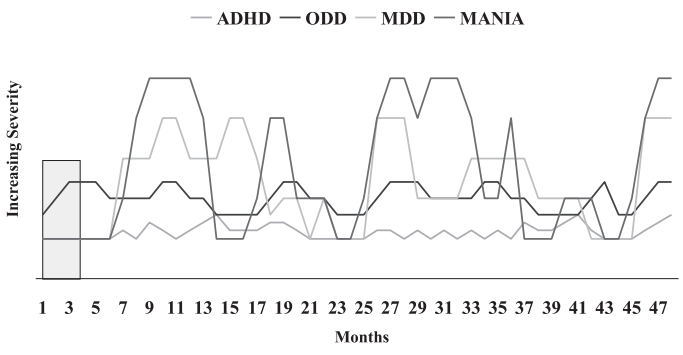
BY F. J. V. BROUSSAIS,
MARCH 1831.

"Furious mania, is the highest degree of insanity; that which approaches to frenzy".

Irritability vs. Furiosity

- The irritable child is hypersensitive to provoking stimuli from authorities and may or may not be able to self-regulate
- The furious bipolar child is hypersensitive and experiences extremes of emotion that are impossible to self-regulate

Heterogeneity of Irritability in Children



Mick et al, 2007

Juvenile Mania

- The type of irritability observed in manic children is very severe, persistent, and often violent.
- The outbursts often include threatening or attacking behavior towards others, including family members, other children, adults, and teachers.

Biederman et al. *J Am Acad Child Adolesc Psychiatry*. 1996; 35(8): 997-1008.

Heterogeneity of Irritability

- Labile mood/hot temper: ODD
- Severe irritability: MDD
- Explosive/violent irritability: BPD

Mick et al. *Biological Psychiatry.* 2005; 58:576-582.

Can Irritability be Distinguished for Deficient Emotional Regulation?

Deficient Emotional Regulation (DESR)

(Barkley, JARD, 2010; Gottman & Katz, Devel Psychol, 1989)

- Difficulty with emotional regulation skills:
  - Inhibition of inappropriate behavior related to strong negative or positive emotion
  - Self-soothing of physiological arousal that the strong affect has induced
  - Refocusing attention from strong emotions
  - Organizing subsequent behavior in the service of an external goal.

DESR vs. Irritability and Furiosity

- DESR does not necessarily lead to extreme moods but always leads to poor self-regulation of mood.
- DESR subsides relatively rapidly and does not form a distinct protracted episode of the type that would qualify for a mood disorder.

Clinical Features of DESR

- Low frustration tolerance
- Temper outbursts
- Mood lability

These have long been associated with ADHD (Barkley, 1997; Nigg & Casey, 2005; Wender, 1995)

Previous Studies of Deficits in Emotional Regulation in ADHD

- **60% of ADHD vs. 15% of Controls in a community sample: impatient, quick to anger, easily frustrated, overreacted emotionally, easily excited (Barkley et al, 2008)**
- **32% of 529 adults in Atomoxetine trial**
- **40% of 47 adults in OROS-mph trial had:Abnormal temper, affective lability, emotional overreactivity (Reimherr et al, 2005, 2007)**

DESR Vs. Mood Disorders

- DESR is phenomenologically distinct from mood disorders, which are characterized by the experience of strong emotions, not their self-regulation (Rosen & Epstein, 2010)
- Unlike DESR, mood disorders require the presence of non-mood criteria including somatic and behavioral impairments
- Mood disorder patients show dysregulted mood throughout each episode, not only in response to provoking stimuli

DESR Vs. Mood Disorder

- Mood is not abnormal all the time
- Emotional behavior subsides rapidly

(Barkley, JARD, 2010; Gottman & Katz, Dev. Psychol, 1989)

DESR vs. Mood Disorders

- In contrast to mood disorders, subjects with DESR do not have distinct episodes of DESR
- Unlike mood episodes, DESR subsides relatively rapidly and does not form a distinct protracted episode of the type that would qualify for a mood disorder
- Thus, subjects with DESR have normal moods but can become easily frustrated or angry with unexpected emotional challenges

Deficient Emotional Self Regulation in Pediatric ADHD

Methods

- Subjects were 242 children with ADHD and 224 children without ADHD of both sexes and their first-degree relatives

CBCL Mood Dysregulation Profiles

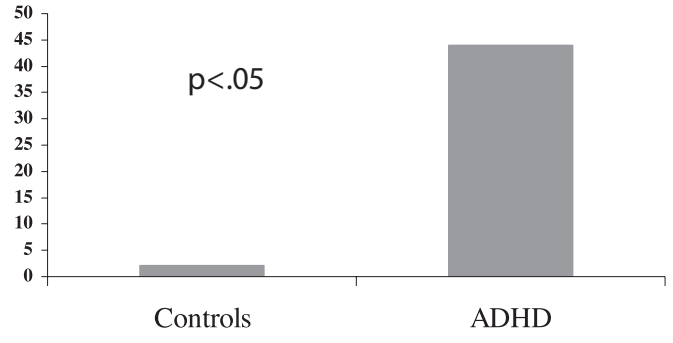
- **CBCL-DESR** was operationalized using an aggregate score ≥180 and <210 in the Anxious/Depressed, Attention, and Aggression scales (AAA profile) of the CBCL
- **CBCL-Severe Dysregulation (BP)** profile was defined as ≥210 on the CBCL-AAA scale

CBCL-DESR Profile

- This profile was selected because of its conceptual congruence with the clinical concept of DESR
- Because its extreme (>210) form had been previously associated with severe forms of mood and behavioral dysregulation in children with ADHD

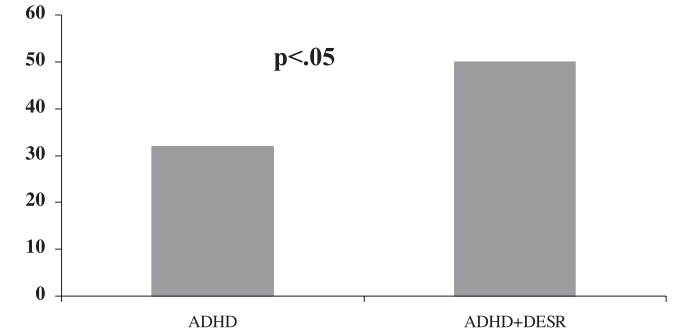
Rates of DESR in ADHD and Control Youth

(Spencer et al., Postgrad Med 2012)

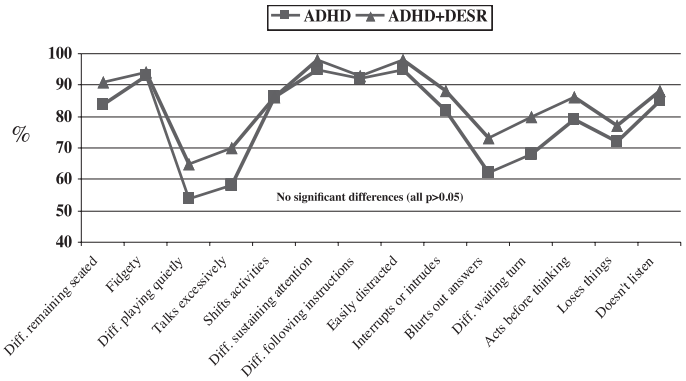


Percent of subjects with ADHD-Associated Severe Impairment

(Spencer et al., Postgrad Med 2012)

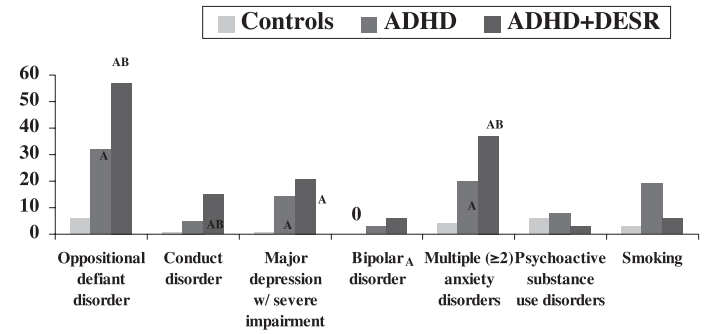


ADHD Symptoms



DESR and Lifetime Psychopathology

(Spencer et al., Postgrad Med 2012)



A: p<0.05 vs. Controls; B: p<0.05 vs. ADHD

ADHD predicts DESR Independent of Lifetime History of Comorbidity

(Spencer et al., Postgrad Med 2012)

Regression model included individual comorbid disorders and ADHD as DESR predictors

RED= association with DESR

Oppositional Defiant Disorder
Conduct Disorder
Multiple Anxiety Disorders
Bipolar Disorder
Major Depression
Substance Use Disorders

ADHD remained associated with DESR when covaried with each comorbidity

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Toward Defining Deficient Emotional Self-Regulation in Children with Attention-Deficit/Hyperactivity Disorder Using the Child Behavior Checklist:

A Controlled Study

Thomas J. Spencer, MD; Stephen V. Faraone, PhD; Craig B. H. Surman, MD; Carter Petty, MA; Allison Clarke, BA; Holly Batchelder, BS; Janet Wozniak, MD; and Joseph Biederman, MD

DOI: 10.3810/pgm.2011.09.2459

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Abstract: Objective. Deficient emotional self-regulation (DESR) is characterized by deficits in self-regulating the physiological arousal caused by strong emotions. We examined whether a unique profile of the Child Behavior Checklist (CBCL) would help identify DESR in children with attention-deficit/hyperactivity disorder (ADHD). **Methods:** Subjects included 197 children with ADHD and 224 children without ADHD. We defined DESR if a child had an aggregate cut-off score of > 180 but < 210 on the Anxiety/Depression, Aggression, and Attention scales of the CBCL (CBCL-DESR). This profile was selected because of: 1) its conceptual congruence with the clinical concept of DESR; and 2) because its extreme (> 210) form has been previously associated with severe forms of mood and behavioral dysregulation in children with ADHD. All subjects were comprehensively assessed with structured diagnostic interviews and a wide range of functional measures. **Results:** Forty-four percent of children with ADHD had a positive CBCL-DESR profile versus 2% of controls ($P < 0.001$). The CBCL-DESR profile was associated with elevated rates of anxiety and disruptive behavior disorders, as well as significantly more impairments in emotional and interpersonal functioning. **Conclusions:** The CBCL-DESR profile helped identify a subgroup of children with ADHD who had a psychopathological and functional profile consistent with the clinical concept of DESR.

Keywords: attention-deficit/hyperactivity disorder; affective symptoms; severity of illness index; youth; emotional self-regulation

Spencer et al. *Postgrad Med* 2011;123(5):50-9

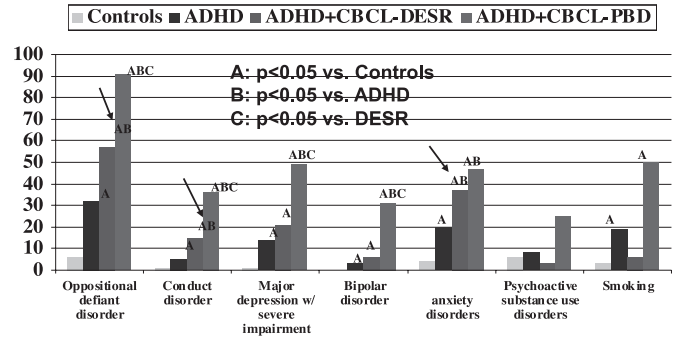
Can the Severity of the CBCL Profile Distinguish Two Types of Deficits in Mood Regulation?

Comparisons between the CBCL-DESR Profile with the CBCL-Juvenile BP Profile

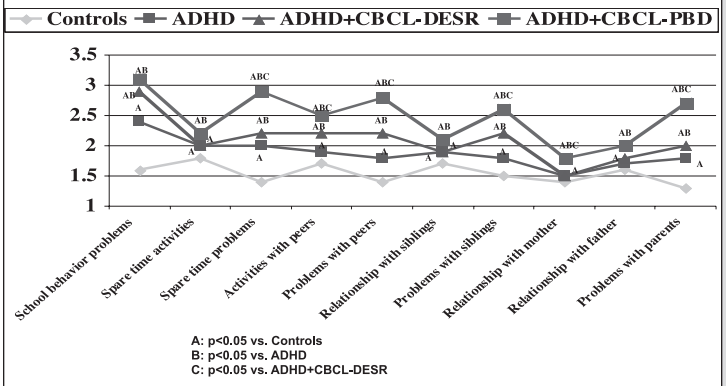
Two Types of CBCL Mood Dysregulation Profiles Based on Elevations of A-A-A Scales

- A-A-A=Attention, Anxiety/Depression/ Aggression
- Intermediate (1 SD)= DESR
- Severe (2SDs)+ Juvenile BP

CBCL Dysregulation Profiles and Rates of Lifetime Psychopathology



SAICA Profiles: Baseline

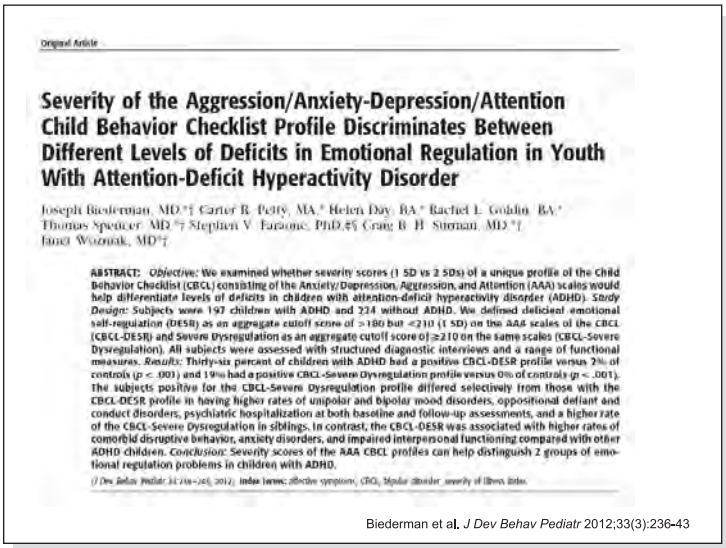


Main Findings

- 44% of ADHD children had a + CBCL- DESR profile vs. 2% of controls (p<0.001)
- The CBCL-DESR profile was associated with elevated rates of anxiety disorders, CD and ODD but not major depression or bipolar disorder

Main Findings

- The CBCL-DESR profile was associated with more impairments in interpersonal functioning
- These findings suggest that the CBCL-DESR profile can help identify a subgroup of ADHD children with a psychopathological and functional profile that differs from that of BPD and is consistent with the clinical concept of DESR



Original Article

Severity of the Aggression/Anxiety-Depression/Attention Child Behavior Checklist Profile Discriminates Between Different Levels of Deficits in Emotional Regulation in Youth With Attention-Deficit Hyperactivity Disorder

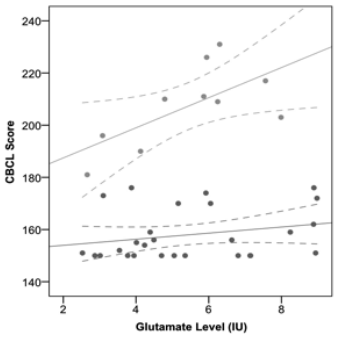
Joseph Biederman, MD,*† Carter R. Petty, MA,* Helen Day, BA,* Rachel L. Goldin, BA,* Thomas Spencer, MD,*† Stephen V. Faraone, PhD,‡§ Craig B. H. Surman, MD,*† Janet Wozniak, MD*†

ABSTRACT: *Objective:* We examined whether severity scores (1 SD vs 2 SDs) of a unique profile of the Child Behavior Checklist (CBCL) consisting of the Anxiety/Depression, Aggression, and Attention (AAA) scales would help differentiate levels of deficits in children with attention-deficit hyperactivity disorder (ADHD). *Study Design:* Subjects were 197 children with ADHD and 224 without ADHD. We defined deficient emotional self-regulation (DESR) as an aggregate cutoff score of >180 but <210 (1 SD) on the AAA scales of the CBCL (CBCL-DESR) and Severe Dysregulation as an aggregate cutoff score of ≥210 on the same scales (CBCL-Severe Dysregulation). All subjects were assessed with structured diagnostic interviews and a range of functional measures. *Results:* Thirty-six percent of children with ADHD had a positive CBCL-DESR profile versus 2% of controls ($p < .001$) and 19% had a positive CBCL-Severe Dysregulation profile versus 0% of controls ($p < .001$). The subjects positive for the CBCL-Severe Dysregulation profile differed selectively from those with the CBCL-DESR profile in having higher rates of unipolar and bipolar mood disorders, oppositional defiant and conduct disorders, psychiatric hospitalization at both baseline and follow-up assessments, and a higher rate of the CBCL-Severe Dysregulation in siblings. In contrast, the CBCL-DESR was associated with higher rates of comorbid disruptive behavior, anxiety disorders, and impaired interpersonal functioning compared with other ADHD children. *Conclusion:* Severity scores of the AAA CBCL profiles can help distinguish 2 groups of emotional regulation problems in children with ADHD.

J Dev Behav Pediatr 32:236–243, 2012. Index terms: affective symptoms, CBCL, bipolar disorder, severity of illness, links.

Biederman et al. *J Dev Behav Pediatr* 2012;33(3):236-43

CBCL scores vs Glutamate levels

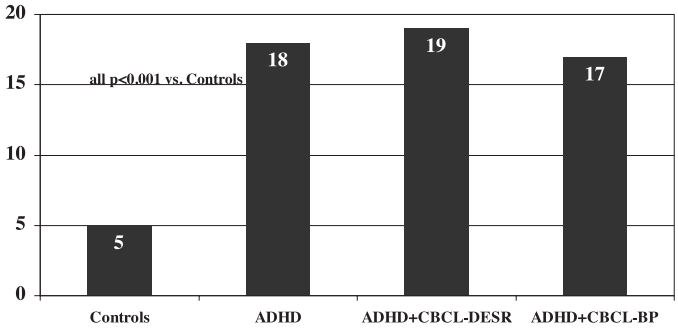


Wozniak et al 2012

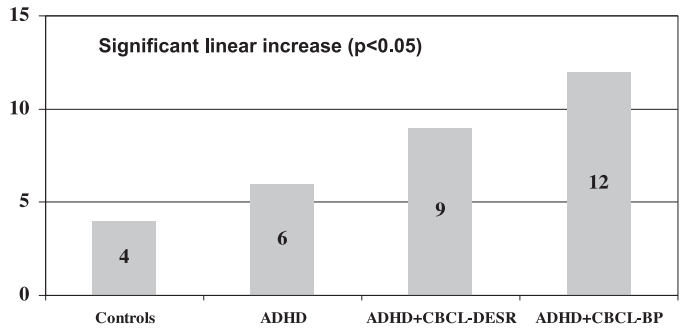
Solid lines represent the linear fits to the low score group data (blue) and high score group data (green). Dashed lines represent 95% confidence intervals.

Is DESR Familial?

Familial Risk Analysis: ADHD



Familial Risk Analysis: CBCL-DESR in Siblings



Results

- There was a significant linear increase in the prevalence of CBCL-DESR in siblings in the three ADHD groups but no pairwise significant differences among the groups

Results

- There was a significant correlation between the CBCL-DESR scale score and current ADHD symptoms (r=.70, p<.001) and lifetime ADHD symptoms (r=.69, p<.001)
- For siblings, these correlations were .60 (p<.001) and .60 (p<.001), respectively

Main Results

- Relatives of ADHD probands with and without DESR were at elevated risk for having ADHD indicating that the familial transmission of ADHD is not influenced by DESR in the proband

Main Results

- There was a significant linear increase in the prevalence of CBCL-DESR in siblings in the three ADHD groups

Comments

- For both probands and siblings considered separately, ADHD symptoms were associated with the CBCL-DESR profile
- Siblings with ADHD had higher rates of CBCL-DESR than those without ADHD
- These findings are consistent with prior work indicating that ADHD is associated with DESR (Barkley & Fischer, 2010 ; Barkley *et al.* 2008; Reimherr *et al.* 2005a; Reimherr *et al.* 2007)

Comments

- Because the comorbidity among siblings cannot be attributed to artifacts of clinical referral such as Berkson's bias, the association between ADHD and DESR is strengthened

Comments

- The increasingly higher rates of the CBCL-DESR with increases in the CBCL-AAA scores in the siblings of our proband groups could indicate that DESR is best conceptualized as being on a continuum with CBCL-BP profile

Psychological Medicine (2012), 42, 639–646. © Cambridge University Press 2011
doi:10.1017/S0033291711001644

ORIGINAL ARTICLE

Deficient emotional self-regulation and pediatric attention deficit hyperactivity disorder: a family risk analysis

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[2] *Psychiatry Department, Harvard Medical School, Cambridge, MA, USA*
[3] *Departments of Psychiatry and of Neuroscience and Physiology, SUNY Upstate Medical University, Syracuse, NY, USA*

Background. Although deficient emotional self-regulation (DESR) is associated with attention deficit hyperactivity disorder (ADHD), little research investigates this association and little is known about its etiology. Family studies provide a method of clarifying the co-occurrence of clinical features, but no family studies have yet addressed ADHD and DESR in children.

Method. Subjects were 242 children with ADHD and 224 children without ADHD. DESR was operationalized using an aggregate score ⩾180 and <210 in the anxious/depressed, attention and aggression scales (AAA profile) of the Child Behavior Checklist (CBCL), termed the CBCL-DESR profile. The CBCL-bipolar (CBCL-BP) profile was defined as ⩾210 on the CBCL-AAA scale. We examined the familial transmission of ADHD and the CBCL-AAA scale in families selected through probands with and without these conditions.

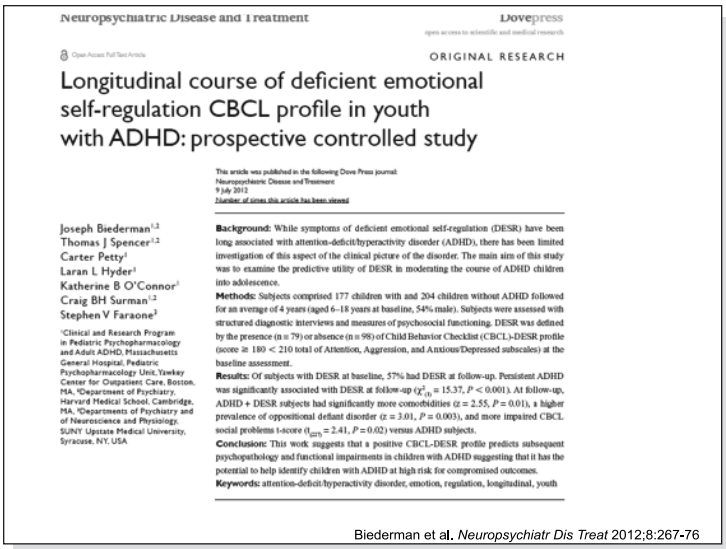
Results. We found a linear increase in the prevalence of CBCL-DESR in siblings as indexed by the Control, ADHD, ADHD + CBCL-DESR and ADHD + CBCL-BP proband groups. While the ADHD siblings were at elevated risk for both the CBCL-DESR and CBCL-BP compared with non-ADHD siblings, a significantly higher rate of CBCL-BP in the siblings of ADHD + CBCL-BP probands was found compared with siblings of the Control probands.

Conclusions. ADHD shows the same degree of familial transmission in the presence or absence of DESR. CBCL-DESR and CBCL-BP are familial, but further work is needed to determine if these definitions are distinctly familial or represent a continuum of the same psychopathology.

Received 17 March 2011; Revised 19 July 2011; Accepted 25 July 2011; First published online 24 August 2011

Key words: ADHD, deficient emotional self-regulation, pediatric.

Biederman et al. *Psychol Med* 2012 Mar;42(3):639-46



Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

Longitudinal course of deficient emotional self-regulation CBCL profile in youth with ADHD: prospective controlled study

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
9 July 2012
Number of times this article has been viewed

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Background: While symptoms of deficient emotional self-regulation (DESR) have been long associated with attention-deficit/hyperactivity disorder (ADHD), there has been limited investigation of this aspect of the clinical picture of the disorder. The main aim of this study was to examine the predictive utility of DESR in moderating the course of ADHD children into adolescence.

Methods: Subjects comprised 177 children with and 204 children without ADHD followed for an average of 4 years (aged 6–18 years at baseline, 54% male). Subjects were assessed with structured diagnostic interviews and measures of psychosocial functioning. DESR was defined by the presence (n = 79) or absence (n = 98) of Child Behavior Checklist (CBCL)-DESR profile (score ≥ 180 < 210 total of Attention, Aggression, and Anxious/Depressed subscales) at the baseline assessment.

Results: Of subjects with DESR at baseline, 57% had DESR at follow-up. Persistent ADHD was significantly associated with DESR at follow-up ($\chi^2_{(1)} = 15.37$, $P < 0.001$). At follow-up, ADHD + DESR subjects had significantly more comorbidities ($z = 2.55$, $P = 0.01$), a higher prevalence of oppositional defiant disorder ($z = 3.01$, $P = 0.003$), and more impaired CBCL social problems t-score ($t_{(207)} = 2.41$, $P = 0.02$) versus ADHD subjects.

Conclusion: This work suggests that a positive CBCL-DESR profile predicts subsequent psychopathology and functional impairments in children with ADHD suggesting that it has the potential to help identify children with ADHD at high risk for compromised outcomes.

Keywords: attention-deficit/hyperactivity disorder, emotion, regulation, longitudinal, youth

Biederman et al. *Neuropsychiatr Dis Treat* 2012;8:267-76

Deficient Emotional Self Regulation in Adult ADHD

DESR in Adults with ADHD Study

- **Study Population**
  - **206 Adults with ADHD**
  - **123 Controls**

Deficient Emotional Self Regulation (DESR) in Adults with ADHD

- **Methods**
  - **Barkley's Current Behavior Scale**
  - **SCID / KSADS modules for Axis I disorders**
  - **Quality of Life, Enjoyment, Satisfaction Scale-Short Form**
  - **Social Adjustment Scale - Self Report**
  - **Functional outcomes questionnaire**

Deficient Emotional Self Regulation (DESR) in Adults with ADHD

- **Study Population**
  - **206 Adults with ADHD or ADHD NOS (late onset)**
  - Full/late-onset ADHD demonstrate similar correlates (Faraone SV et al, 2006, 2006, 2006, 2009)
  - **123 Adults without ADHD**

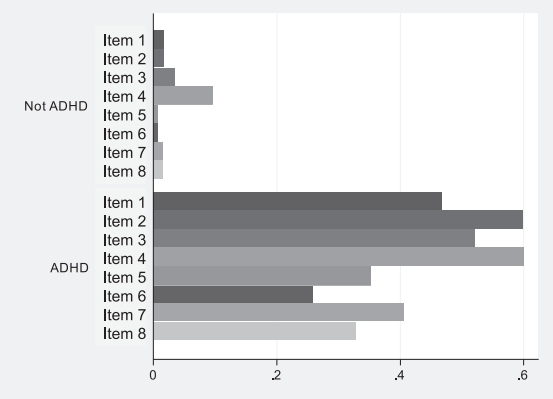
Deficient Emotional Self Regulation Inventory Items

1. Quick to get angry or become upset
2. Easily Frustrated
3. Over-react emotionally
4. Easily excited by activities going on around me
5. Lose my temper
6. Argue with others
7. Am touchy or easily annoyed by others
8. Am angry or resentful

Severity: None (0), Sometimes (1) Often (2), Very Often (3)

Items from Barkley's Current Behavior Scale

Rate of subjects endorsing DESR symptoms as "Often" or "Very Often."

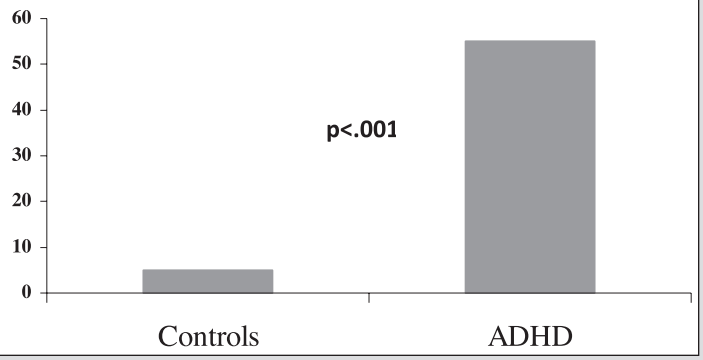


Results

- **Internal Consistency of Items (Cronbach's alpha: 0.90)**
- **Clinically Significant DESR score (="DESR")**
  - **DESR score = total score on 8 items scored 0-3**
  - **Score of 9 was < 5th of control's mean**

DESR in ADHD and Control Adults

(Surman et al., American J Psychiatry, 2011)



Quality of Life Enjoyment / Satisfaction in ADHD+DESR Probands

	Correlation	z	P
1. Work	-0.32	-3.53	< 0.001
2. Household activities	-0.43	-7.43	< 0.001
3. Social relationships	-0.46	-8.31	< 0.001
4. Family relationships	-0.45	-7.58	< 0.001
5. Leisure time activities	-0.44	-8.22	< 0.001
6. Ability to function in daily life	-0.54	-8.40	< 0.001
7. Sexual drive, interest, and/or performance	-0.43	-7.65	< 0.001
8. Economic status	-0.40	-6.62	< 0.001
9. Living or housing situation	-0.38	-9.08	< 0.001

ADHD/NOS n = 206; Control n =123

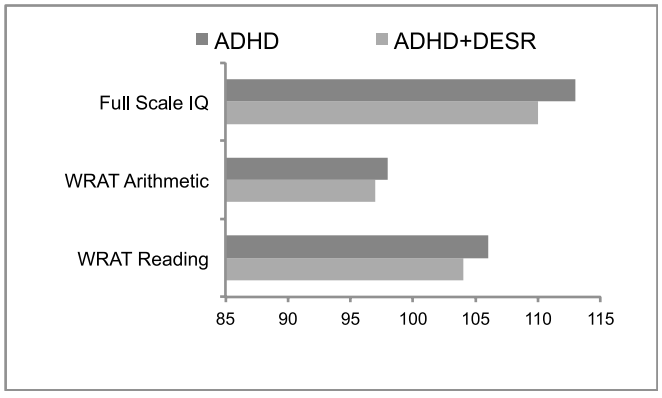
Social Adjustment Scale in ADHD+DESR Probands

Functioning Domain	Correlation Coefficient	Z	p
1. Work	0.45	4.56	< 0.001
2. Social/Leisure	0.58	11.01	< 0.001
3. Extended Family	0.49	8.26	< 0.001
4. Primary Relationship	0.50	5.16	< 0.001
5. Parenting	0.06	1.33	0.19
6. Family Unit	0.49	5.75	< 0.001
7. **Total SAS Scale Score**	0.66	11.75	< 0.001

ADHD/NOS n = 206; Control n =123

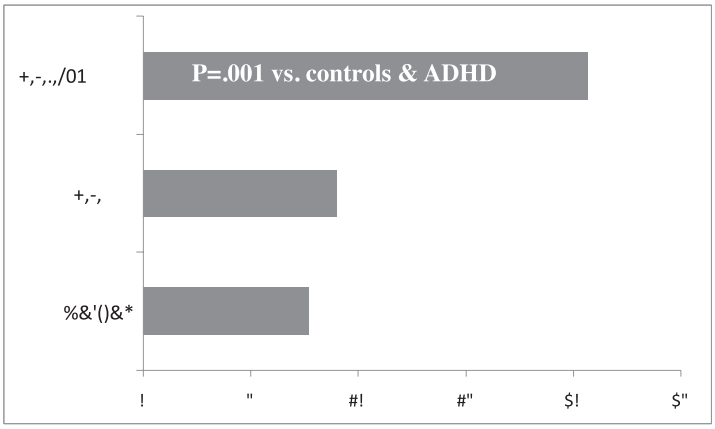
Intellectual Functioning and DESR

(Surman et al., American J Psychiatry, 2011)



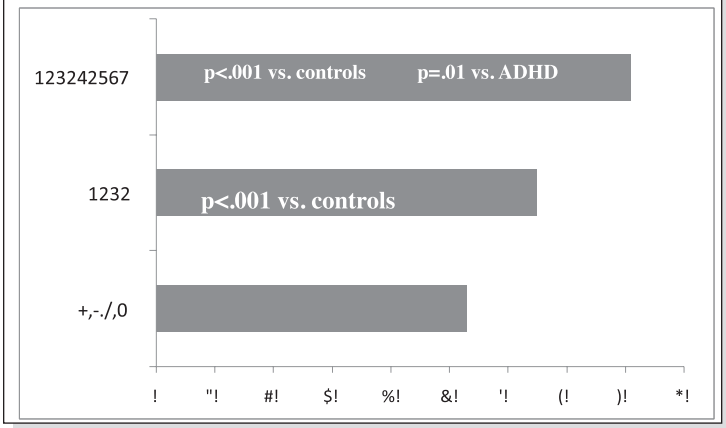
Rates of Divorce by Proband Diagnosis

(Surman et al., American J Psychiatry, 2011)



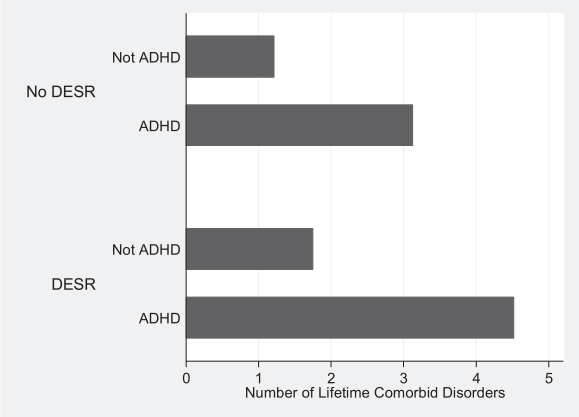
Percent of Subjects who Ever Had an Auto Accident

(Surman et al., American J Psychiatry, 2011)



Number of Lifetime Comorbid Disorders

(Surman et al., American J Psychiatry, 2011)



Significant, independent effects of DESR (p<.001) and ADHD (p<.001)

ADHD predicts DESR Independent of Lifetime and Current Comorbidity

(Surman et al., American J Psychiatry, 2011)

Regression model included individual comorbid disorders and ADHD as DESR predictors

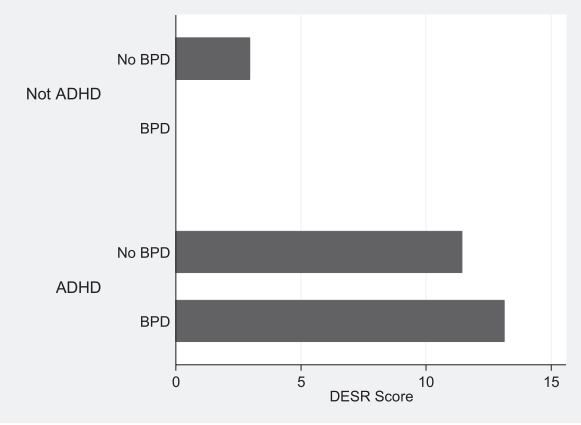
RED= association with DESR

ADHD remained associated with DESR when covaried with each comorbidity

Disruptive Behavior Disorders
Major Depression
Anxiety Disorders
Alcohol Abuse
Substance Dependence
Bipolar Disorder
Substance Abuse
Alcohol Dependence

Prediction of DESR from ADHD and Lifetime Bipolar Disorder

(Surman et al., American J Psychiatry, 2011)

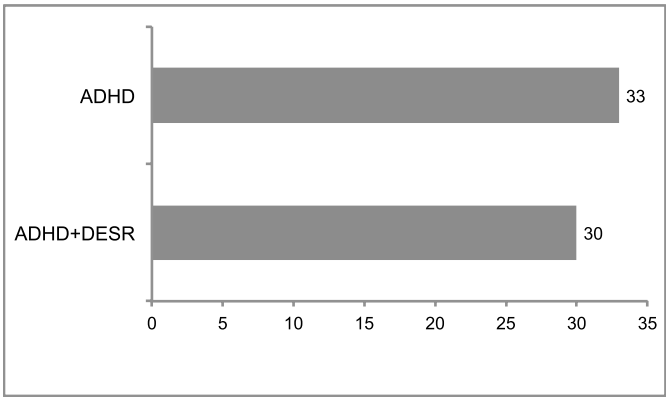


DESR Association with Comorbidity in ADHD Probands

- DESR associated with ADHD <u>independently of</u> Psychiatric comorbidity (lifetime and current) including Current/ lifetime ODD

Rates of Executive Function Disorder in ADHD Adults with and Without DESR

(Surman et al., American J Psychiatry, 2011)



Neuropsychological correlates of emotional lability in children with ADHD

No association between EFDs and EL

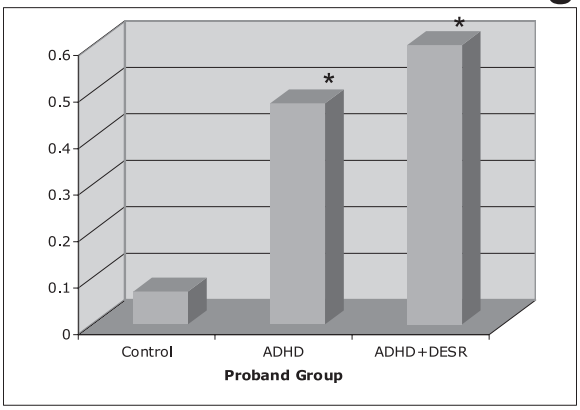
Banaschewski et al. *J Child Psychol Psychiatry* 2012 Nov; 53(11):1139-1148

Family Risk Analysis

Methods

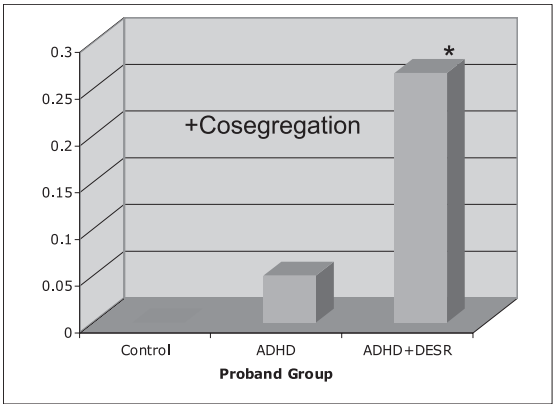
- Probands
  - 27 ADHD+DESR probands and 45 siblings
  - 23 ADHD probands and 40 siblings
  - 33 Control probands and 43 siblings

Rates of ADHD in Siblings



* Compared to control siblings, ADHD more prevalent in siblings of probands with ADHD irrespective of DESR, $p < .001$

Rates of DESR in Siblings



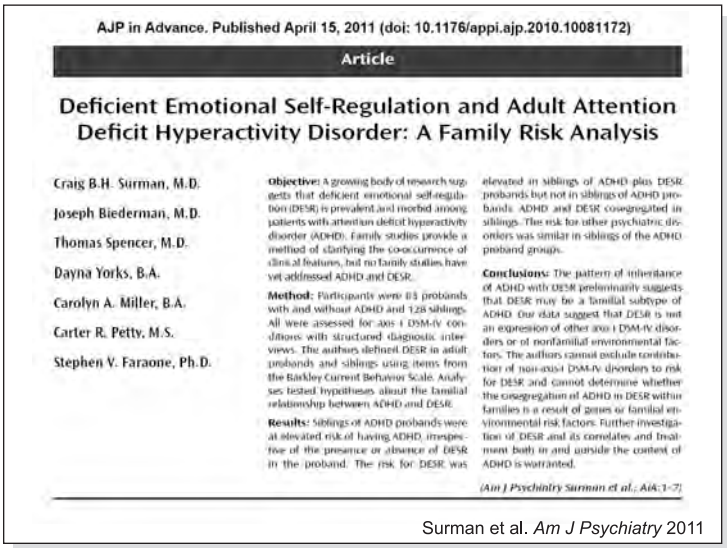
* DESR was more prevalent in siblings of ADHD+DESR probands than siblings of Controls or ADHD probands, $p < .01$

Comments

- Findings Support the Hypothesis that ADHD+DESR is a distinct subtype of ADHD or independent familial condition
  - Could be genetically distinct form of ADHD

Summary

- **A Large Community Sample of Adults with and without ADHD reveals:**
- **DESR questionnaire validity**
  - Acceptable internal consistency
  - Correlated with functional impairment
- **The majority of ADHD Adults had DESR**
- **Comorbidity does not fully account for DESR in ADHD adults**



AJP in Advance. Published April 15, 2011 (doi: 10.1176/appi.ajp.2010.10081172)

Article

Deficient Emotional Self-Regulation and Adult Attention Deficit Hyperactivity Disorder: A Family Risk Analysis

Craig B.H. Surman, M.D.
Joseph Biederman, M.D.
Thomas Spencer, M.D.
Dayna Yorks, B.A.
Carolyn A. Miller, B.A.
Carter R. Petty, M.S.
Stephen V. Faraone, Ph.D.

Objective: A growing body of research suggests that deficient emotional self-regulation (DESR) is prevalent and morbid among patients with attention deficit hyperactivity disorder (ADHD). Family studies provide a method of clarifying the co-occurrence of clinical features, but no family studies have yet addressed ADHD and DESR.

Method: Participants were 83 probands with and without ADHD and 128 siblings. All were assessed for axis I DSM-IV conditions with structured diagnostic interviews. The authors defined DESR in adult probands and siblings using items from the Barkley Current Behavior Scale. Analyses tested hypotheses about the familial relationship between ADHD and DESR.

Results: Siblings of ADHD probands were at elevated risk of having ADHD, irrespective of the presence or absence of DESR in the proband. The risk for DESR was elevated in siblings of ADHD plus DESR probands but not in siblings of ADHD probands. ADHD and DESR cosegregated in siblings. The risk for other psychiatric disorders was similar in siblings of the ADHD proband groups.

Conclusions: The pattern of inheritance of ADHD with DESR preliminarily suggests that DESR may be a familial subtype of ADHD. Our data suggest that DESR is not an expression of other axis I DSM-IV disorders or of nonfamilial environmental factors. The authors cannot exclude combination of non-axis I DSM-IV disorders to risk for DESR and cannot determine whether the cosegregation of ADHD in DESR within families is a result of genes or familial environmental risk factors. Further investigation of DESR and its correlates and treatment both in and outside the context of ADHD is warranted.

(Am J Psychiatry Surman et al.; AiA:1–7)

Surman et al. *Am J Psychiatry* 2011

Neurobiological Underpinning of DESR

NEW RESEARCH

Abnormal Amygdalar Activation and Connectivity in Adolescents With Attention-Deficit/Hyperactivity Disorder

Jonathan Posner, M.D., Bonnie J. Nagel, Ph.D., Tiago V. Maia, Ph.D., Anna Mechling, B.A., Milim Oh, M.A., Zhishun Wang, Ph.D., Bradley S. Peterson, M.D.

Objective: Emotional reactivity is one of the most disabling symptoms associated with attention-deficit/hyperactivity disorder (ADHD). We aimed to identify neural substrates associated with emotional reactivity and to assess the effects of stimulants on those substrates. **Method:** We used functional magnetic resonance imaging (fMRI) to assess neural activity in adolescents with (n = 15) and without (n = 15) ADHD while they performed a task involving the subliminal presentation of fearful faces. Using dynamic causal modeling, we also examined the effective connectivity of two regions associated with emotional reactivity, i.e., the amygdala and the lateral prefrontal cortex (LPFC). The participants with ADHD underwent scanning both on and off stimulant medication in a counterbalanced fashion. **Results:** During the task, we found that activity in the right amygdala was greater in adolescents with ADHD than in control subjects. In addition, in adolescents with ADHD, greater connectivity was detected between the amygdala and LPFC. Stimulants had a normalizing effect on both the activity in the right amygdala and the connectivity between the amygdala and LPFC. **Conclusions:** Our findings demonstrate that in adolescents with ADHD, a neural substrate of fear processing is atypical, as is the connectivity between the amygdala and LPFC. These findings suggest possible neural substrates for the emotional reactivity that is often present in youths with ADHD, and provide putative neural targets for the development of novel therapeutic interventions for this condition. J. Am. Acad. Child Adolesc. Psychiatry, 2011;50(8):828–837. **Key Words:** ADHD, amygdala, effective connectivity, fear, stimulant medication

Posner et al. *J Am Acad Child Adolesc Psychiatry* 2011;50(8):828-837

Abnormal Amigdalar Activation and Connectivity in ADHD

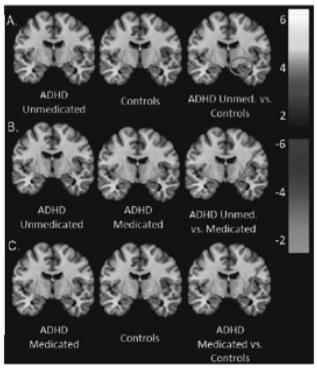


FIGURE 1 Group × task interactions. Note: The figure shows coronal slices through the Montreal Neurological Institute (MNI) y-coordinate −10. Activations are shown in red/orange. Deactivations are shown in blue/purple. Results are based on the contrast: subliminal fearful face blocks versus neutral face blocks. (A) The unmedicated attention-deficit/hyperactivity disorder (ADHD) participants compared with the healthy controls demonstrated greater activation in the amygdala as indicated by the green circle. (B) The unmedicated as compared with the medicated ADHD participants demonstrated greater activation in the right amygdala, but the difference was not statistically significant, as indicated by the green arrow. (C) No differences were detected in amygdalar activation between the medicated ADHD participants and healthy controls, as indicated by the green arrow.

Posner et al. *J Am Acad Child Adolesc Psychiatry* 2011;50(8):828-837

ORIGINAL ARTICLE

Hippocampus and Amygdala Morphology in Attention-Deficit/Hyperactivity Disorder

Disrupted connections Between amygdala and PF/OF cortex may contribute to behavioral disinhibition in ADHD

Kerstin J. Plessen, MD; Ravi Bansal, PhD; Hongtu Zhu, PhD; Ronald Whiteman, BA; Jose Amat, MD; Georgette A. Quackenbush, MA; Laura Martin, BS; Kathleen Durkin, MS; Clancy Blair, PhD, MPH; Jason Royal, DMA; Kenneth Hugdahl, PhD; Bradley S. Peterson, MD

Context: Limbic structures are implicated in the genesis of attention-deficit/hyperactivity disorder (ADHD) by the presence of mood and cognitive disturbances in affected individuals and by elevated rates of mood disorders in family members of probands with ADHD.

Objective: To study the morphology of the hippocampus and amygdala in children with ADHD.

Design: A cross-sectional case-control study of the hippocampus and amygdala using anatomical magnetic resonance imaging.

Setting: University research institute.

Patients: One hundred fourteen individuals aged 6 to 16 years, 51 with combined-type ADHD and 63 healthy controls.

Main Outcome Measures: Volumes and measures of surface morphology for the hippocampus and amygdala.

Results: The hippocampus was larger bilaterally in the ADHD group than in the control group (t = 3.35; P < .002). Detailed surface analyses of the hippocampus further localized these differences to an enlarged head of the hippocampus in the ADHD group. Although conventional measures did not detect significant differences in amygdalar volumes, surface analyses indicated the presence of reduced size bilaterally over the apex of the basolateral complex. Correlations with prefrontal measures suggested abnormal connectivity between the amygdala and prefrontal cortex in the ADHD group. Enlarged subregions of the hippocampus tended to accompany fewer symptoms.

Conclusions: The enlarged hippocampus in children and adolescents with ADHD may represent a compensatory response to the presence of disturbances in the perception of time, temporal processing (eg, delay aversion), and stimulus seeking associated with ADHD. Disrupted connections between the amygdala and orbitofrontal cortex may contribute to behavioral disinhibition. Our findings suggest involvement of the limbic system in the pathophysiology of ADHD.

Arch Gen Psychiatry. 2006;63:795-807

Plessen et al, *Arch Gen Psychiatry* 2006;63:795-807

ORIGINAL ARTICLE

Reduced Structural Connectivity of a Major Frontolimbic Pathway in Generalized Anxiety Disorder

Reduced structural connectivity of frontolimbic pathway (Uncinate fasciculus connecting amigdala & pgACC suggests a neural basis for emotional regulation deficits in GAD

Do P. M. Tromp, MS; Daniel W. Grupe, MS; Desmond J. Oathes, PhD; Daniel R. McFarlin, PhD; Patric J. Hernandez, MPA; Tammi R. A. Kral, BS; Jee Eun Lee, PhD; Marie Adams, MS; Andrew L. Alexander, PhD; Jack B. Nitschke, PhD

Context: Emotion regulation deficits figure prominently in generalized anxiety disorder (GAD) and in other anxiety and mood disorders. Research examining emotion regulation and top-down modulation has implicated reduced coupling of the amygdala with prefrontal cortex and anterior cingulate cortex, suggesting altered frontolimbic white matter connectivity in GAD.

Objectives: To investigate structural connectivity between ventral prefrontal cortex or anterior cingulate cortex areas and the amygdala in GAD and to assess associations with functional connectivity between those areas.

Design: Participants underwent diffusion-tensor imaging and functional magnetic resonance imaging.

Setting: University magnetic resonance imaging facility.

Participants: Forty-nine patients with GAD and 39 healthy volunteer control subjects, including a matched subset of 21 patients having GAD without comorbid Axis I diagnoses and 21 healthy volunteers matched for age, sex, and education.

Main Outcome Measures: The mean fractional anisotropy values in the left and right uncinate fasciculus, as measured by tract-based analysis for diffusion-tensor imaging data.

Results: Lower mean fractional anisotropy values in the bilateral uncinate fasciculus indicated reduced frontolimbic structural connectivity in patients with GAD. This reduction in uncinate fasciculus integrity was most pronounced for patients without comorbidity and was not observed in other white matter tracts. Across all participants, higher fractional anisotropy values were associated with more negative functional coupling between the pregenual anterior cingulate cortex and the amygdala during the anticipation of aversion.

Conclusions: Reduced structural connectivity of a major frontolimbic pathway suggests a neural basis for emotion regulation deficits in GAD. The functional significance of these structural differences is underscored by decreased functional connectivity between the anterior cingulate cortex and the amygdala in individuals with reduced structural integrity of the uncinate fasciculus.

Arch Gen Psychiatry. 2012;69(9):925-934

Tromp et al *Arch Gen Psychiatry* 2012;69(9):925-934

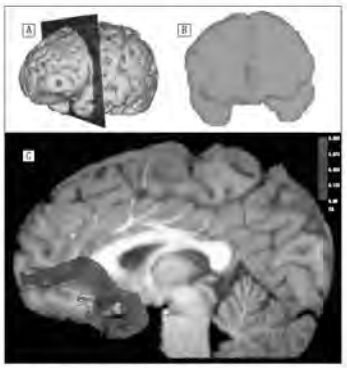


Figure 1. Region-of-interest placement for delineation of the bilateral uncinate fasciculus. A, The most posterior coronal section that showed clear separation of the frontal and temporal lobes bilaterally was identified in each individual. B, Bilateral frontal and temporal lobe seed regions of interest were then manually drawn on this section. The Boolean *AND* term was used to select only fibers that crossed through both the temporal and frontal seed regions of interest for tract-based analysis. C, Uncinate fasciculus tracts overlaid on an anatomical T1-weighted image for a single individual. FA indicates fractional anisotropy. For a 3-dimensional rendering, see the video.

Tromp et al *Arch Gen Psychiatry* 2012;69(9):925-934

Summary

- **DESR is frequently associated with ADHD in both children and adults**
- **DESR is associated with other psychiatric disorders but not bipolar disorder**
- **Psychiatric comorbidity does not account for DESR in pediatric or adult patients with ADHD**
- **DESR is associated with functional impairment in both pediatric and adult patients with ADHD**

Summary

- **DESR is associated with functional impairment**
- **DESR is independent of intellectual functioning and executive dysfunction**
- **DESR has a familial association with ADHD, but not with bipolar disorder or other comorbidities**
- **Psychiatric comorbidity does not account for DESR in ADHD patients**

Clinical Implications

- ADHD strongly tied to emotional symptoms
- Presence of DESR may define a distinct group of ADHD individuals
- Etiology and management of DESR requires further study
- Limited evidence for Rx effect in ADHD studies

Population Management of ADHD in the Era of Healthcare Redesign

Michael Jellinek, MD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

Population Management of ADHD in the Era of Healthcare Redesign

Michael Jellinek, M.D.

March 15, 2013

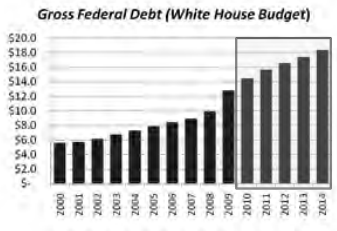
Disclosure

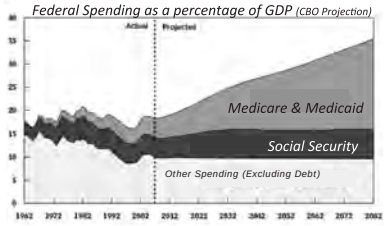
- Dr. Jellinek has reported no significant relationships with industry

Health Care Reform: Drivers

- Extend Coverage (Social justice and efficiency)
- Cost (How fast, How deep, How likely?)

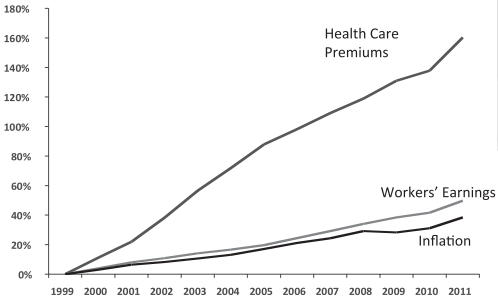
The Economic Picture





Rising health care costs have been squeezing employers and employees for years

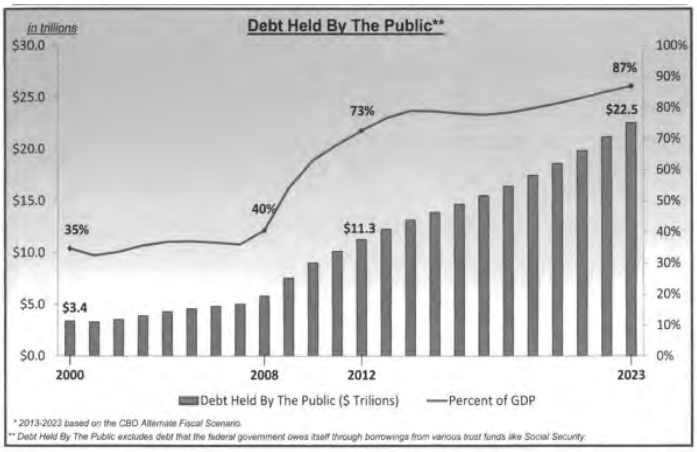
Cumulative Increase in national Health Care Premiums, Wages and Inflation (1999 base)



"The growing costs of health insurance have absorbed a large portion of the… increase in total compensation"

- Robert D. Reischauer
Former Director of the Congressional Budget Office

Debt Growth*



Despite All The Discussions, A Lot More Needs To Be Done

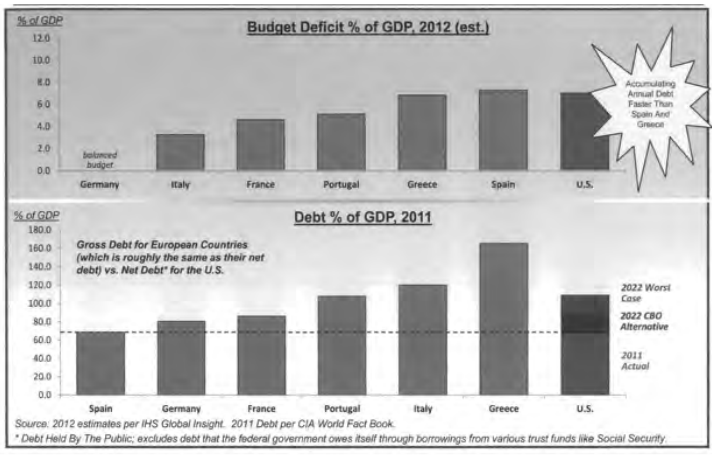
Historical Comparisons

	Year	Net Debt % GDP*
Revolutionary War	1790	38%
Civil War	1866	31%
World War I	1919	31%
World War II	1946	109%
Reagan Budgets	1993	49%
Today	2012	73%

* Debt Held By The Public excludes debt that the federal government owes itself through borrowings from various trust funds like Social Security.

Current Debt to GDP of 73% Eclipsed Only By World War II

Comparison With Europe



Comparison With Europe Not Encouraging

As predicted, society is addressing rising costs in 3 ways

Contain rates through regulation

- ☑ Slow or stop rate increases for Medicaid/ Medicare
- ❑ ✓ Mandate lower commercial insurer or provider rates
- ❑ ✓ Government pressure for voluntary rate reductions

Implement payment reform

- ☑ Make physicians economically sensitive; promote care integration
  - ☑ Global payment by commercial insurer (Blue Cross AQC)
  - ☑ MA payment reform commission
  - ☑ Bundled payments for acute/chronic diseases

Turn patients into consumers

- ☑ Make consumers economically sensitive
  - ☑ Tiered or limited provider networks
  - ☑ Differential co-pays and deductibles

Transition

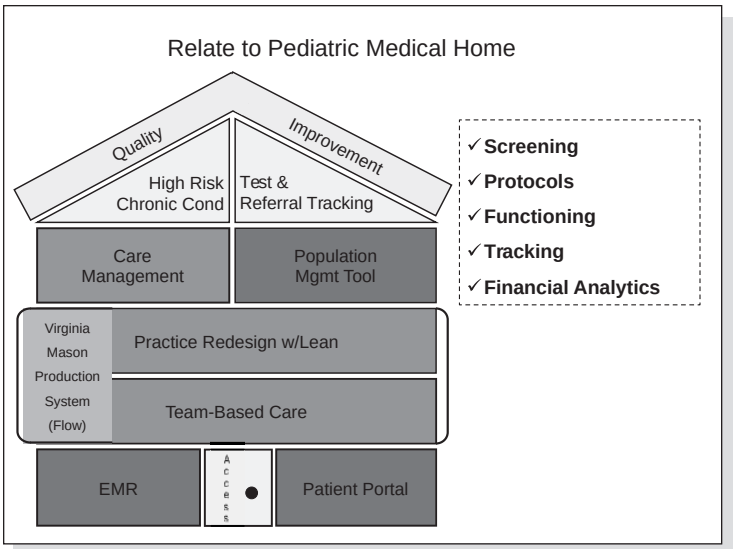
- Fee for Service (FFS) To:
  - –Value Based cost/quality; outcomes
  - –Risk Sharing
  - –ACO
  - –Capitation
  - –Global Payment

Fee For Service

- Reimburse for services, face to face, volume
- Little emphasis or reward for quality
- Modest incentives for process measures
- Little focus on outcome, long-term
- No sharing of financial risk
- Silo view of EMR
- Individual incentives
- Limits reimbursement for many Child Psych Services

Likely Future

- Global budget payer for costs of care (MH,MRI)
- Focus on quality, outcome, practice guidelines, quality assurance, process improvement, unit cost⇩
- Focus on high risk, high cost, outcome, readmissions, palliative care
- Focus on coordination
- IT facilitation for broad system of care
- Carefully designed incentives, care coordination
- Sub-Populations, Extensive Analytics: Medicare, Commercial, Self-insured, Medicaid and Duals
- Return on Investment (Opportunity for mental health?)



Transition Questions

- Pace of transition
- Extent → Living in 2 worlds
- IT, Infrastructure (Need for Capital)
- Who will hold risk (loss/gain) – Third party ins, Hospitals, Systems, Physicians

ADHD Risks and Costs

—Children with ADHD healthcare cost $775-1330 more per year and $3000 more per year as adults (mainly Psych.)

—Persistent ADHD ➡ 3x increase nicotine and substance use (even higher with conduct disorder; Fx history of SUD not predictive of SUD or age of onset.

—ADHD ➡ Medical and educational cost higher (about double in England and U.S.)

ADHD OUTCOMES

- 2 ½ Years less schooling (31% vs. 4% did not finish high school)
- 16% Antisocial
- 14% Substance use
- 30% Nicotine dependence
- 24% (vs. 6%) Psychiatric Hospitalizations

Global View of Costs related to ADHD:

- Alcohol Abuse
- Tobacco Use
- Substances
- ? Adherence, chronic diseases

How are societal costs or opportunity costs integrated into decision-making?

Implications for Child Psychiatry

- Screening of Population (Pediatric Collaboration)
- Evaluation (Hierarchy of interventions by severity)
- Functional tracking (establishing goals & baseline)
- Protocols (Q/A, prevention of secondary issues)
- Outcomes (engagement, parent groups, education, devices)
- Cost Analysis, shared risk
- Quality Assurance (Fidelity)
- Integration into Population Health Management

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Mechanism of Action of Psychostimulants in Animal Models

Pradeep Bhide, PhD

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Mechanism of Action of Psychostimulants in Animal Models

Pradeep G. Bhide, Ph.D.
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Director, Center for Brain Repair
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Tallahassee FL 32306

Disclosure

- Dr. Bhide has indicated that neither he nor his spouse/partner has a financial relationship with a commercial entity to disclose

Animal Models of ADHD

Prenatal nicotine exposure mouse model of ADHD

Prenatal nicotine exposure mouse model of ADHD

Shares the following features with ADHD

Hyperactivity
Frontal cortical hypo-dopaminergic state
Responsiveness to stimulant treatment
Reduced volume of cingulate cortex
and
Ecological validity

Prenatal nicotine exposure mouse model of ADHD

Animal models offer insights into mechanisms of etiology and treatment of ADHD that would be difficult to derive from clinical observations alone

Prenatal nicotine exposure mouse model of ADHD

The mouse model has shown for the first time that the hyperactivity

1. may be ameliorated by opioid receptor antagonists (novel ADHD treatment?)
2. may be heritable (transgenerational effects)

1. Hyperactivity is ameliorated by opioid receptor antagonists
A novel non-stimulant ADHD treatment

The prenatally nicotine-exposed mice show upregulation of kappa opioid receptor activity in the frontal cortex

Naltrexone, an opioid receptor antagonist, ameliorates the Hyperactivity in these mice

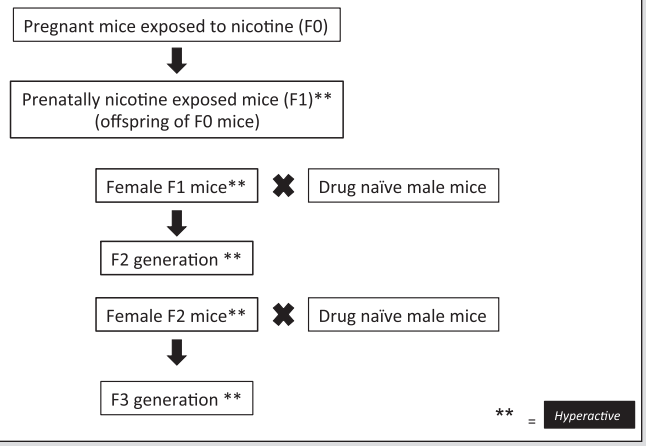
Therefore, opioid receptor antagonists, especially *selective kappa receptor antagonists may be a novel non-stimulant treatment for ADHD*

2. Transgenerational transmission of hyperactivity

Prenatally nicotine exposed (hyperactive) female mice (F1 generation) when bred with drug naïve males
transmit the hyperactivity to their offspring (F2 generation)

F2 females (also hyperactive) when bred with drug naïve males
transmit the hyperactivity to their offspring (F3 generation)

Transgenerational transmission of hyperactivity



Transgenerational transmission of hyperactivity

In contrast,
prenatally nicotine exposed (hyperactive) **male** mice (F1 generation)
when bred with drug naïve females
do not transmit the hyperactivity to their offspring (F2 generation)

Therefore, transgenerational transmission of hyperactivity
appears to be a sex-linked phenomenon in our mouse model

Our findings in the mouse model suggest that hyperactivity

1.may be ameliorated by opioid receptor antagonists
(A novel, non-stimulant treatment for ADHD)

1.may be heritable (transgenerational effects)

Treatment of Pediatric ADHD with Stimulants

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Treatment of Pediatric ADHD with Stimulants

Timothy E. Wilens, M.D.

Massachusetts General Hospital
Harvard Medical School

Disclosures

Dr. Wilens has served as a consultant, speaker, or has received grant support from the following (past 3 years)

- NIH (NIDA, NIMH)
- Euthymics, Shire

- Some of the products discussed are not FDA approved for ADHD or other psychopathology; others may not be FDA approved in the manner discussed (e.g. dosing, combination therapy)

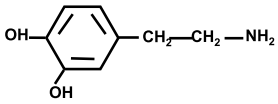
ADHD: Overview

- **ADHD is the most commonly diagnosed neurobehavioral disorder of childhood**
- **Treatment of ADHD should include consideration of pharmacotherapy**
- **Stimulants are among first-line therapy for ADHD**
- **Stimulants are among the most well studied and safest agents used in pediatrics**

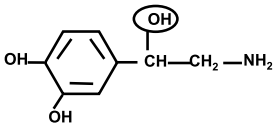
(ADHD Practice Parameters. *JAACAP* 1997;36:89S: Greenhill L et al., JAACAP 2002
Wilens & Spencer, *Postgraduate Medicine*, 2011)

Structural Comparisons

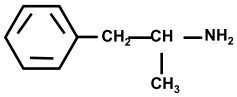
Dopamine



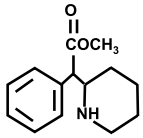
Norepinephrine



Amphetamine



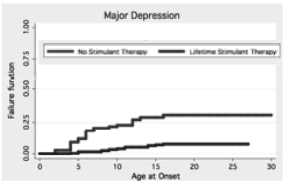
Methylphenidate

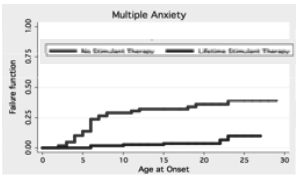


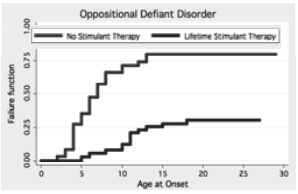
Protective Effect of Stimulants on Comorbidity

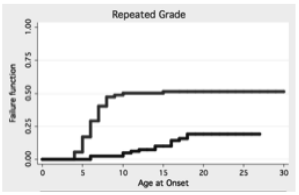
N= 140 boys with ADHD at entry; 10 year follow-up data

N=82 subjects receiving stimulants [mean duration of 6 yrs] & 30 not on stimulants





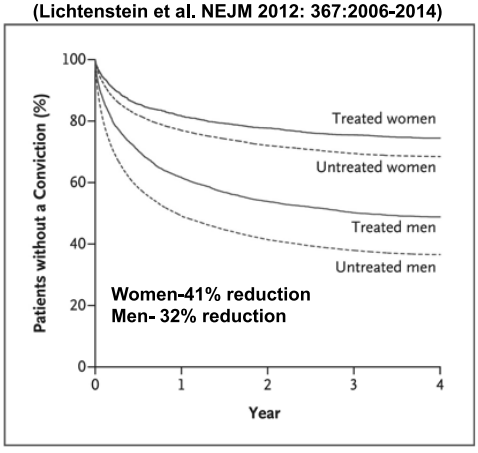




Biederman et al. *Pediatrics* 2009 Jul;124(1):71-8.

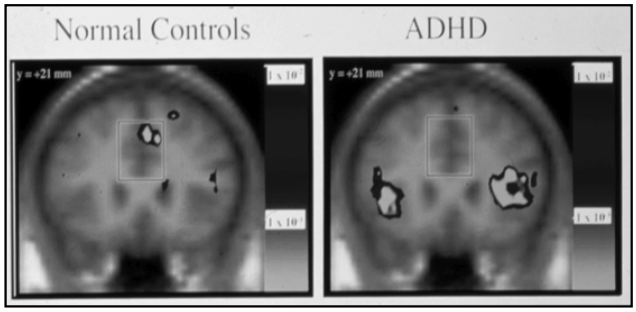
Medication for ADHD Reduces Criminality

(Lichtenstein et al. NEJM 2012: 367:2006-2014)



Swedish national registers (N= 25,656 with ADHD-about 50% on medications). No difference in type of ADHD medication (stimulants, nonstimulants) or level of crime.

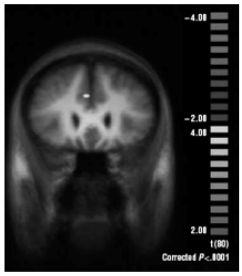
fMRI in Adults with ADHD

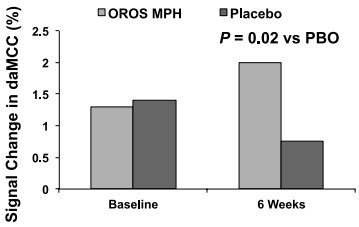


MGH-NMR Center & Harvard- MIT CITP

Bush G, et al. *Biol Psychiatry*. 1999;45(12):1542-1552; Tx response: Bush et al. Arch Gen Psych Jan 2008.

Methylphenidate Activates Dorsal Anterior Midcingulate Cortex





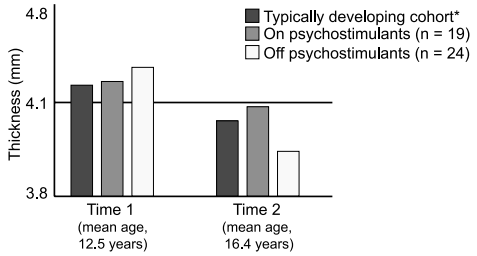
- fMRI at baseline and again at week 6
- OROS MPH group showed higher daMCC activation at 6 weeks vs placebo
- N=21 adults with ADHD; dosing to 1.3 mg/kg/day OROS MPH or placebo

Bush et al. *Arch Gen Psychiatry.* 2008:65:102-114.

Effect of Psychostimulants on Cortical Development

Prospective study utilizing two neuroanatomic MRI scans in 43 youths (age 9-20 years) with ADHD.

Mean baseline and endpoint raw cortical thickness (±SEM) in the left middle/inferior frontal gyrus

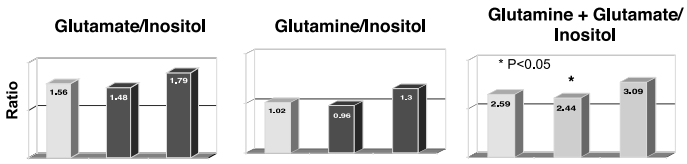


For most participants, cognitive data was not collected at both timepoints. Increased cortical thinning in the group that stopped taking stimulants was not associated with any difference in clinical outcome. Effects of treatment with nonstimulants cannot be excluded, although prevalence of nonstimulant use was low

*Derived from 620 scans of 294 typically developing youths

Shaw et al. *Am J Psychiatry.* 2009;166:58-63.

Magnetic Resonance Spectroscopy in ADHD Youth



MRS Study using 4 Tesla Scanner (McLean Hospital, Belmont)
Treated with OROS MPH: mean dose of 54 mg (0.9 mg/kg/day)
Controls- no ADHD (single scan)
ADHD- Scanned off drug baseline and again 6-8 weeks later

(Hammerness et al. World Psych 2012)

Methylphenidate

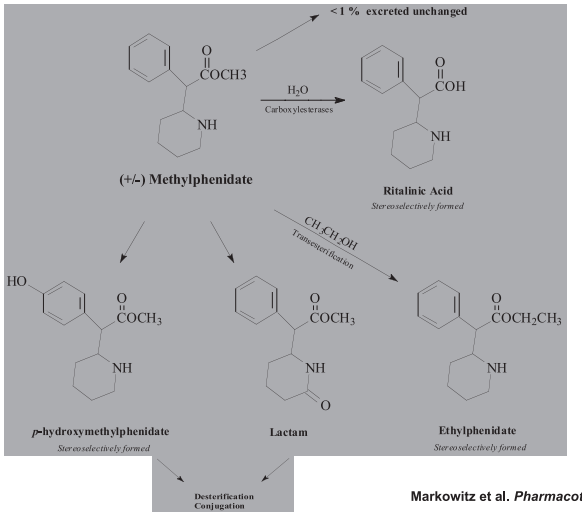
- Low bioavailability (~20 – 25%)
  - (+)-MPH isomer much greater bioavailability than the (–)-MPH isomer
- Typical therapeutic doses provide
  - T_{max} = 1.5 – 2.5 h
  - C_{max} = 6 – 15 ng/mL
  - $T_{½}$ = 2 – 3.5 h

Wilens and Spencer. *Child Adolesc Psychiatr Clin N Am* 2000;9:573-603.
Patrick and Markowitz. *Hum Psychopharmacol Clin Exp* 1997;12:527-546.

Methylphenidate

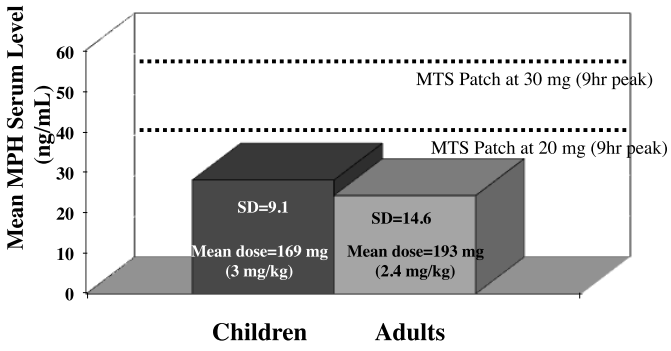
- Primarily de-esterified-may be susceptible to genetic polymorphisms (ultra slow metabolizer)
- Prominent metabolism (L-MPH) in intestinal wall
- Stereo-isomeric metabolism (L>D)
- Linear pharmacokinetics at moderate doses
- No pharmacokinetic drug interactions
- No food effects noted

Wilens and Spencer. *Child Adolesc Psychiatr Clin N Am* 2000;9:573-603. Stevens and Wilens; ADHD Across the Lifespan, 2013 In press; Zhu et al. Clin Pharm 2009 270: 59-65.



Markowitz et al. *Pharmacotherapy* 2003.

High-Dose OROS MPH in Youth (N=21) and Adults (N=4)



(Stevens et al J Child Adoles Psychopharm 2010)

Amphetamine

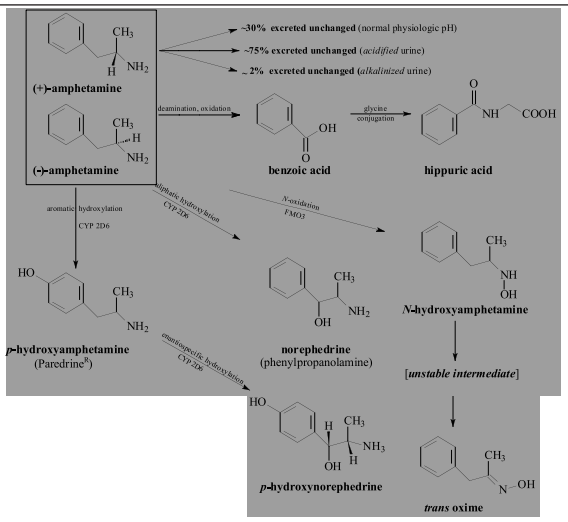
- **High bioavailability (~75%)**
- **Typical therapeutic doses of *dextroamphetamine* provide**
  - **T_{max} = 2 – 3 h**
  - **C_{max} = 40 – 70 ng/mL**
  - **$T_{½}$ = 7 h**

Wilens and Spencer. *Child Adolesc Psychiatr Clin N Am* 2000;9:573-603. . Stevens and Wilens; ADHD Across the Lifespan, 2013 In press
Patrick and Markowitz. *Hum Psychopharmacol Clin Exp* 1997;12:527-546.

Amphetamine

- Redundant hepatic metabolism
- Linear pharmacokinetics
- No pharmacokinetic drug interactions
- Food effects noted

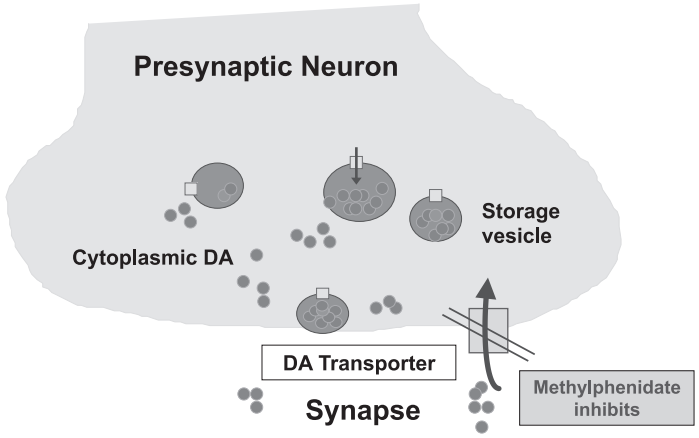
Wilens and Spencer. *Child Adolesc Psychiatr Clin N Am* 2000;9:573-603.
Patrick and Markowitz. *Hum Psychopharmacol Clin Exp* 1997;12:527-546.



Markowitz et al. *Pharmacotherapy* 2003.

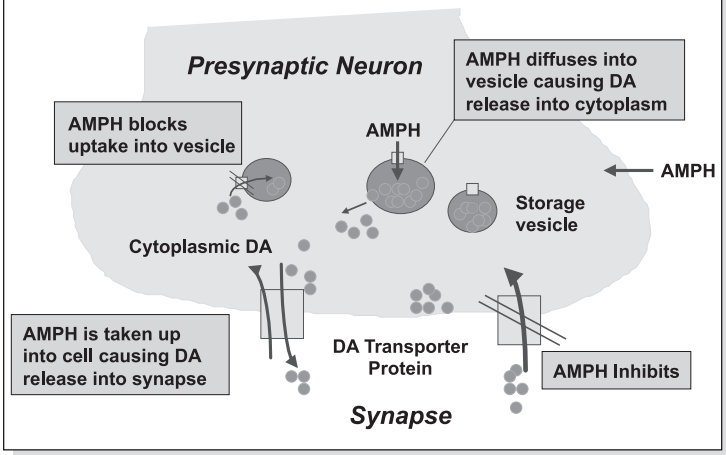
Mechanism of Action of Methylphenidate

(Wilens T. J Clin Psych 2006).

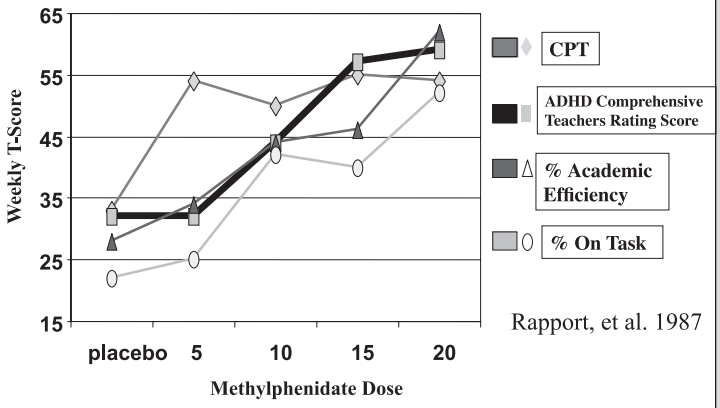


The Mechanisms of Action of Amphetamine

(Wilens T. J Clin Psych 2006).

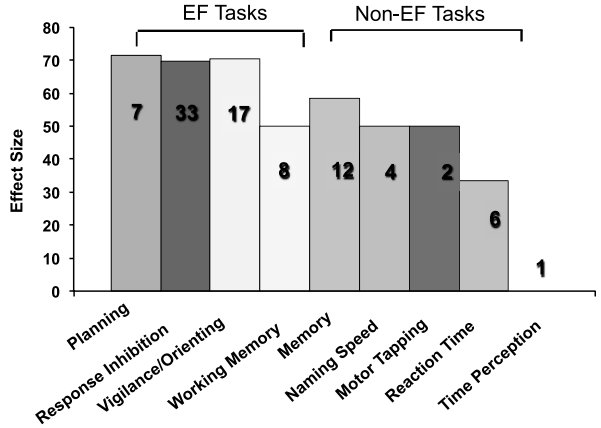


ADHD and Methylphenidate: Dose Effects on Attention in Clinic and Classroom



Rapport, et al. 1987

Studies Reporting Positive Effects of MPH on Executive Functioning (EF)

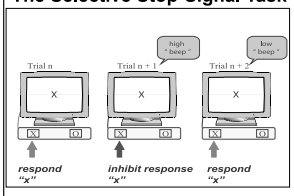


Pietrzak RH, et al. *Neurosci Biobehav Rev.* 2006;30(8):1225-1245.

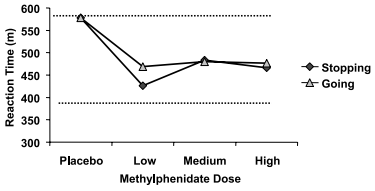
IR MPH Improved Response Inhibition in ADHD

A[1-3*]

The Selective Stop-Signal Task



B[4]

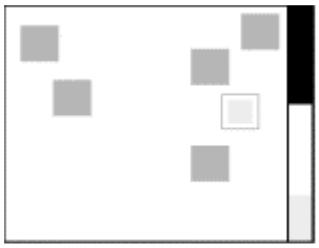


NB: Community Control Mean Going (▪▪▪) and Mean Stopping (▪▪▪)

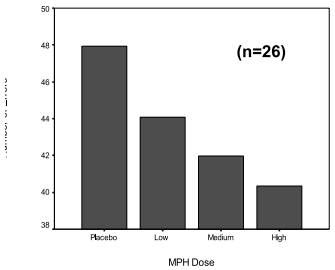
1. Tannock R, et al. *J Abnorm Child Psychol*. 1989;17(5):473-491. 2. Tannock R, et al. *J Abnorm Child Psychol*. 1995;23(2): 235-266. 3. Scheres A, et al. *J Abnorm Child Psychol.* 2003;31(1):105-120. 4. Bedard AC, et al. *J Abnorm Child Psychol.* 2003;31(3):315-327. 5. Bedard AC, et al. *J Child Adolesc Psychopharmacol*. 2002;12(4):301-309.

IR MPH Improved Spatial Working Memory

CANTAB Spatial Working Memory Task



Spatial Working Memory Tasks



No drug effects were demonstrated on strategy, indicating real effect on working memory.

CANTAB = Cambridge Neuropsychological Test Automated Battery.

Bedard AC, et al. *J Am Acad Child Adolesc Psychiatry.* 2004;43:260-268.

ADHD Stimulant Dosing

(Dosing may exceed FDA approved limits*)

Medication	Starting Dose	Maximum Dose*	Usual Dosing (h)
Amphetamine			
Adderall®	2.5 to 5 mg QD	1.5 mg/kg/day	BID (6 hr)
AdderallXR®	5-10 mg		QD (12 hr)
Dexedrine®	2.5 to 5 mg QD	1.5 mg/kg/day	BID/TID (4hr)
Dex Spansule	5 mg		BID (6 hr)
Vyvanse	20 mg	1 mg/kg/day	Once (12-14h)

(Wilens, Spencer, Biederman, *Ann Review Medicine 53*:2002; Wilens CNS Drug 2008; Wilens and Spencer, PostGraduate Medicine 2011 Stevens & Wilens in ADHD Across the Lifespan 2013; Pfizer PI)

ADHD Stimulant Dosing

(Dosing may exceed FDA approved limits*)

Medication	Starting Dose	Maximum Dose*	Usual Dosing (h)
Methylphenidate			
Ritalin®	5 mg QD/BID	2 mg/kg/day	TID (4 hr)
Focalin®	2.5 mg	1 mg/kg/day	BID (5-6hr?)
Concerta®	18 mg QD	2 mg/kg/day	Once (12h)
MetadateCD®	10 mg QD		Once (8-10h)
Ritalin LA	10 mg QD		Once
Focalin (XR)	5 mg QD	1 mg/kg/day	Once
MTS patch	10 mg		Once
Quillivant XR	20 mg	2 mg/kg/day (?)	Once (12h)

(Wilens, Spencer, Biederman, *Ann Review Medicine 53*:2002; Wilens CNS Drug 2008; Wilens and Spencer, PostGraduate Medicine 2011 Stevens & Wilens in ADHD Across the Lifespan 2013; Pfizer PI)

NIMH Preschool ADHD Treatment Study (PATS): Study Design

- Patients
  - Ages 3-5.5 years
- Parent Training (10 weeks)
- Open-label Safety Lead-in (1 week)
- Double-blind Crossover Titration (5 weeks)
  - Placebo and 4 doses of MPH (1.25, 2.5, 5, 7.5 mg tid*)
- Double Blind Parallel Phase (4 weeks)
  - Random assignment to placebo or best dose from crossover
- Open-label Maintenance (10 months)
- Placebo Discontinuation (6 weeks)

*tid=three times a day

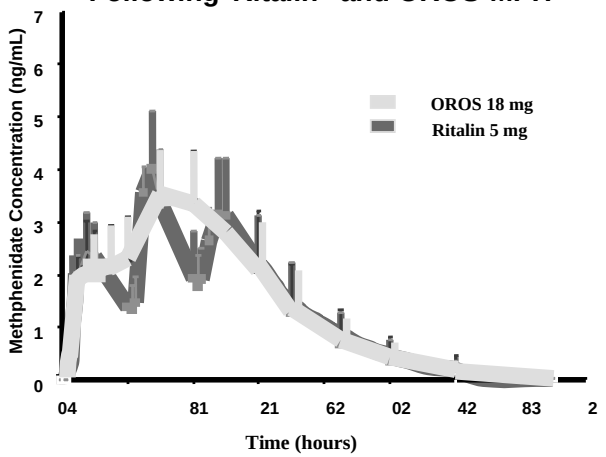
Kollins S, et al. *JAACAP*. 2007; Greenhill LL, et al. *JAACAP*. 2007

NIMH Preschool ADHD Treatment Study (PATS): Study Results

- N=303
- MPH given tid decreased ADHD symptoms in a dose-dependent fashion
- Effect size was lower than observed in school-age children
  - dose was limited for safety reasons
- Rates of adverse events were higher and were different
  - e.g., crying, irritability, outbursts were very common

Kollins S, et al. *JAACAP*. 2007; Greenhill LL, et al. *JAACAP*. 2007

Comparison of MPH Concentration Following Ritalin® and OROS-MPH



OROS MPH: 2 year followup study

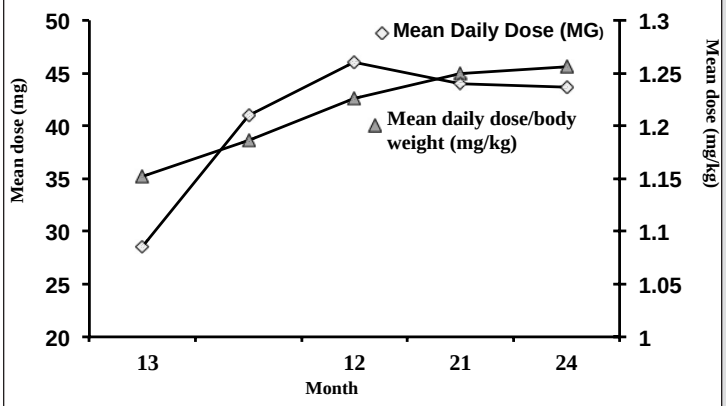
(N=230/407 completers)

- **Effectiveness:**
  - **Sustained effectiveness through 21/ 24 month period**
  - **Parent, investigator, teacher**
  - **Some dose escalation required**
- **Tolerability/Safety:**
  - **Well tolerated, with a safety profile corresponding to that expected for MPH**
  - **Little impact on sleep quality**
  - **Did not appear to worsen or induce tics**
  - **Minimal impact on appetite**
  - **Did not adversely effect growth (weight and height)**
  - **Did not adversely effect vital signs**
  - **Did not adversely effect blood chemistries (CBC, LFTs)**

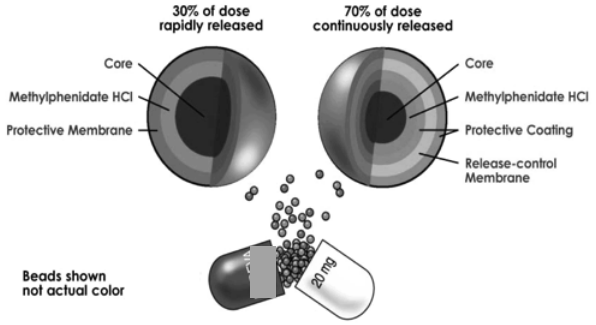
(Wilens et al. JAACAP:2006)

Dose of OROS® MPH Over Two Year Study

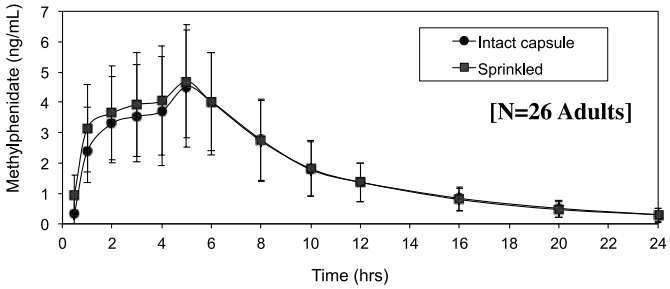
(Wilens et al. JAACAP:2006)



Methylphenidate Extended-Release Capsules for ADHD Biphasic Release (Metadate CD)



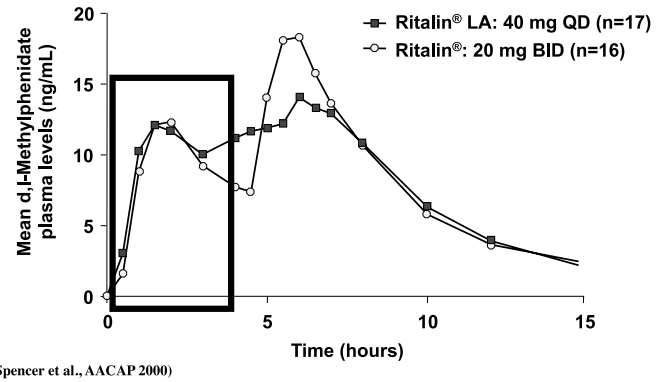
Mean MPH Concentration-Time Profiles: MPH ER (Metadate® CD) 20 mg Intact Capsule vs Sprinkled (Tbsp soft food)



MPH LA (Ritalin® LA): Pharmacokinetics/ Bioavailability

- Beaded technology
- Use of Ritalin (vs MPH)
- Mean half-life
  - ~3 hours
- Dose-proportional pharmacokinetics

MPH LA (Ritalin LA): Pharmacokinetic Profile



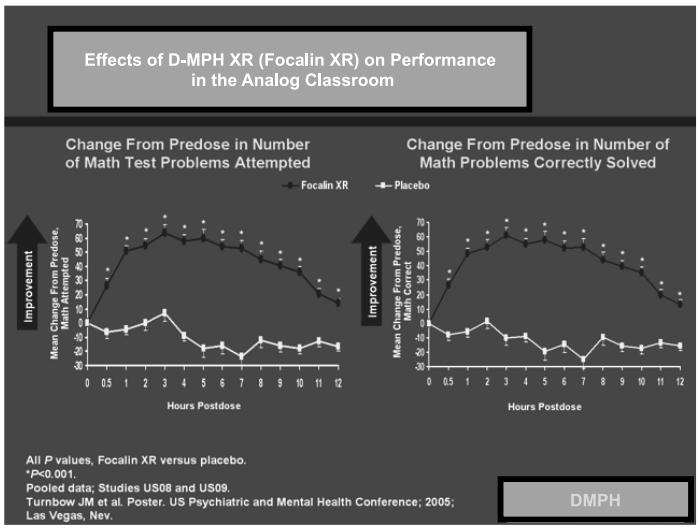
(Spencer et al., AACAP 2000)

Focalin (Dexmethylphenidate) Pharmacokinetics

Comparison to racemate

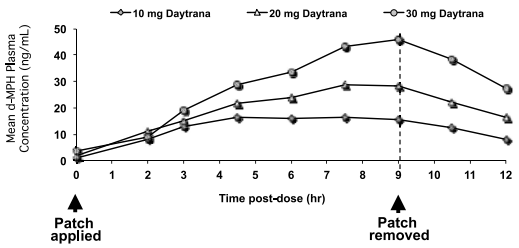
	Dexmethylphenidate d-methylphenidate	*Ritalin®* d,l-methylphenidate
T_{max}	1.3-1.8 h	1.6-2 h
C_{max} of *d*-MPH (5 mg/10 mg)	10.5 ng/mL	10.1 ng/mL
$T_{1/2}$	2-2.5 h	2.4 h

Data on file



Methylphenidate Pharmacokinetics with MTS (Daytrana)

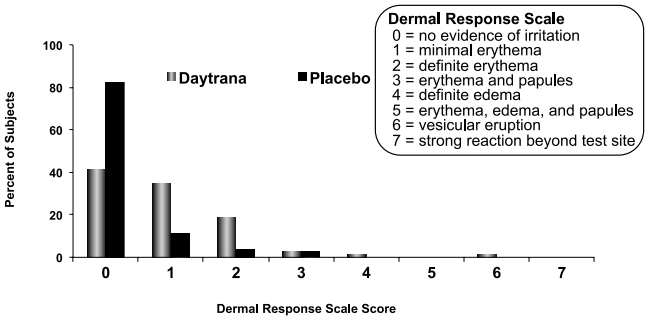
Mean Plasma Concentration of *d*-methylphenidate



Lower limit of quantification 0.25 ng/mL.

Pierce et al. Poster presented at the AACAP Annual Meeting. Toronto. October 20, 2005.

MTS School Study: Dermal Response

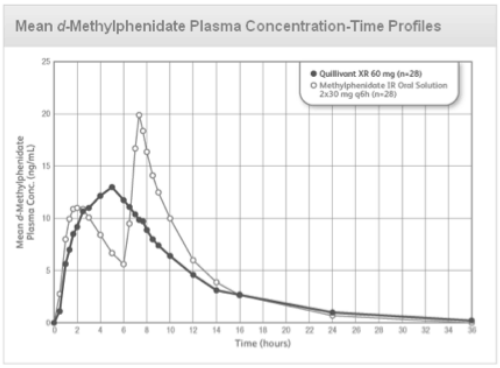


Week 7 – Laboratory Classroom Study.

McGough et al. J Child Adoles Psychopharm: 2007

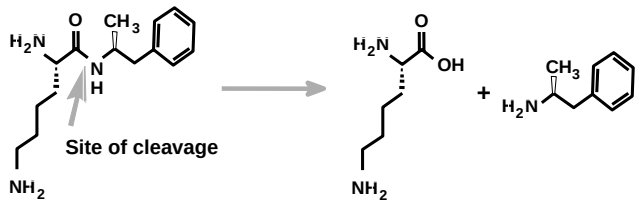
N=80

MPH-Extended Release (Quillivant®) vs Immediate Release Oral Solution Pharmacokinetic Data



RTC classroom data: Onset in 45 min, behavioral effects to 12 hours;
Pfizer Inc PI: : Wigal et al 2013 J Child Adoles Psychopharm 2013: 23: 310)

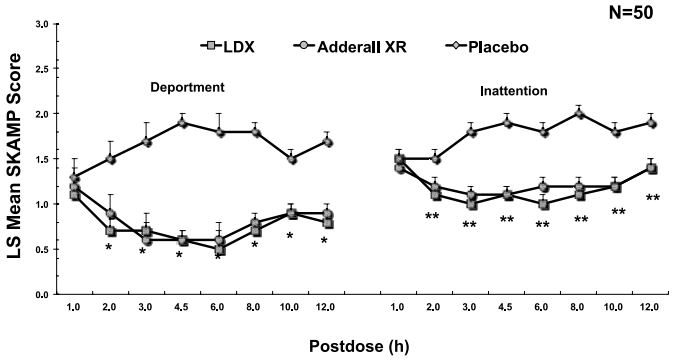
(Lisdexamfetamine) LDX; Vyvanse Chemistry



Lisdexamfetamine ***l*-lysine** ***d*-amphetamine**

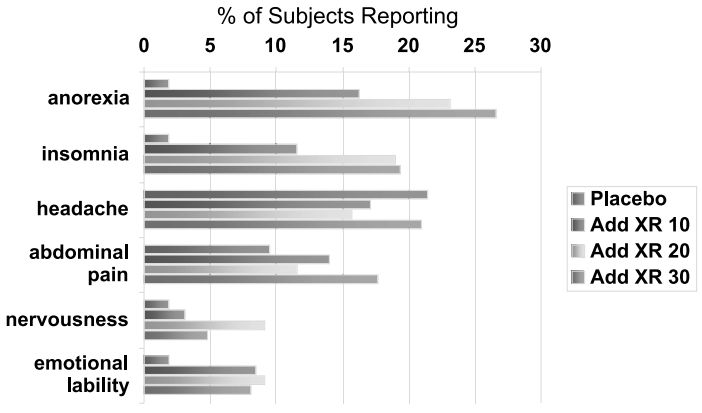
- Lisdexamfetamine dimesylate (LDX)
  - Amphetamine prodrug
  - L-lysine covalently linked to d-amphetamine
- Metabolically hydrolyzed to release d-amphetamine after oral administration

LDX : Duration of Action SKAMP Time Course



*P < .0001, **P < .01, LDX and Adderall XR vs placebo;
LS = Least Square.

MAS XR Study in Youth with ADHD: Frequently Reported Adverse Effects



MAS XR
24 Month f/u study

24 Month Open Label Extension
- Children 6-12 years
- 568 entered; 273 completed 24 months

Safety and Tolerability
- No serious adverse effects
- Minor, clinically insignificant changes in growth, vital signs

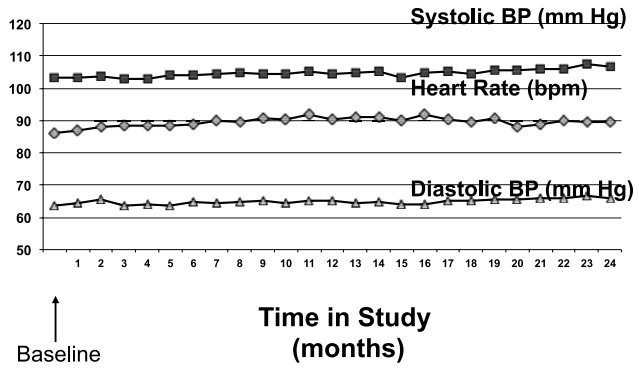
Effectiveness
- No evidence of attenuation of response
- Improvements in CGIS-P maintained at all time points

(Chandler, AmPsychAssoc 2002; Findling et al. J Ped:2006)

STIMULANT CONTROVERSIES

- **Adverse cardiovascular (CV) outcomes**
- **Growth suppression**
- **Development of tics**

Mixed Amph Salts:
Mean Blood Pressure and Heart Rate



(Findling, Biederman, Wilens et al. J Ped:2006)

ADHD Meds are Not Associated with Adverse CV Outcomes: Children

ADHD Drugs and Serious Cardiovascular Events in Children and Young Adults

ABSTRACT

Cooper et al. *The New England Journal of Medicine* 2011; 365(20) 18960-1904.

ADHD Meds are Not Associated with Adverse CV Outcomes:Children

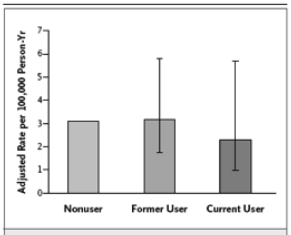


Figure 1. **Adjusted Rates of Serious Cardiovascular Events, According to the Use of ADHD Drugs.**
Rates per 100,000 person-years were adjusted by multiplying the rate in the reference group (nonusers) by the hazard ratios for former and current users. Hazard ratios were estimated with the use of Cox regression models, which were adjusted for the site-specific propensity-score decile, study site, medical conditions (serious cardiovascular disease and serious chronic illness), psychiatric conditions (major psychiatric illness, substance abuse, and antipsychotic use), utilization variables (medical hospitalization and general access to medical care), age, and calendar year. The I bars indicate 95% confidence intervals.

Cooper et al. *The New England Journal of Medicine* 2011; 365(20) 18960-1904.

ADHD Meds are Not Associated with Adverse CV Outcomes: Adults

ADHD Medications and Risk of Serious Cardiovascular Events in Young and Middle-aged Adults

Habel et al. *JAMA* 2011; 306(24) 2673-2683.

What to Do at Evaluation
(AHA Guidelines)

- **Medical History (*essentially screening of sudden death risk*)**
  - **Personal congenital or acquired cardiac disease**
  - **Palpitations, chest pain, syncope, seizures, post-exercise symptoms**
  - **Family history or premature cardiac disease (< 30 yrs of age)**
  - **Other meds (including OTC)**
  - **Routine med history (neurological, etc.)**
- **BP / heart rate - particularly in adults**
- **Peds: no ECG, Holter, or GXT**
- **Adults: work-up as indicated**
- ***Suspicion* of CV defect (e.g. IHSS, ARVD) --w/u as indicated**
- **Monitor above during treatment**
- **Issues of informed consent**

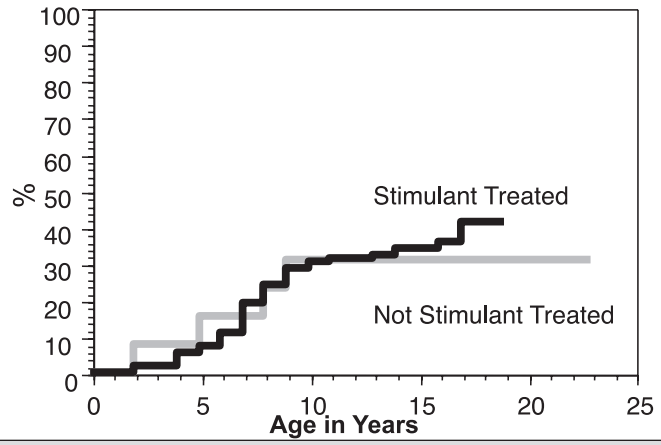
Gutgesell H et al., *Circulation* 1999:99:979-982; AAP Guidelines 2008; Perrin et al Pediatrics, 2008; Wilens et al. Pediatrics 2006; Cooper et al. NEJM 2012; Cooper et al JAMA 2012)

STRATEGIES FOR COMMON STIMULANT SIDE EFFECTS

- **Decreased appetite : Dose with or after meals. Encourage frequent snacks and evening snacks; caloric enhancing foodstuff. Decrease dose. Drug holidays. Consider adjunct peractin, nortriptyline**
- **Behavioral rebound: Change preparation to a sustained-release stimulant. Add reduced IR dose in late afternoon.**
- **Edginess: Change preparation or class of medication. Consider adjunct beta blocker or alpha agonist.**
- **Irritability/dysphoria: Try sustained-release preparation or another stimulant class. Consider coexisting conditions (e.g., depression) or medications (e.g., antidepressants); adjunct treatment (psychotherapy, antidepressants, second generation antipsychotics).**
- **Sleep problems: Sleep hygiene review. Reduce or eliminate afternoon dose. Reduce overall dose. Restrict or eliminate caffeine & activities: consider melatonin, alpha agonists, TCA**

(Wilens and Spencer, Postgraduate Med 2010: Stevens and Wilens, in press)

Onset of Tic Disorders in ADHD Probands Stratified by Stimulant Treatment



Issues in the Use of Stimulant Medication: Tics (cont'd)

- Management Strategies
  - Evaluate response
  - Take a drug holiday to be sure tics are drug-related
  - Consider risk vs benefit for mild tics that abate after 7-10 days of no medication
  - Switch stimulants or consider atomoxetine, clonidine, guanfacine,or tricyclic antidepressants

Kurlan et al. Neurology 2002; Hazel et al. JAACAP 2003

Wilens T, Spencer TJ. *Child Adolesc Psychiatr Clin N Am.* 2000;9(3):573-602; Stevens and Wilens 2013.

Do Stimulants Lead to Shorter Stature?

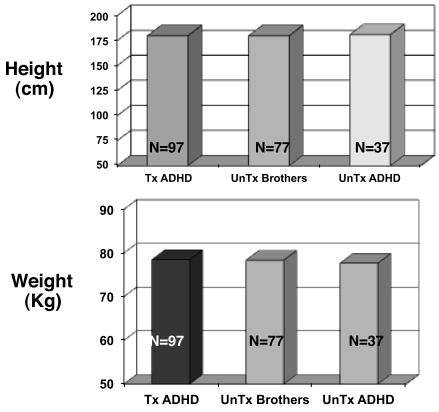
Controversies in the Use of Stimulants: Height and Weight Suppression

- **Concern: Potential suppression of height and weight gain associated with stimulant medications**
  - **Recent 14 mo and 3 yr MTA data indicating up to 1 CM/Year deficits**
  - **Small group of youth may have significant weight/height issues**
  - **May be attenuation in height weight effect**
  - **Drug holidays may offset more severe weight/height issues**
  - **Lag in growth may be ADHD related**
  - **Adult data suggests lack of evidence of subtle effects on height/weight**

Safer D, et al. *N Engl J Med.* 1972;287:217-220.
Spencer TJ, et al. *J Am Acad Child Adolesc Psychiatry.* 1996;35:1460-1469.
Kramer, et al. *J Am Acad Child Adolesc Psychiatry.* 2000;39:517-524.
MTA Study, Pediatrics 2004; Swanson et al. JAACAP 2007; Faraonet et al JAACAP 2007.

Height and Weight In Treated and UnTreated Adults with ADHD

Kramer, et al. *J Am Acad Child Adolesc Psychiatry.* 2000;39:517-524.



Youth aged 4 -12 yrs
MPH exposure = 36 mo
Reeval @ 21-23 years

Effect of Stimulants on Height and Weight: A Review of the Literature

STEPHEN V. FARAONE, PH.D., JOSEPH I BIEDERMAN, M.D.,
CHRISTOPHE P. MORLEY, M.A., AND THOMAS J. SPENCER, M.D.

ABSTRACT
Objective: Stimulant medications are effective treatments for attention-deficit/hyperactivity disorder, but concerns remain about their effects on growth. Method: We provide a quantitative analysis of longitudinal studies about deficits in expected growth among children with attention attention-deficit/hyperactivity disorder treated with stimulant medication. Study selection
criteria were use of DSM criteria or clear operational definitions for hyperactivity or minimal brain dysfunction; outcome measures including raw, standardize standardized, or percentile measurement of change in height and/or weight; first assessment of effects on growth occurred during childhood; and follow-up for at least 1 year. For issues not suitable for quantitative analyses, we provide a systematic, qualitative review. Results: The quantitative analyses showed that treatment with
stimulant medication led to statistically significant delays in height and weight. This review found statistically significant evidence of attenuation of these deficits over time. The qualitative review suggested that growth deficits may be dose dependent, deficits may not differ between methylphenidate date and amphetamine, treatment cessation may lead to normalization of growth, and further research should assess the idea that attention deficit/hyperactivity disorder itself maybe associated with dysregulated growth.
Conclusions:Treatment with stimulants in childhood modestly reduced expected height and weight. Although these effects attenuate over time and some data suggest that ultimate adult growth parameters are not affected, more work is needed to clarify the effects of continuous treatment from childhood to adulthood. Although physicians should monitor height, deficits in height and weight do not appear to be a clinical concern for most children treated with stimulants. J. Am. Acad. Child Adolesc. Psychiatry, 2008;47(9)
R E V I E W

Chris Kaman

Scott Eyre

Jason Kidd

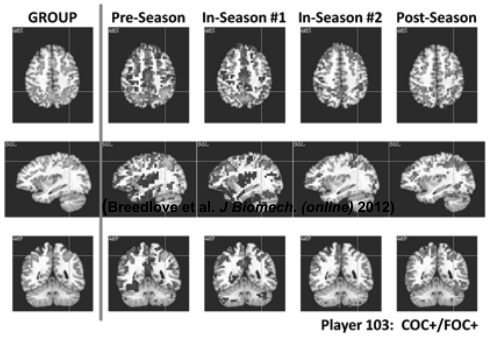
Terry Bradshaw

League Rules & Stimulant Use

- **High School Sports**
  - Generally not urine tested
  - Generally no specific rules for stimulant use
- **College Sports/ NCAA**
  - Urine tested for drugs of abuse
  - Requires documented clinical diagnosis and ongoing monitoring by physician

League Rules & Stimulant Use

- **Professional Sports**
  - Urine tested for steroids & drugs of abuse
  - Generally requires physician monitoring and waiver
- **International Olympic Committee**
  - Urine tested for steroids & drugs of abuse
  - Generally not allowed



(Breedlove et al. *J Biomech. (online)* 2012)

Brain scans show differences among high school football players in a two-year study that suggests concussions are likely caused by many hits over time and not from a single blow to the head . (Purdue University image/Thomas Talavage)

'The changes in brain activity we are observing suggest that a player is having to use a different strategy to perform a task, and that is likely because functional capacity is reduced," Talavage said. "The level of change in the fMRI signal is significantly correlated to the number and distribution of hits that a player takes. Performance doesn't change, but brain activity changes, showing that certain areas are no longer being recruited to perform a task."

ADHD, Post-concussion, & Treatment

- Treatment of ADHD may also improve post-concussive syndrome
- Use of stimulants & modafinal for concussion and/or (traumatic) brain injury
  - » Targeted symptoms: arousal, disinhibition
  - » General focus and concentration
  - » Enhanced processing speeds
  - » Unclear effects on complex processing
- Non-specific response to stimulants
  - » Nonspecific response (Rapoport et al. Science, 1978)
- Caveats-
  - » Careful with side effects: some indication of increased adverse effects with more "brain injury" (vs ADHD)
  - » To "return to play" faster, some players are using stimulants to improve post-concussive testing

Wilens & Spencer, Stimulants Revisited, Psych Clin N Am 2000
Willmott C and Ponsford J. *J Neurol Neurosurg Psychiatry* 2009 May; 80:552.)

Summary: Stimulants in ADHD

- Highly effective in treating ADHD
- Improvements in the release mechanisms of the stimulants
- Largely predictable adverse effects
- Longer term effects encouraging at both neurobiological and outcome levels
- Data on combination with other medications emerging
- Future research

QUESTIONS?

Treatment of Pediatric ADHD with Non-Stimulants

Timothy E. Wilens, MD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

Treatment of Pediatric ADHD with Non-Stimulants

Timothy E. Wilens, M.D.

Massachusetts General Hospital
Harvard Medical School

Disclosures*

Dr. Wilens has served as a consultant, speaker, or has received grant support from the following

- NIH (NIDA, NIMH)
- Euthymics
- Shire
- Published Straight Talk About Psychiatric Medications for Kids (Guilford Press)
- Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), age groups, dosing, or in context to other disorders (e.g. bipolar disorder, substance abuse)
- * past 3 years

Heterogeneity of ADHD

- DSM-IV subtypes
  - » Inattentive
  - » Hyperactive/impulsive
  - » Combined
- Genetic subtypes
  - » D4
  - » DAT
  - » 5HT
  - » Nepi
- Cognitive subtypes
  - » LD
  - » Executive function deficits subtypes
  - » Various attentional defects (e.g. arousal; motivation, EF)
- Comorbid subtypes
  - » Disruptive Behavior disorders (CD/ODD)
  - » Mood and anxiety disorders
  - » Substance abuse

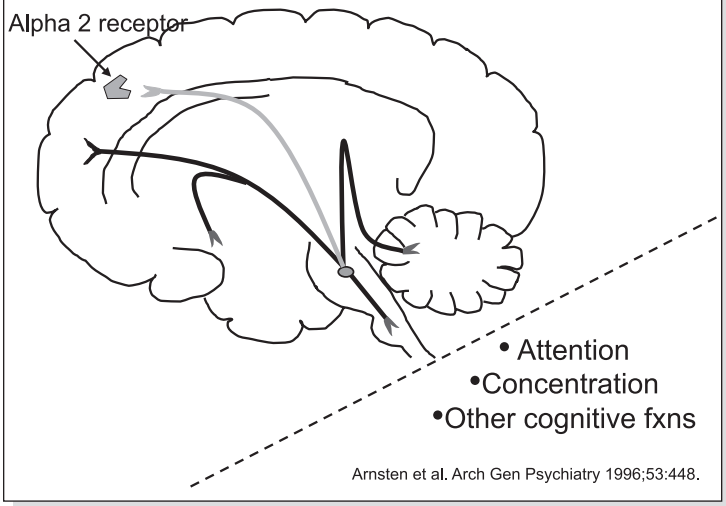
Courtesy T. Spencer

Pharmacotherapy for ADHD

- Stimulants (FDA approved)
  - Methylphenidate
  - Amphetamine compounds
- Atomoxetine (FDA-approved)
- Alpha agonists (FDA-approved)
  - Guanfacine extended-release
  - Clonidine extended-release
- Combined alpha agonists plus stimulants (FDA approved)
  - Extended-release guanfacine plus stimulants
  - Extended-release clonidine plus stimulants
- Antidepressants
  - Bupropion
  - Tricyclics
- Modafinil
- Research
  - Natural agents
  - Anti-Alzheimers/cog enhancing agents

(Wilens & Spencer, Postgraduate Medicine, 2010)

Norepinephrine Frontal



Arnsten et al. Arch Gen Psychiatry 1996;53:448.

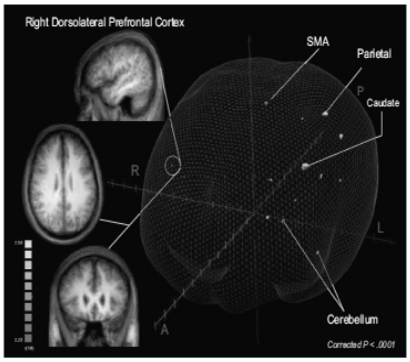


Fig. 1. Atomoxetine produces higher fMRI activation at 6 weeks. Six weeks of ATMX significantly increased activation of right DLPFC, parietal cortex, supplementary motor cortex, caudate, cerebellum and other brain regions, but not within daMCC (cf. Table 2). The regional activations depicted passed a multi-step masked random effects repeated measures ANOVA GLM analysis, showing *both* (1) significant activation during a voxelwise mask representing all voxels showing $MSIT_{Interference} > MSIT_{Control}$ activity for all 32 subjects (ATMX, MPH, and Placebo) and (2) significantly higher $MSIT_{Interference}$ fMRI activation at 6 weeks of ATMX treatment than at baseline. The above figure at right depicts the resulting GLM statistical map data superimposed on a pseudo-3D wire mesh brain representation (R=right, L=left, A=anterior, P=posterior). At left are shown 3 orthogonal (sagittal, axial and coronal) views of the right DLPFC activation (*x/y/z*=45/22/28). A stringent cluster constraint was used throughout resulting in corrected regional thresholds of $P < 1 \times 10^{-4}$.

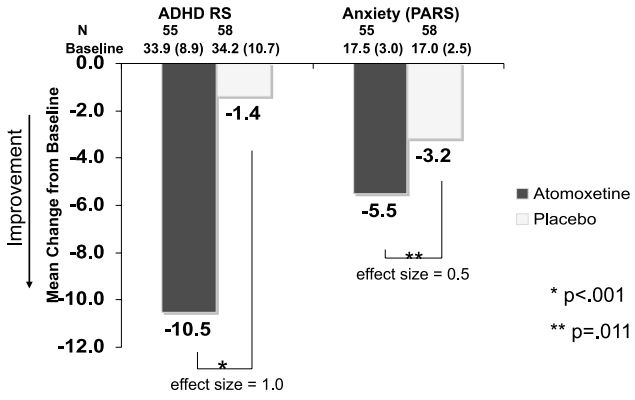
Safety and Tolerability of Atomoxetine Over 3 to 4 Years in Children and Adolescents With ADHD.

DONNELLY, CRAIG, BANGS, MARK, TRZEPACZ, PAULA, JIN, LING, ZHANG, SHUYU, WITTE, MICHAEL, BALL, SUSAN, SPENCER, THOMAS

Objective: To assess the long-term safety and tolerability of atomoxetine hydrochloride in children and adolescents with attention-deficit/hyperactivity disorder treated for >=3 years. **Method:** Data from 13 double-blind, placebo-controlled trials and 3 open-label extension studies were pooled. Outcome measures were patient-reported treatment-emergent adverse events (AEs); discontinuations due to AEs, serious AEs, and changes in body weight, height, vital signs, electrocardiogram, and hepatic function tests. **Results:** In total, 714 patients were treated with atomoxetine for >=3 years (mean follow-up 4.8 years [SD 1.1 years]), including a subset of 508 treated for >=4 years (mean follow-up 5.3 years [SD 0.8 years]). Most subjects were younger than 12 years at entry (73.8%), male (78.4%), and white (88.9%). The mean final daily dose of atomoxetine was 1.35 mg/kg (SD 0.37 mg/kg). No new or unexpected AEs were observed compared with acute-phase treatment. Less than 6% of patients exhibited aggressive/hostile behaviors, and less than 1.6% reported suicidal ideation/behavior. No clinically significant effects were seen on growth rate, vital signs, or electrocardiographic parameters, and <=2% of patients showed potentially clinically significant hepatic changes. **Conclusion:** Atomoxetine was safe and well tolerated for children and adolescents with >=3 and/or >=4 years of treatment.

Donnelly et al. J AM Acad Child Adolesc Psychiatry, 48:2, Feb 2009

Atomoxetine for Youth with ADHD & Anxiety



Dose of ATMX = 1.26 mg/kg/day

(Geller et al. JAACAP 2007)

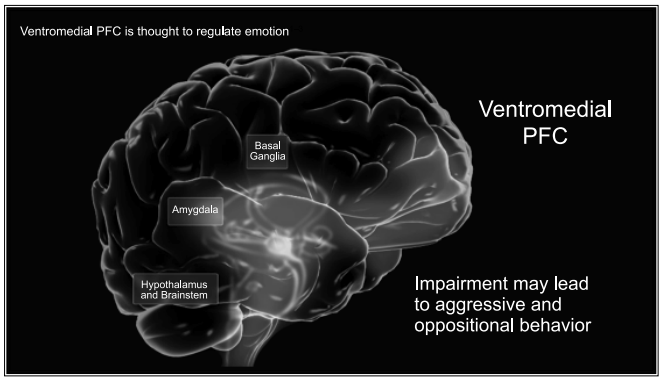
Atomoxetine

- **Dosing (Wilens' method):**
  - **Start at 0.5 mg/kg/day for two weeks, then increase to 1.2 mg/kg/day. After six weeks if partial response, increase to 1.8-2 mg/kg/day**
- **Adverse effects:**
  - **Rare hepatic injury (2 cases): advise, LFTs NOT required**
  - **Suicidality (0.37% vs 0%): black box**
  - **Somnolence, appetite suppression, GI upset/dyspepsia, blood pressure/pulse (adults), sexual dysfunction (adults), irritability**
  - **Potential drug interactions (lower dose if using with p448 inhibitor)**

Atomoxetine: When to Use

- **Monotherapy (higher likelihood of response as first start)**
- **Stimulant nonresponders**
- **Stimulant partial responders (monotherapy, adjunctive therapy-no drug interactions with stimulants)**
- **Adverse effects to stimulants**
- **Concerns of stimulant diversion**
- **Comorbid ADHD plus**
  - **Oppositional disorder**
  - **Anxiety**
  - **Tics**
  - **Substance abuse**

The Ventromedial Prefrontal Cortex (PFC): Emotional Regulation

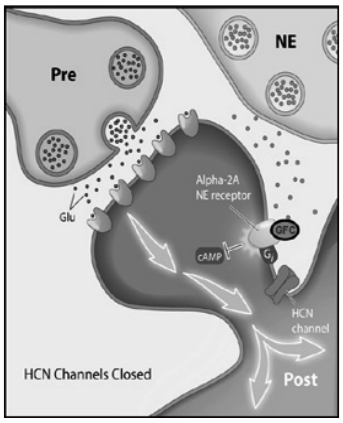


[1]Anderson SW, et al. *Nat Neurosci.* 1999;2:1032-1037.
[2]Arnsten AFT, et al. *J Child Adolesc Psychopharmacol.* 2007;17:393-406.
[3]Price JL, et al. *Prog Brain Res.* 1996;107:523-536.

Alpha Agonists: Clonidine & Guanfacine

- Alpha agonist agents
  - **Mimics Norepinephrine at alpha and beta receptors**
  - **Presynaptic Alpha 2a (guanfacine more specific)**
  - **Post synaptic alpha 1, 2 a-c (alpha 2a in PFC)**
- Effect on Prefrontal cortex (PFC)
  - **May be dose dependent effects on pre/post 2a**
  - **Largely inhibitory**
  - **Modulated by "stress" dependent release of Nepi**
  - **Improves PFC blood flow and functioning in animal models**
- Effect on Locus Coerulus
- **Modulate of neurotransmission of other neuronal systems (glutamate, GABA, cholinergic, opioid)**

(Arnsten and Li, Biol Psych 2005; Wilens J Clin Psych 2006)



Arnsten, Cerebral cortex, epub 2007

Extended Release Clonidine for ADHD

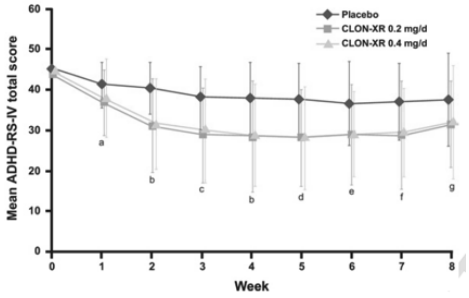


FIGURE 3 Mean Attention-Deficit/Hyperactivity Disorder Rating Scale—IV (ADHD-RS-IV) total score from baseline to week 5 using a last observation carried forward (LOCF) method. Note: ADHD-RS-IV total score was significantly improved at week 1 for the CLON-XR 0.2-mg/day group. Significant improvement was achieved in both CLON-XR groups beginning at week 2 and continued through study termination. Error bars represent standard deviations. CLON-XR= clonidine hydrochloride extended-release tablets; a $p = .0219$ for CLON-XR 0.2 mg/day. b $p < .0001$ for both groups. c $p < .0003$ for both groups. d $p = .0005$ for both groups. e $p < .0054$ for both groups. f $p < .0074$ for both groups. g $p \leq .0288$ for both groups.

N=236; 61% completion rate

Jain et al. JAACAP epub 2011

Extended Release Clonidine for ADHD

TABLE 3 TEAEs That Occurred in ≥5% of Treatment Groups and Had at Least Twice the Incidence of Placebo (Safety Population)

TEAE	Placebo, n (%) (n = 76)	CLON-XR 0.2 mg/day, n (%) (n = 76)	CLON-XR 0.4 mg/day, n (%) (n = 78)
Somnolence	5 (6.6)	30 (39.5)	24 (30.8)
Fatigue	1 (1.3)	12 (15.8)	10 (12.8)
Irritability	3 (3.9)	7 (9.2)	6 (7.7)
Pharyngolaryngeal pain	3 (3.9)	6 (7.9)	6 (7.7)
Increase in body temperature	2 (2.6)	4 (5.3)	2 (2.6)
Insomnia	1 (1.3)	4 (5.3)	5 (6.4)
Ear pain	1 (1.3)	4 (5.3)	0 (0)
Emotional disorder	1 (1.3)	3 (3.9)	4 (5.1)
Nightmare	0 (0)	3 (3.9)	7 (9.0)
Constipation	0 (0)	1 (1.3)	5 (6.4)
Dry mouth	1 (1.3)	0 (0)	4 (5.1)

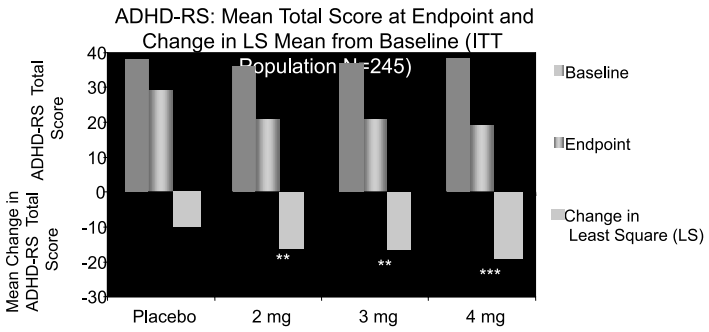
Note: CLON-XR = clonidine hydrochloride extended-release tablets; TEAE = treatment-emergent adverse event.

Jain et al. JAACAP epub 2011

Extended-release Clonidine

- **BID Dosed preparation FDA approved for pediatric ADHD (Kapvay)**
  - **Tablet (0.1 and 0.2 mg)**
  - **Start at 0.1 mg qHS; increase 0.1 mg/week**
- **QD Dosed preparation FDA approved for adult hypertension (Nexiclon) but NOT ADHD**
  - **Chewable tablet form (0.17 mg; 0.26 mg)**
  - **Oral suspension (0.09 mg/cc)**

Guanfacine ER: Efficacy

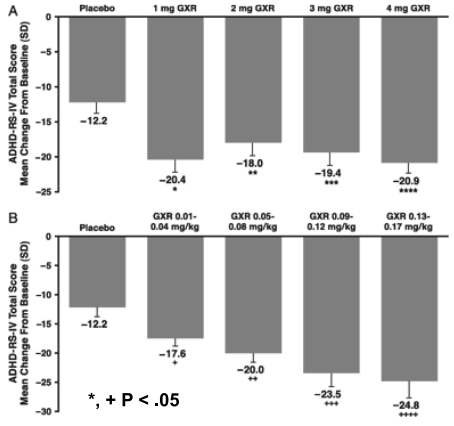


*8-week, double-blind, placebo-controlled, parallel-group safety and efficacy study; **p<0.001; *** p<0.0001 (adjusted Dunnett test compared to placebo following ANCOVA with baseline score as covariate)

Biederman et al. Pediatrics 121; e73-84 2008

Guanfacine Extended-Release in ADHD

(N=324 [51 sites]; 6 weeks active*, Mean Age 11±3 yrs)



Effect size: 0.41-0.89

*3 weeks titration
3 weeks maintenance (endpoint)
3 weeks taper

Sallee et al. J AM Acad Child Adolesc Psychiatry, 48: 155-165; 2009

Guanfacine Extended-Release in ADHD

(N=324 (51 sites); 6 weeks, mean age 11±3 yrs)

- Adverse effects
  - Discontinuation rate similar between med and placebo
  - Somnolence (27% vs 12%[placebo]) and fatigue (9% vs 3%)
    - » Improved after titration
  - Headache (21% vs 11%)

Sallee et al. J AM Acad Child Adolesc Psychiatry, 48:2, Feb 2009

Guanfacine Extended-Release in ADHD

(N=324 (51 sites); 6 weeks, mean age 11±3 yrs)

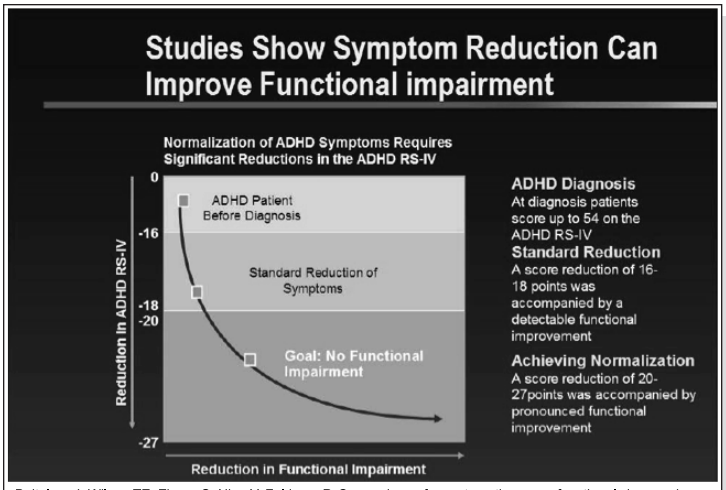
- Cardiovascular changes (dose related)
  - Heart rate (-9.5 bpm at 4 mg [average change vs baseline])
    - » 6-7% of subjects at 3-4 mg with HR<50
    - » 1 subject with dizziness with standing (HR =64)
  - Systolic BP (-7.4 mmHg at 4 mg)
  - Diastolic BP (-5.4 mmHg at 4mg)
- No apparent attenuation of CV effects with adjunct stimulants (Spencer et al. JCAP 2009)

Sallee et al. J AM Acad Child Adolesc Psychiatry, 48:2, Feb 2009

Alpha Agonists: When to Use

- Monotherapy
- Stimulant or nonstimulant nonresponders
- Medication partial responders (adjunctive therapy)
  - Studied with stimulant coadministration (N=5 studies)
- Adverse effects to stimulants or nonstimulants
- Comorbid ADHD plus
  - Oppositional disorder
  - Anxiety
  - Tics
  - "Emotional dysregulation" (needs to be studied)
- Potentially younger children (needs to be studied)

Studies Show Symptom Reduction Can Improve Functional impairment



Buitelaar J, Wilens TE, Zhang S, Ning Y, Feldman P. Comparison of symptomatic versus functional changes in children and adolescents with ADHD during randomized, double-blind treatment with psychostimulants, atomoxetine, or placebo. J Child Psychol Psychiatry 2009; 50(3):335–342

Combination of Guanfacine XR plus Stimulants in the Treatment Of ADHD

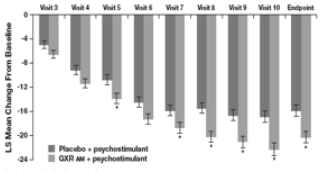
-Multisite, controlled 9 week trial in 455 subjects
-Dosing: 1 - 4 mg daily; mean of 3.2 mg (0.1 mg/kg)
-Inclusion: Stimulant partial responders (> 4 wk use with improvement; ADHD RS ≥24 and CIG ≥3) age 6-17 urs
-Exclusion: Other psych, CV abnl, Weight <55 or > 176 lb
-Design: 5 week optimization and 3 week dose maintenance period (visits 7-10)
-Primary outcome: ADHD RS IV (Investigator)

Wilens et al. J Am Acad Chld Adoles Psych: 2012

Guanfacine XR plus Stimulants in the Treatment Of ADHD (N=455)

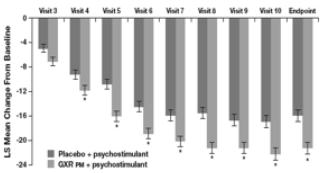
(Wilens et al. J Am Acad Child Adoles Psych: 2012)

Figure 1. GXR AM dosing plus psychostimulant group: change in ADHD-RS-IV total score from baseline by visit (FAS).



*P<0.05 vs placebo, based on Dunnett's test.
Effect size at endpoint was 0.377.
Endpoint is the last valid assessment obtained after baseline and before dose taper.

Figure 2. GXR PM dosing plus psychostimulant group: change in ADHD-RS-IV total score from baseline by visit (FAS).



*P<0.05 vs placebo, based on Dunnett's test.
Effect size at endpoint was 0.447.
Endpoint is the last valid assessment obtained after baseline and before dose taper.

Combination of Guanfacine XR plus Stimulants in the Treatment Of ADHD:Adverse Events

Serious adverse effects -all unrelated to medication: 1) syncope, 2) poison ivy, 3) emotional outbursts

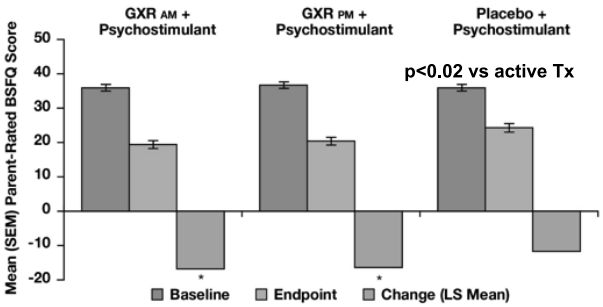
Cardiovascular indices at endpoint

- **Heart rate: -5.6 bpm**
- **Systolic blood pressure: -2.2 mm HG**
- **Diastolic BP: -1.2 mm Hg**
- **No ECG abnl, no QT prolongation**

Wilens et al. J Am Acad Chld Adoles Psych: 2012

Combined GXR plus Stimulant Improves Morning Functioning

Figure 2.



BSFQ: Before School Functioning Scale (7-9 AM rating by parent)

(Wilens et al. Presented at AACAP 2012; JAD 2013; *submitted*)

Combination of Clonidine XR plus Stimulants in the Treatment Of ADHD

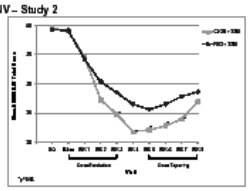
- **Study of clonidine XR coadministration to partial responders on stimulants (>ADHD RS 26 score)**
- **N= 197**
- **Dosing to 0.4 mg daily (in 0.2 mg BID dosing)**
- **Duration: 5 weeks (then taper)**

Figure 4. Change Scores for ADHDRS-IV – Study 2

Figure 4 shows the change in ADHD-RS-IV scores by week of treatment.

Statistical separation from PBO+ST was observed as early as Week 3 for CLON+ST.

(N=197)



Statistically significant differences favoring the CLON groups also were observed for the following secondary endpoints: ADHD-RS-IV Inattention subscale, ADHD-RS-IV Hyperactivity/Impulsivity subscale, CPRS-L, CGI, and PGA. No statistica. significant differences were observed for the HADS or SSR-CP scale.

(Kollins et al. Pediatrics epub 2011)

Clonidine plus Methyphenidate: ADHD plus Tic Disorders

- Prospective data indicating improved outcome for ADHD (Kurlan et al. Neurology 2002; Hazel et al. JAACAP 2003; Palumbo et al JAACAP 2007)
  - » MPH + Clon > MPH > Clon > PBO
- Prospective data indicating improved outcome for tics (Kurlan et al. Neurology 2002; Hazel et al. JAACAP 2003; Palumbo et al JAACAP 2007)
  - » No worsening systematically of tics vs PBO
- No cardiovascular issues in prospective data
  - » No recent "events" reported

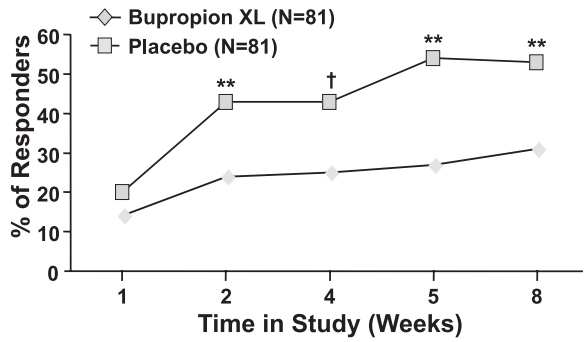
Bupropion

- Combined Dopaminergic/Noradrenergic mechanism of action
- Effective anti-ADHD agent
- Effective antidepressant (adults)
- Anti-smoking (Zyban)

Bupropion

- Superior to placebo in children
  - —N= 3 studies (104 subjects)
- Effective in ADHD adults
  - —N= 4 controlled
  - —Recent multisite study positive

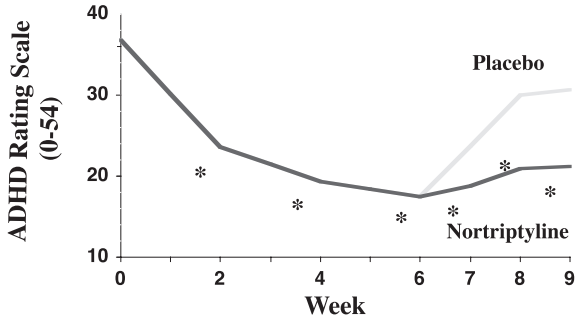
Bupropion XL in Adults with ADHD: Percent Responders*



*≥30% reduction from baseline; **p≤0.01, †p<0.05

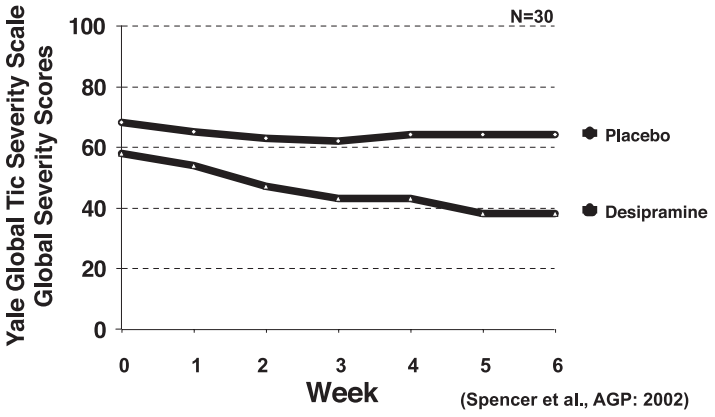
(Wilens et a l. Biol Psych 2005)

Nortriptyline in Pediatric ADHD



(Prince, et al., JCAP, 2000)

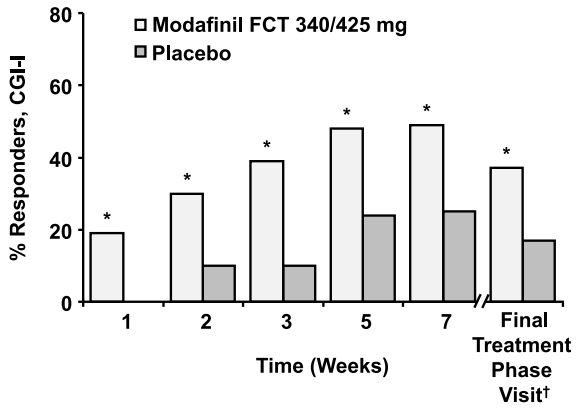
Desipramine in ADHD and Tics: Effects on Tics



(Spencer et al., AGP: 2002)

Modafinil Effects on Overall Clinical Response

(Biederman, Lopez, Wilens APA, 2005



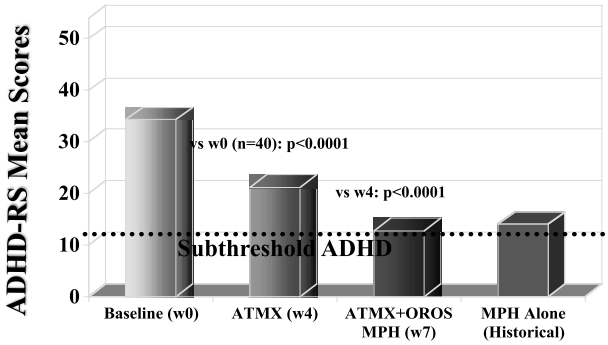
Responders defined as patients rated as much improved or very much improved on CGI-I.
*$P \leq .001$ vs placebo.
†Last observation carried forward analysis.

Modafinil: When to Use

- Stimulant or nonstimulant non or partial responders (monotherapy, adjunctive therapy-no drug interactions with stimulants)
- Adverse effects to medications
- Concerns of diversion or misuse of stimulants
- Need for renewable agent
- Cardiovascular risk factors (still cautionary in PI)
- Predominately cognitive deficits (e.g. motivation, arousal of attention)
- Comorbid ADHD (?)
  - Oppositional disorder
  - Bipolar/moody (evidence of usefulness in adults)

Combined OROS MPH plus Atomoxetine: ADHD

ADHD Outcome



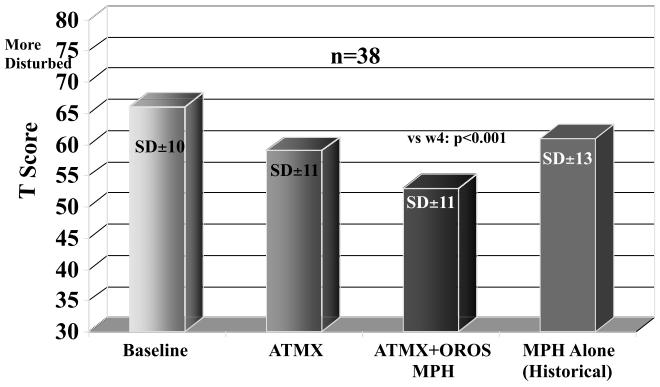
▪Phase I initiated ATMX for a minimum of 4 weeks

n=40 n=50 n=50

▪ Phase II entered only ATMX partial responders and added OROS MPH to their treatment regimen

OROS MPH plus ATMX: Improvement in Executive Functioning (BRIEF)

Initiation



(Wilens et al. J Child Adolesc Psychopharm: 2009)

Omega -3/Omega-6 Fatty Acids for ADHD

- Metanalysis of 10 studies; N= 699 children
  - Examined EPA, DHA (Omega-3), and g-linoleic acid (Omega 6)
  - Indicating mild improvement in ADHD overall with good tolerability (ES = 0.28 monotherapy; 0.18 adjunct)
  - Potential dose response effect of EPA
  - May be useful for mood symptoms in ADHD

Bloch MH, Qawasmi A, J Am Acad Child Adoles Psych 2011

Melatonin for Sleep Disturbances

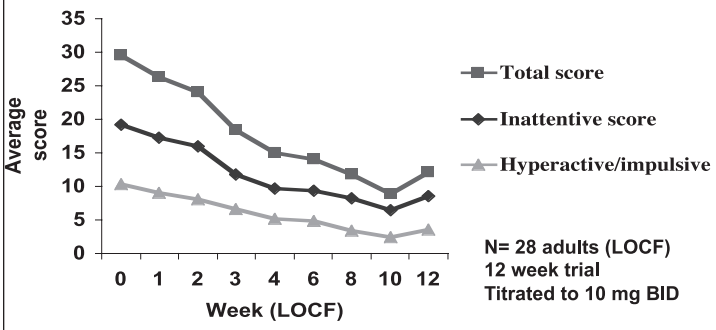
(Smits et al., JAACAP:42:1286-1293; Carr et al. J Pineal Res 2007:43:351-359)

- Controlled study of melatonin (5 mg) vs placebo
- N= 4 Week RCT Cross over of 62 youth (aged 6-12); 40% with ADHD receiving stimulants

  Findings:
  - Improvement in sleep questionnaire (RAND-GHRi)
  - Improvement in time of sleep onset (57 minutes earlier), and decreased sleep latency by 17 minutes
  - Well tolerated
- Long term open follow-up of 44 developmentally disabled youth for up to 3.8 years
  - Entered from cross-over study
  - Age 9.9 yrs at followup
  - Continued effectiveness for sleep, behavior & cognition
  - No apparent adverse effects, or deleterious effects on puberty noted

Memantine for ADHD: MGH Open Trial

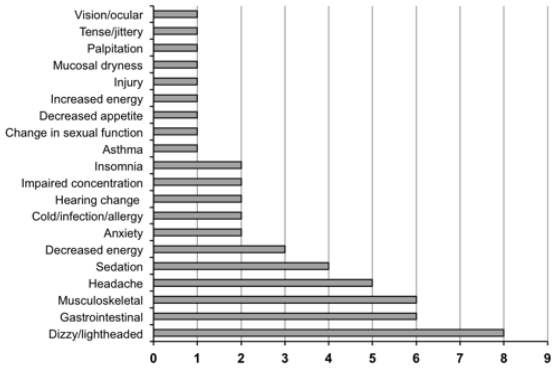
AISRS Total, Inattentive & Hyperactive /Impulsive Scores



N= 28 adults (LOCF)
12 week trial
Titrated to 10 mg BID

Surman et. al. World J Bio Psych: 2012

Memantine: Adverse Effects



Surman et. al. World J Bio Psych: 2012

Pharmacological Treatments Not Generally Demonstrated Efficacious for ADHD

- ✓-Buspirone (failed multisite study)
- ✓-St John's Wort (Webber et al. JAMA 2008)
- ✓-Herbal remedies
- ✓ Blue green algai, huperzine, ginko, pycnogenol,
- ✓- Dietary manipulations: variable response (Pediatrics, 2012)
  - ✓Overall weak effect
  - ✓Best outcomes for supplementation in deficient individuals
- ✓-Antipsychotics and mood stabilizers: Studies largely in mood disordered individuals: Mixed outcomes for ADHD

Pharmacological Treatments Not Demonstrated Efficacious for ADHD

Experimental pharmaceuticals

- **Prohistaminergic agents** (Herring et al. 2012
- **Cholinesterase inhibitors** (Wilens et al. 2005, Biederman et al 2006
- **Nicotinic partial agonist** (Wilens et al. JAACAP 2011)
- **Mixed catecholamine inhibitor** (Wilens et al. Behav Brain Funct. 2008)
- **Amino acids** (Wender, Reimherr, Wood et al. 1980, 84)

Experimental Pharmaceuticals

- **Efficacy to be established**
- **alpha4beta2 nicotinic partial agonist [894]** (Bain E et al. Neuropsychopharmacology 38: 2013)
- **A4b2 nicotinic partial agonist [089]**
  - **Positive x-over study (Apostle et al Psychopharmacology 2012)**
  - **2 Negative parallel design studies** (Wilens et al. J Am Acad Child Adoles Psych 2012: Bain et al. J Clin Psych 2012)
- **Ampakines-mixed: useful in IA subtype** (Adler et al. APSARD, 2011)

Pharmacotherapy of ADHD Comorbidity

- **Evidence of improved ADHD outcome with *treated comorbidity***
  - **Anxiety**
  - **Depression**
  - **Bipolar disorder**

Summary: Non-Stimulant Pharmacotherapy of ADHD

- A number of non-stimulant medications for ADHD
- Often lower effect size than stimulants
- A variety of effective drugs
  - Noradrenergic agents (ATMX) -(FDA Approved)
  - Alpha agonists – (FDA approved)
  - Antidepressants /arousal agents -second line

- Both FDA (alpha agonist) and nonFDA (ATX, TCA) stimulant combinations that may be effective
- Useful in comorbidity
- Stay tuned: New compounds in development

Late Onset and Atypical Forms of ADHD

Stephen V. Faraone, PhD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

Late Onset and Atypical Forms of Attention Deficit Hyperactivity Disorder

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Medical Genetics Research Center and Departments of Psychiatry and Neuroscience & Physiology
SUNY Upstate Medical University

Disclosures of Potential Conflicts

Source	Research Funding	Advisor/ Consultant	Employee	Speakers' Bureau	Books, Intellectual Property	In-kind Services (example: travel)	Stock or Equity	Honorarium or expenses for this presentation or meeting
NIH	X							
Guilford Press					X			
Akili Interactive Labs		X						
Phoenix Group		X						
Oxford Univ. Press					X			

Reporting period is past 2 years .

Overview: Atypical Forms of ADHD

- Late onset ADHD: Patient meets all DSM criteria except for age at onset
- Subthreshold ADHD: Patient has never met full DSM criteria for ADHD, yet has impairing ADHD symptoms
- Low IQ ADHD: Patient meets all DSM criteria but has a low IQ
- High IQ ADHD: Patient meets all DSM criteria but has a high IQ

Study Groups: MGH Family Study of Late Onset and Subthreshold ADHD Adults

(Faraone et al., Am J Psychiatry, 2006)

- ADHD groups: All showed impairing symptoms of ADHD as adults
  - Full ADHD: Met full childhood diagnostic criteria (N=127)
  - Late onset ADHD: Met all childhood criteria except for age at onset (N=79)
  - Subthreshold ADHD: Only reported subthreshold symptoms of ADHD in childhood (N=41)
- Not ADHD Group (N=123)

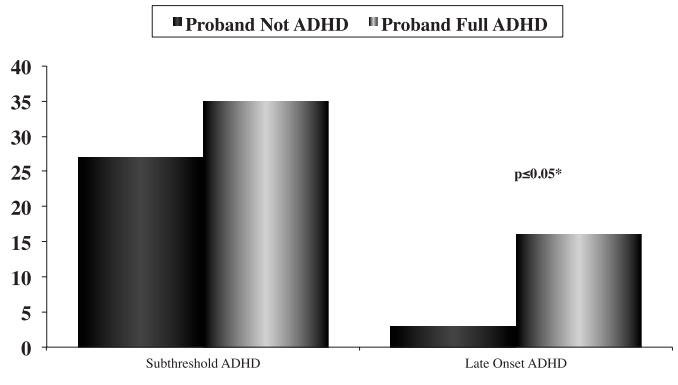
Validating Atypical Forms with Family History Data

(Faraone et al., Am J Psychiatry, 2006)

- ADHD is known to be highly heritable
- If an atypical form of ADHD is truly ADHD, then:
  - People related to patients having the Full ADHD gold standard diagnosis should be at elevated risk for the atypical forms
  - People related to atypical ADHD patients should be at elevated risk for the Full ADHD gold standard diagnosis

Subthreshold and Late Onset ADHD among Adult Relatives without Full ADHD

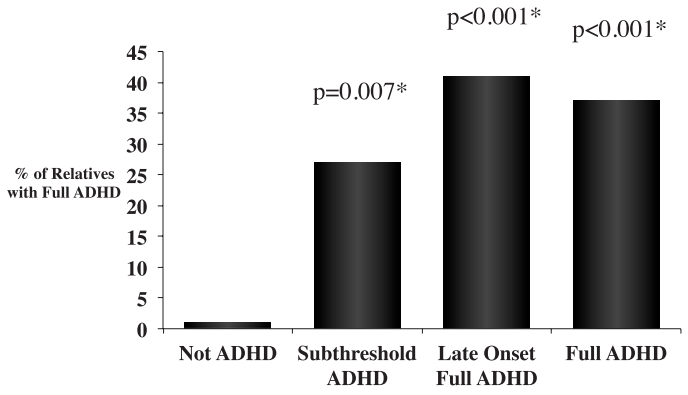
Faraone et al., Am J Psychiatry, 2006



* vs. Proband Not ADHD group

Rates of Full ADHD in Relatives

Faraone et al., Am J Psychiatry, 2006



* vs. Not ADHD group

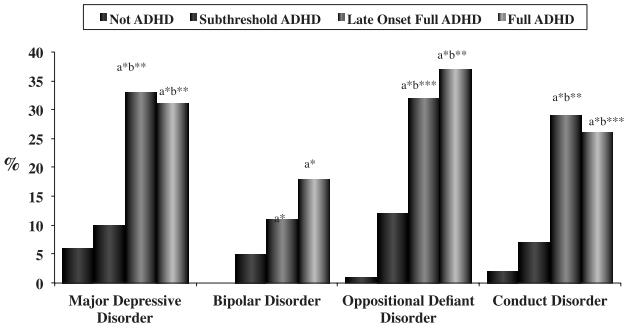
Validating Atypical Forms with Psychiatric Comorbidity Data

(Faraone et al., Am J Psychiatry, 2006)

- Patients with ADHD are at high risk for antisocial, mood, anxiety and substance use disorders.
- If an atypical form of ADHD is truly ADHD, then patients with atypical ADHD should also be at risk for these comorbidities

Lifetime History of Mood and Disruptive Behavior Disorders in Probands

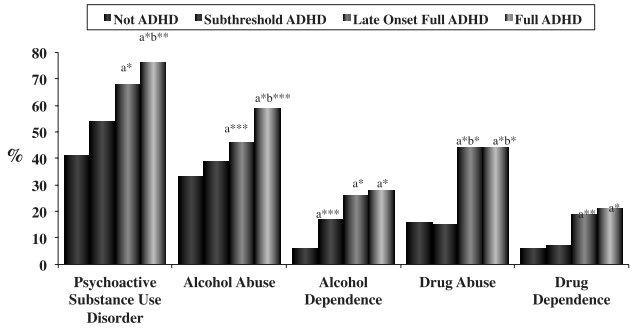
Faraone et al., Am J Psychiatry, 2006



[a] vs. Not ADHD, [b] vs. Subthreshold ADHD
*p≤0.001, **p≤0.01, ***p≤0.05

Lifetime History of Psychoactive Substance Use Disorders in Probands

Faraone et al., Am J Psychiatry, 2006



[a] vs. Not ADHD, [b] vs. Subthreshold ADHD
*p≤0.001, **p≤0.01, ***p≤0.05

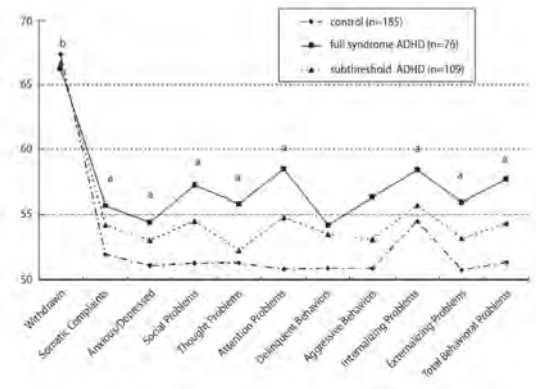
Psychiatric Comorbidity in late Onset Adult ADHD

(Karam et al., J Psychiat Research, 2009)

Comorbidities	Early-onset (n = 174)	Late-onset (n = 175)	Analysis[b]	
	n (%)[a]	n (%)[a]	w	p
Major depression	48 (27.60)	45 (25.70)	0.17	0.683
Bipolar disorder (I and II + ciclotymia)	26 (14.90)	33 (18.90)	1.70	0.193
Anxiety disorders	65 (37.40)	77 (44.00)	2.29	0.130
Panic disorder	6 (05.50)	10 (10.40)	0.25	0.613
Social phobia	16 (14.60)	19 (19.80)	1.97	0.160
OCD	41 (23.60)	33 (18.90)	0.15	0.692
GAD	24 (13.80)	39 (22.30)	6.33	0.012
Alcohol dependence	16 (09.20)	22 (12.60)	1.35	0.245
Alcohol abuse or dependence	26 (14.90)	29 (16.60)	0.36	0.549
Substance dependence	12 (06.90)	6 (03.40)	1.52	0.218
Substance abuse or dependence	19 (10.90)	16 (09.10)	0.005	0.944
ODD	79 (45.40)	70 (40.00)	0.55	0.459
Childhood conduct disorder	41 (23.60)	33 (18.90)	0.35	0.555
Anti-social personality disorder	18 (10.30)	10 (05.70)	1.41	0.234

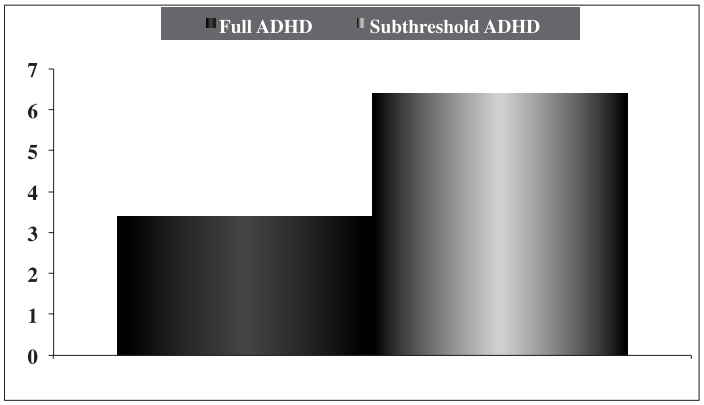
CBCL Psychopathology in Subthreshold ADHD Adolesents

(Cho et al., Eur Child Adol Psychiat, 2009)



Community Study of Full and Subthreshold ADHD in US Adolescents

Lewinsohn et al., Psychol Med 2004



Community Study of Full and Subthreshold ADHD in US Adolescents

Lewinsohn et al., Psychol Med 2004

- Subthreshold ADHD adolescents had significantly increased rates of:
  - Major depression
  - Substance use disorders
  - Conduct disorder

Community Study of Subthreshold ADHD in Swedish Adolescents

Malberg et al., Acta Paediatrica 2011

Diagnostic class and items	n = 312 ADHD_comb OR (95%CI)	 DBD OR (95%CI)
Alcohol abuse		
Quantity	4.25** (1.66–10.90)	10.73*** (4.90–23.50)
Frequency drinking	2.55 (0.23–28.00)	14.59* (1.45–146.17)
Concern from others about drinking	2.20 (0.55–8.85)	13.62*** (3.82–48.61)
Smoking		
>2 cigarettes/day	7.70*** (3.52–16.84)	11.77*** (5.11–21.13)

Table gives increased risk (odds ratio) for substance use disorders among subthreshold ADHD and Disruptive Behavior Disorder (DBD) patients.

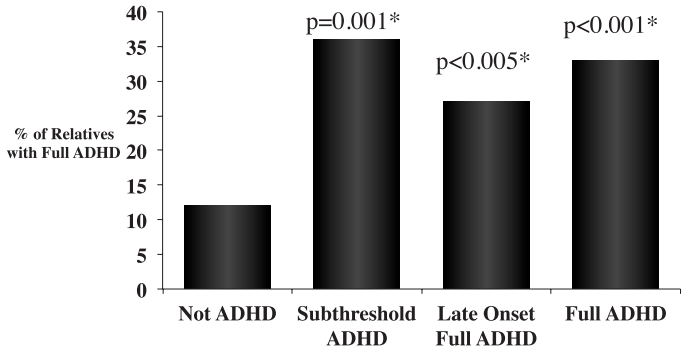
Validating Atypical Forms with Neuropsychological Data

(Faraone et al., Am J Psychiatry, 2006)

- Patients with ADHD are at high risk for executive dysfunction.
- If an atypical form of ADHD is truly ADHD, then patients with atypical ADHD should also be at risk for executive dysfunction.

Executive Function Disorder

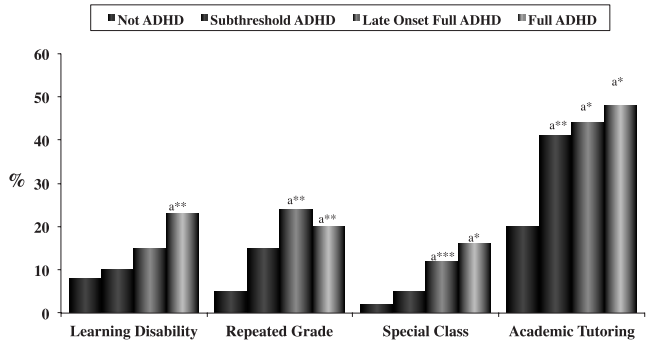
Faraone et al., Biological Psychiatry, 2006



* vs. Not ADHD group

School Functioning of Probands

Faraone et al., Am J Psychiatry, 2006



[a] vs. Not ADHD
*p≤0.001, **p≤0.01, ***p≤0.05

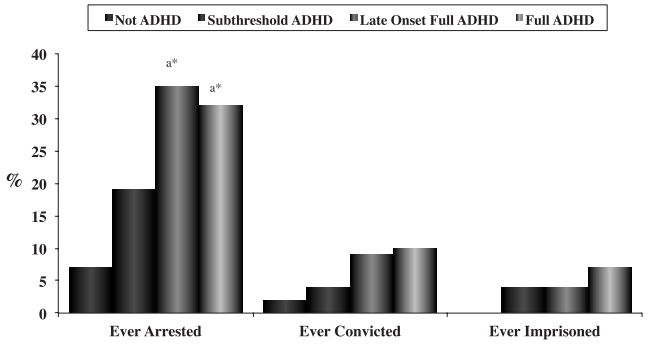
Validating Atypical Forms with Impairment Data

(Faraone et al., Am J Psychiatry, 2006)

- If atypical forms of ADHD are truly disorders, they should show some of the characteristic impairments of ADHD patients.

Legal Problems and Atypical ADHD

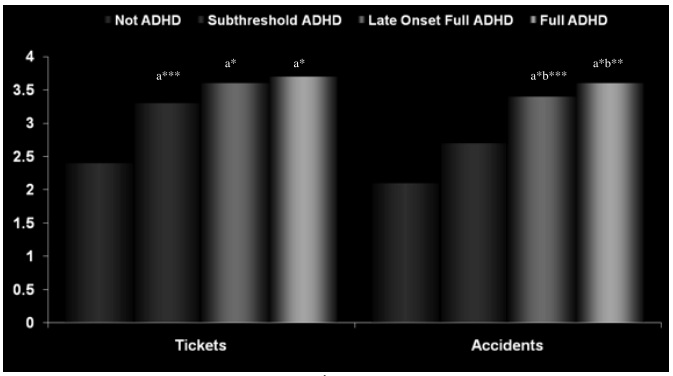
Faraone et al., Am J Psychiatry, 2006



[a] vs. Not ADHD
*p≤0.001

Driving Problems and Atypical ADHD

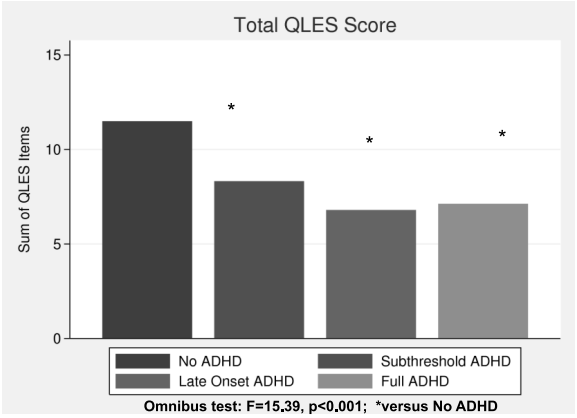
Faraone et al., Am J Psychiatry, 2006



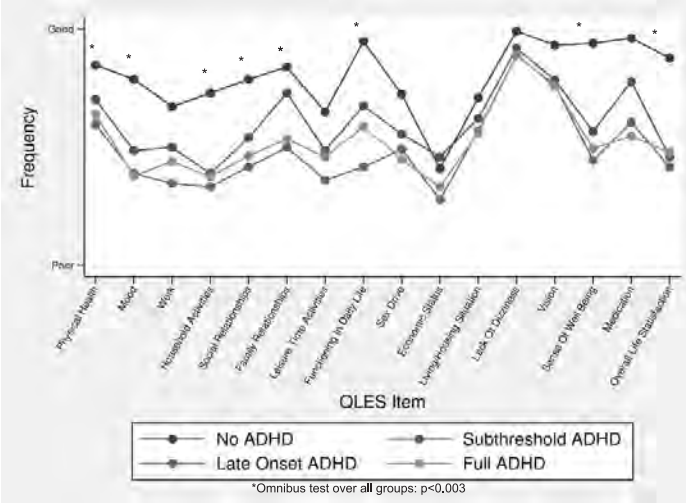
[a] vs. Not ADHD, [b] vs. Subthreshold ADHD
*p≤0.001, **p≤0.01, ***p≤0.05

Quality of Life and Atypical ADHD

Faraone et al., Am J Psychiatry, 2006



Omnibus test: F=15,39, p<0.001; *versus No ADHD



*Omnibus test over all groups: p<0.003

Severity of Subthreshold Adult ADHD

(Karam et al., J Psychiat Research, 2009)

Severity measures	Early-onset (n = 174)	Late-onset (n = 175)	Analysis[b]	
	Mean (±SD)[a]	Mean (±SD)[a]	t	p
Snap-IV scores				
Inattention	1.85 (0.54)	1.78 (0.54)	−1.16	0.240
Hyperactivity	1.60 (0.71)	1.36 (0.72)	−3.18	0.002
Impulsivity	1.65 (0.84)	1.48 (0.88)	−1.89	0.059
ODD	1.06 (0.61)	0.81 (0.51)	−4.11	<0.001
Total	1.52 (0.46)	1.34 (0.48)	−3.65	<0.001
Barkley problem areas				
Self-report last 6 months	1.78 (0.56)	1.64 (0.56)	−8.89	0.374
Family report last 6 months	1.60 (0.64)	1.39 (0.66)	−2.14	0.033

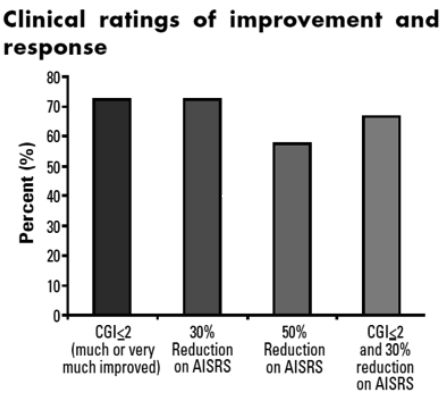
Validating Atypical Forms with Treatment Data

(Faraone et al., Am J Psychiatry, 2006)

- If an atypical form of ADHD is truly ADHD, then patients with atypical ADHD should respond to treatments know to be effective for typical ADHD.

Treatment of Late Onset Adult ADHD with Methylphenidate

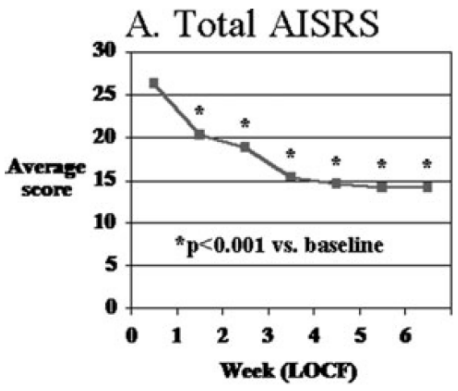
(Biederman et al., CNS Spectrums, 2006)



Open label study of 36 ADHD patients meeting full criteria in adulthood and onset in adolescence.

Treatment of Late Onset Adult ADHD with Atomoxetine

(Surman et al., CNS Neurosci Therapeutics, 2010)



Open label study of 44 late onset ADHD patients and 1 sub-threshold ADHD patient.

Intelligence and ADHD: The DSM-IV View

- In early DSM editions, low IQ was a rule out for ADHD
- DSM-IV: "Symptoms of inattention are common among children with low IQ who are placed in academic settings that are inappropriate to their intellectual ability. In children with mental retardation, an additional diagnosis of ADHD should be made only if the symptoms of inattention or hyperactivity are excessive for the child's mental age."
- DSM-IV gives no guidance for diagnosing ADHD in high IQ people.

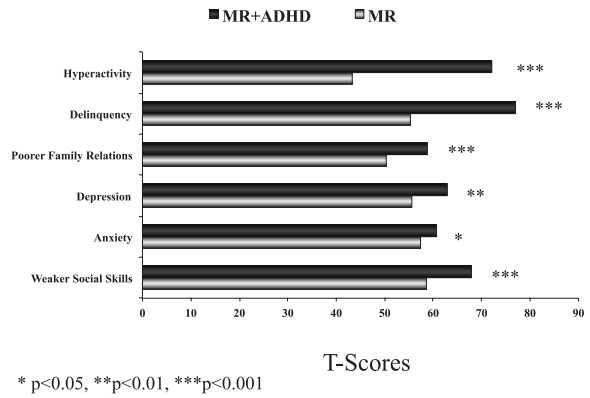
Low IQ and ADHD

(Antshel et al., *Clin Psychology Review*, 2006)

- Relatively little is known about ADHD among low IQ people
- Low IQ ADHD shows similar correlates as ADHD:
  - Core symptoms of ADHD
  - Psychiatric comorbidity
  - Psychosocial and pharmacologic treatment response

Behavioral Symptoms in Children with Mental Retardation vs. Children with Mental Retardation and ADHD

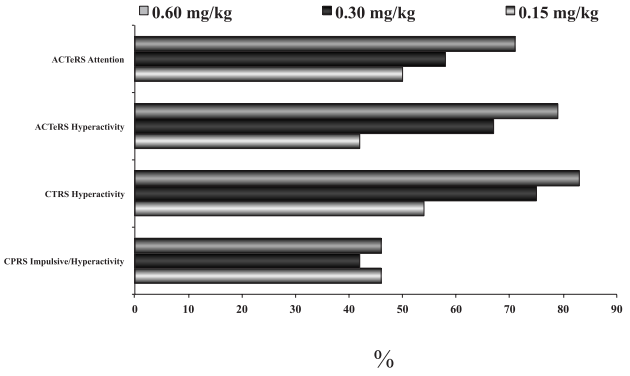
Pearson et al (2000) Am J Mental Retardation 105:236-251



* p<0.05, **p<0.01, ***p<0.001

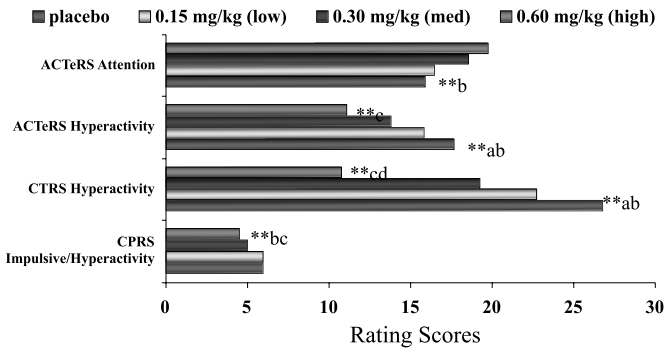
Percentage of MR ADHD Children Showing Any Improvement on Behavioral Ratings on Three Doses of Methylphenidate Relative to Placebo

Pearson et al (2004) J Am Acad Child Adolesc Psychiatry 43:686-698



Effects of Methylphenidate on Behavioral Ratings of MR ADHD Children

Pearson et al (2003) J Am Acad Child Adolesc Psychiatry 42:209-216



* p<0.01, ** p<0.001, a-placebo vs. med, b-placebo vs. high, c-low vs. high, d-med vs. high

High IQ and ADHD

Antshel, Faraone et al., *JCPP*, 2007

- The co-existence of high IQ (IQ > 120) and ADHD is controversial, due, in part, from viewing ADHD as having a substantial cognitive component. (Baum, Olenchak, & Owen, 1998)
- some argue that ADHD among high IQ children is situational and due to boredom fostered by unstimulating environments (Gallagher & Harradine, 1997)
- Prior studies show high IQ ADHD children to have characteristic symptoms and cognitive difficulties (Kaplan et al., 2000; McCoach, 2002).

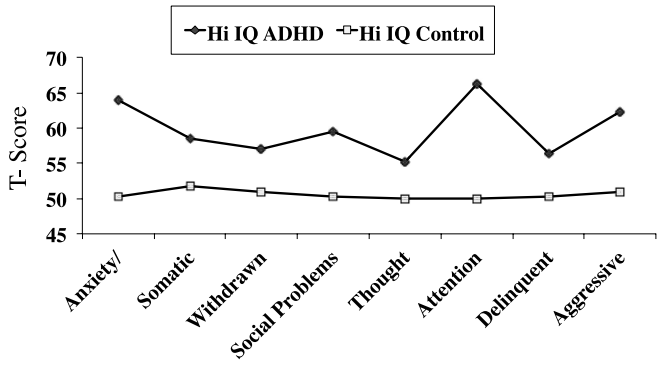
High IQ and ADHD: Studies of Youth

Antshel, Faraone et al., *JCPP*, 2007

- We defined high IQ as having a full scale IQ $\geq$ 120
- We identified 92 children with high IQ who did not have ADHD and 49 with high IQ that had ADHD who had participated in the Massachusetts General Hospital Longitudinal Family Studies of ADHD

Child Behavior Checklist Results

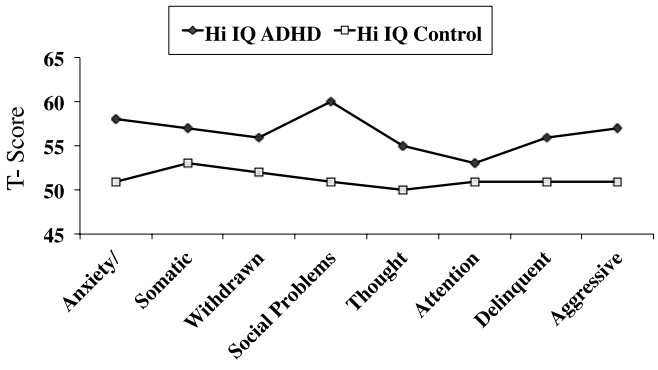
Antshel, Faraone et al., *JCPP*, 2007



CBCL Scale

Child Behavior Checklist at Follow-up

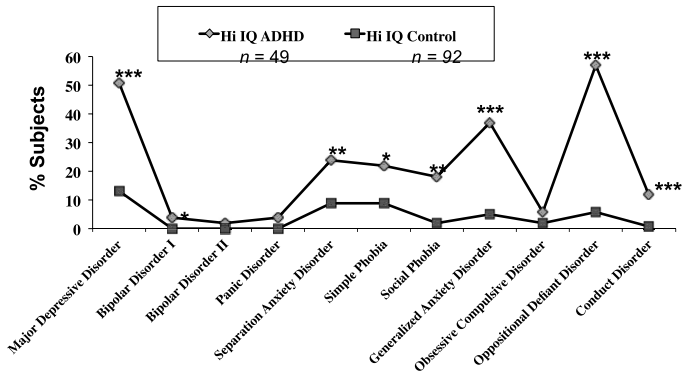
Antshel, Faraone et al., *Psychol Med, 2008*



CBCL Scale

Lifetime History of Psychiatric Disorders

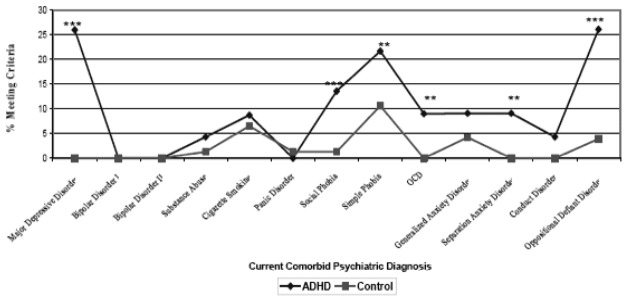
Antshel, Faraone et al., *JCPP*, 2007



* $p <.05$, ** $p < .01$, *** $p < .001$

Lifetime History of Psychiatric Disorders at Follow-up

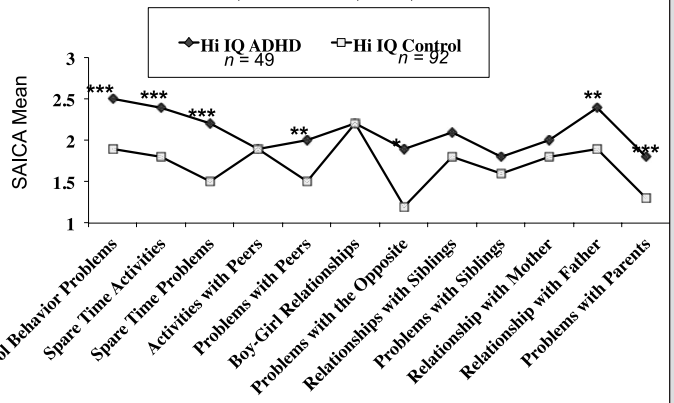
Antshel, Faraone et al., *Psychol Med, 2008*



*** <.001 Level
** <.01 Level

Social Adjustment Inventory for Children and Adolescents

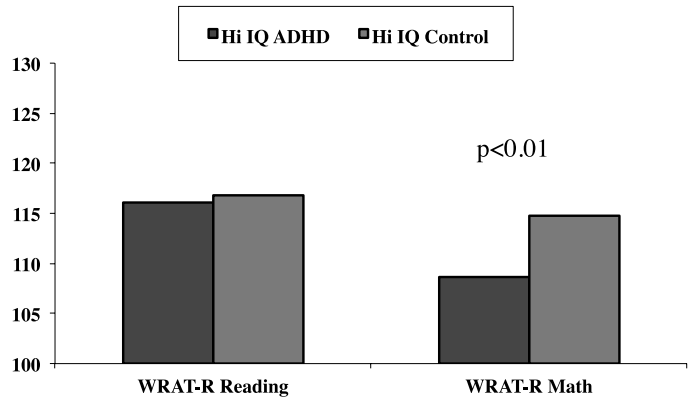
Antshel, Faraone et al., *JCPP*, 2007



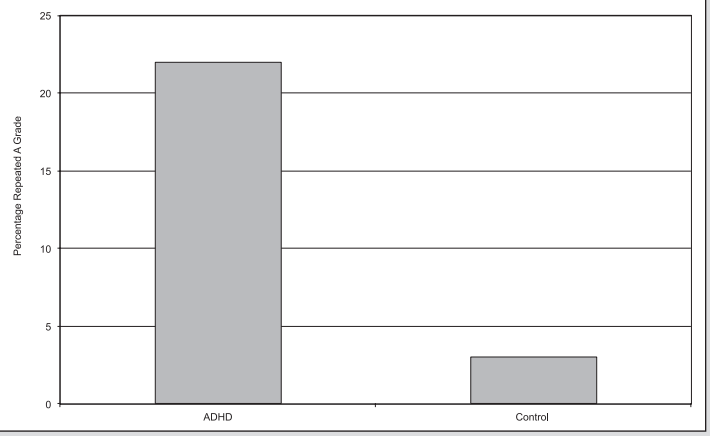
Higher scores indicate worse adjustment * $p <.05$, ** $p < .01$, *** $p < .001$

Achievement in High IQ ADHD

Antshel et al., *JCPP*, 2007

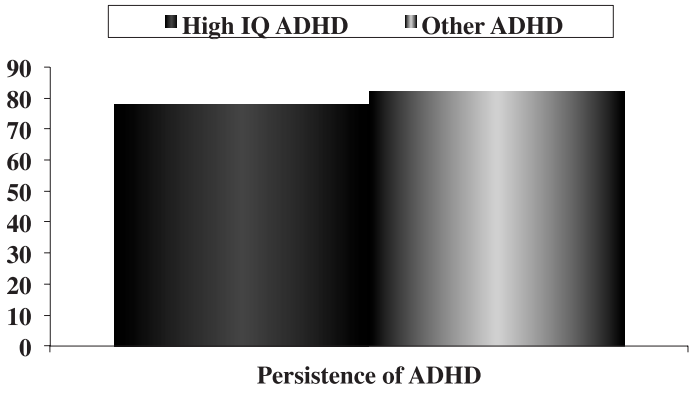


Robins & Guze – Outcomes: Academic Retention rates



Persistence of ADHD at 4 to 5 Year Follow-up

Antshel, Faraone et al., *Psychol Med 2008*

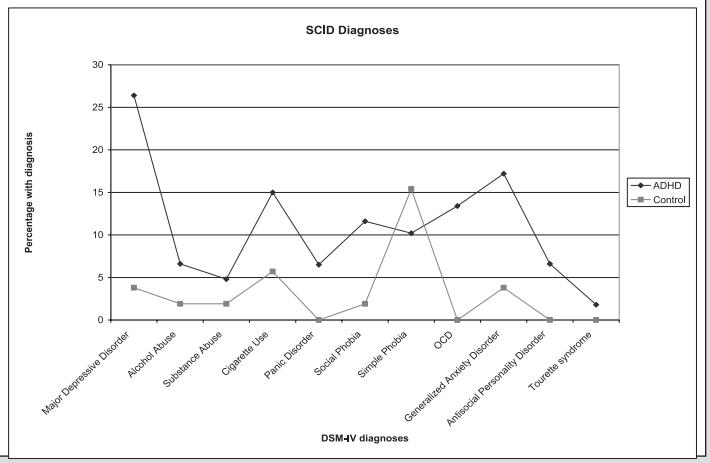


High IQ and ADHD: Studies of Adults

Antshel, Faraone et al., *JCPP*, 2007

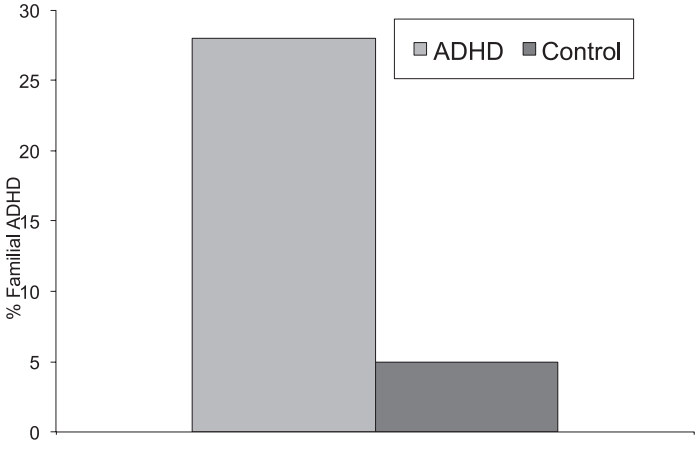
High IQ ADHD Adults: Comorbid Psychiatric Disorders

Antshel, Faraone et al., *JCPP*, 2007



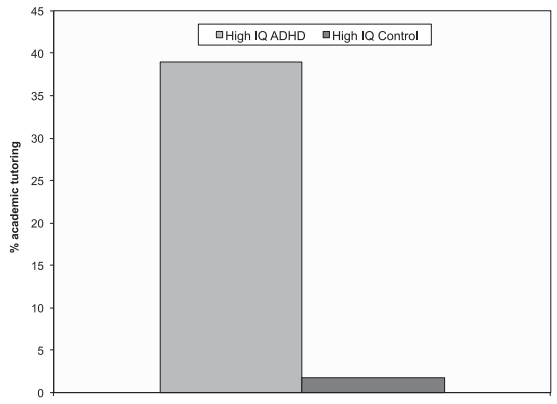
High IQ ADHD Adults: Familial ADHD

Antshel, Faraone et al., *JCPP*, 2007



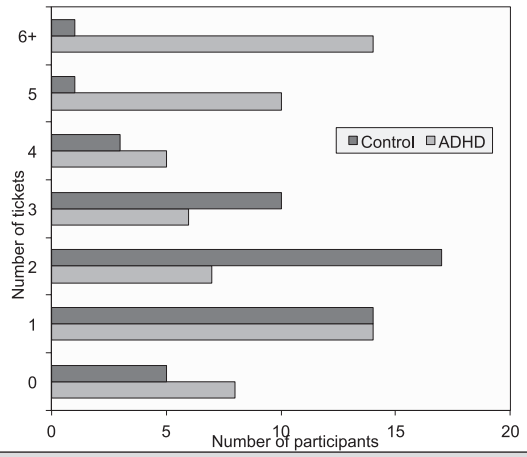
High IQ ADHD Adults: Academic tutoring

Antshel, Faraone et al., *JCPP*, 2007



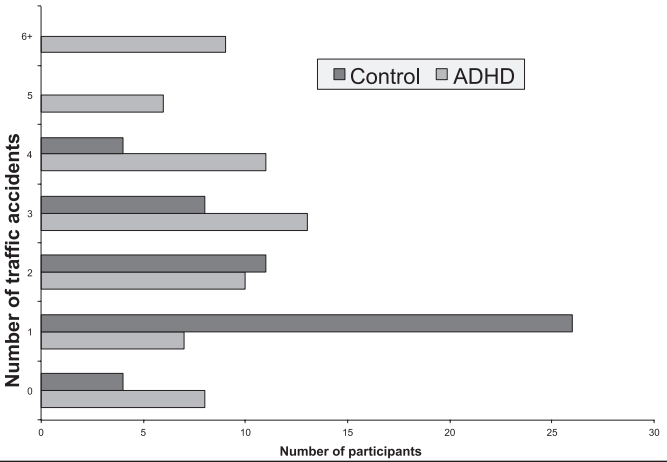
High IQ ADHD Adults: Speeding Tickets

Antshel, Faraone et al., *JCPP*, 2007



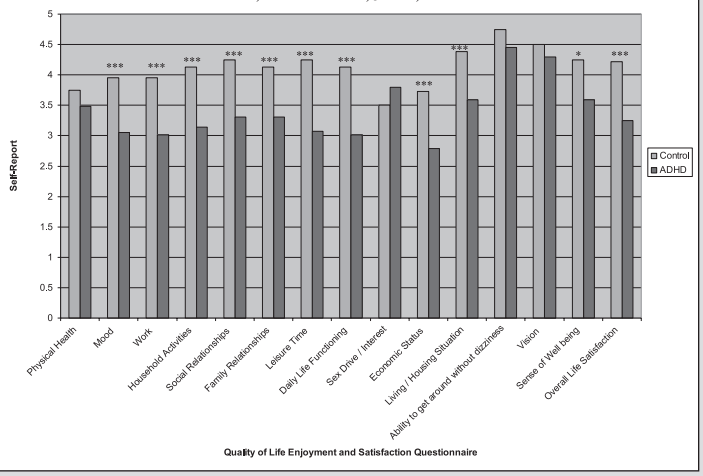
High IQ ADHD Adults: Motor vehicle accidents

Antshel, Faraone et al., *JCPP*, 2007



High IQ Adult ADHD: Quality of Life

Antshel, Faraone et al., *JCPP*, 2007

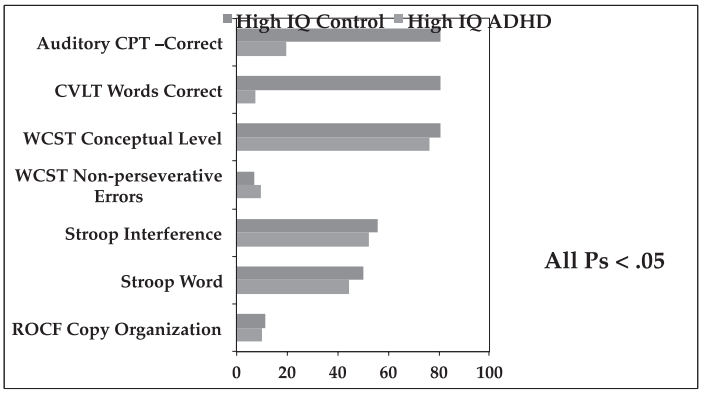


Summary

- *Both children* & *adults* with a high IQ and ADHD show a pattern of familial, cognitive, psychiatric, behavioral and functional features consistent with the diagnosis of ADHD documented in average IQ
- Using Robins & Guze criteria, we believe this is evidence for diagnostic validity

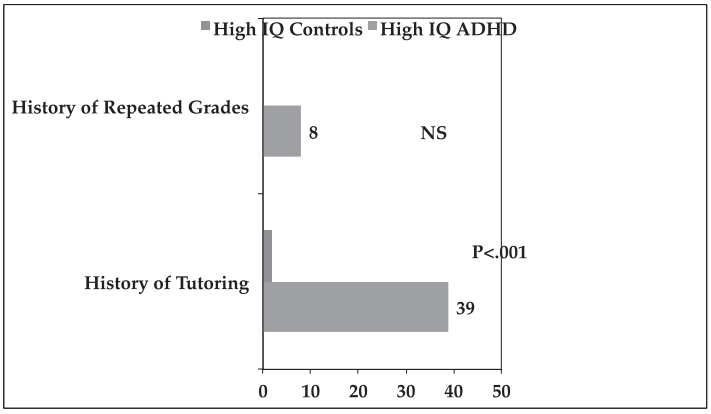
Executive Dysfunction in High IQ ADHD adults

Antshel, Faraone et al., Psychol Med, 2010



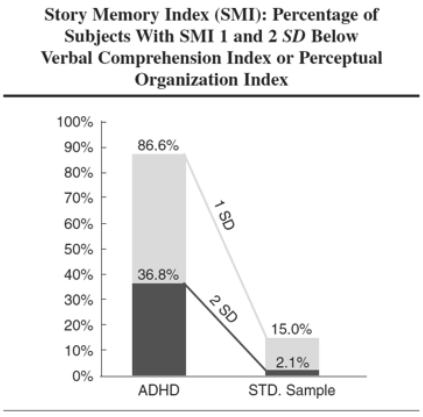
Academic History in High IQ Adults

Antshel, Faraone et al., Psychol Med, 2010



Executive Functioning Deficits in High IQ ADHD Adults

(Brown et al., J Attention Disorders, 2009)



Similar results for working memory and processing speed

Summary: Atypical Forms of ADHD

- Late onset Adult ADHD: Strong evidence for the validity of adolescent onset ADHD.
- Subthreshold Adult ADHD: Evidence for validity is weaker but some cases clearly are valid
- Low IQ ADHD: Poorly studied but some evidence for validity. ADHD symptoms respond to treatment.
- High IQ ADHD: Strong evidence for validity.

Summary: Atypical ADHD in DSM-V

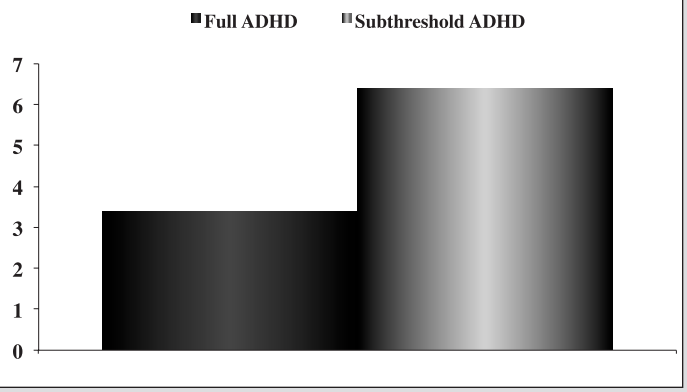
- Late onset ADHD: Adolescent age at onset will be allowed.
- Subthreshold ADHD: A lower number of symptoms will likely abe allowed for adult ADHD
- Low IQ ADHD: Not addressed in criteria
- High IQ ADHD: Not addressed in criteria.

Diagnostic Issues for Subthreshold & Late Onset Adult ADHD

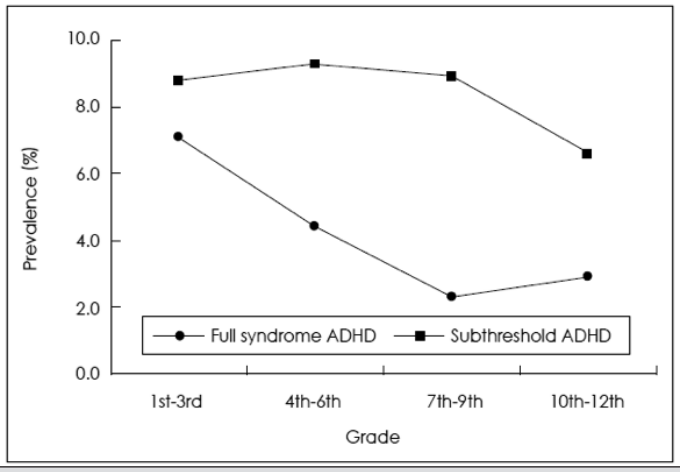
- Difficulty of retrospective recall
- Less severe ADHD
- Supportive, well structured home and school environments
- Self medication
- Subthreshold cases with many symptoms
  - Eg. 5 inattentive & 5 hyperactive-impulsive
- Insensitive diagnostic criteria, e.g. "often leaves seat in classroom…."

Community Study of Full and Subthreshold ADHD in US Adolescents

Lewinsohn et al., Psychol Med 2004



Prevalence of Subthreshold ADHD in Korea
(Kim et al., J Kor Neuropsych, 2009)



Diagnostic Issues for Low IQ ADHD

- For low IQ people DSM requires that symptoms of ADHD are excessive for the child's mental age
- This can be difficult to determine
- Another approach is to document that the symptoms of ADHD lead to impairing behaviors
- Symptoms should cause impairment in two or more settings.

Diagnostic Issues for High IQ ADHD

- For high IQ people DSM does not require that symptoms of ADHD are excessive for mental age. Should it?
- Impairment can be seen in gap between potential and performance
- Assess compensatory behaviors
  - Working overtime to compensate for ADHD symptoms
  - Avoiding tasks requiring concentration
  - Avoiding sedentary tasks
- Assess compensatory resources
  - creativity
  - high intelligence

Caution: IQ is Only Modestly Predictive of Performance

- 25% of the variance for concurrent achievement and grade performance
- 30% of the variance for total years of education
- 20% of the variance for job performance
- 25% of social status variance
- 16% of income variance

Sources: (Neissier et al., 1996; Sternberg, 2001)

Caution: High Educational Achievement is Rare: Professional degrees conferred by all US institutions for 1994-1995

	Total Number	Percent of Population 25-34 years old*
Dentistry (D.D.S. or D.M.D.)	3897	0.01%
Medicine (M.D.)	15537	0.04%
Optometry (O.D.)	1185	0.00%
Veterinary medicine (D.V.M.)	2148	0.01%
Chiropractic (D.C. or D.C.M.)	2968	0.01%
Law (LL.B. or J.D.)	39349	0.10%
Other	75	0.00%
Total, all institutions	75,800	0.19%

* The total population of individuals between 25 and 34 during this year was approximately 40 million.

Clinical Implications

- Ergo….High IQ ≠ 4.0 GPA or other markers of academic success
- Assess functional impairments outside of school

Postscript: Impairment & Atypical ADHD

- DSM requires that ADHD symptoms cause "clinically significant" impairment but gives little guidance otherwise
- Should impairment be defined as:
  - Absolute, i.e., lowest 5% of the population?
  - Relative to IQ or other index of ability?
  - Relative to educational cohort?
- How define impairment for resource allocation/accommodation decisions?

Summary

- Atypical forms of ADHD show evidence of validity in the sense that they are variant forms of ADHD that likely share risk factors and neurobiological features with the "gold standard" form of the disorder.
- Diagnosing atypical forms in clinical practice requires caution and a comprehensive assessment of impairment

Thanks for Listening!

Attention Deficit Hyperactivity Disorder Across the Life Span

FRIDAY MARCH 15, 2013

EVENING SEMINARS

Friday, March 15, 2013

6:30PM – 7:30PM

Evening Seminars

1. **Management and assessment of ADHD in college students with ADHD**
Jefferson Prince, MD

2. **Management of the Complex Adult Patient with ADHD**
Craig Surman, MD

Management and Assessment of ADHD in College Students with ADHD

Jefferson Prince, MD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

Assessment and Management of ADHD in College Students

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Massachusetts General Hospital
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Disclosure

Neither I nor any member of my immediate family has a significant financial interest or affiliation with any manufacturer of commercial product(s) or provider(s) of commercial services discussed in my educational presentations for MGH Psychiatry Programs in 2013.

Available Guidelines & Reviews

- American Academy of Child and Adolescent Psychiatry (**Pliszka SR, et al. *J Am Acad Child Adolesc Psychiatry.* 2007;46:894-921).**
- Canadian ADHD Practice Guidelines, Third Edition, Toronto ON; CADDRA, 2011.
- European consensus statement on diagnosis and treatment of adult ADHD: The European Network Adult ADHD (Kooij et al. BMC Psychiatry 2010, 10:67).

Drowned in a Stream of Prescriptions

By Alan Schwarz New York Times February 2, 2013

Before his addiction, Richard Fee was a popular college class president and aspiring medical student. "You keep giving Adderall to my son, you're going to kill him," said Rick Fee, Richard's father, to one of his son's doctors.

ADHD in the College Student: Is Anyone Else Worried?

- Are symptoms context specific? Due to phase of LIFE?
- Why are you in college?
- Do demands of (this) college exceed abilities?
- How aligned are your goals, talents, strengths and weaknesses?

"The patient is the one with the disease. [And the doctor must survive.]" The Fat Man, 4th Law of the House of God. **The House of God** by Samuel Shem

Diller, L. J Attention Disorders 2010 14 (3): 3-6.

Towards responsible use of cognitive enhancing drugs by the healthy

"Like all new technologies, cognitive enhancement can be used well or poorly. We should welcome new methods of improving our brain function. In a world in which human workspans and lifespans are increasing, cognitive enhancement tools — including the pharmacological — will be increasingly useful for improved quality of life and extended work productivity, as well as to stave off normal and pathological age-related cognitive declines. Safe and effective cognitive enhancers will benefit both the individual and society. But it would also be foolish to ignore problems that such use of drugs could create or exacerbate. With this, as with other technologies, we need to think and work hard to maximize its benefits and minimize its harms.

Greely H et al., Nature (2008) 456: 702-705.

ADHD in College Students: A "Double-Deficit" in Self-Regulation

- College Brings
  - Increase in demands
  - Loss of structure
  - Loss of previously provided supports
- Interaction between EF Development, Motivational Systems and Task Demands.
- Effective Interventions supports self-regulation by:
  - Increasing external supports
  - Decreasing challenging contextual factors

Prevalence ADHD in College Students

- Estimates between 2-8%
  - based on self-report scales or diagnostic status
- US, Italy and New Zealand (N=1,209)
  - 2.9%-8.1% of Men; 0-3.9% of Women; self-report
- UK Undergrad Psychology Students; (N=1,182)
  - 6.9%; Conners' Adult ADHD Rating Scale
- College ADHD Response Evaluation (CARE)
  - 7.5% ≥6 Sx ; but didn't assess additional criteria
- What if you ask about current diagnosis?
  - 3,400 students, 2 Universities; 4.5%; 6.6% private, 2.5% public
- American Freshman: National Norms 2010
  - 201,818 students in 279 Full-time Institutions
  - 5.0% (6.4% M, 3.8% F; Lower 3.8% in Traditionally 'Black Colleges'

Dupaul GJ et al. J Atten Disord 2009;13:234-250
Dupaul GJ et al., J Learn Disabil 2001;34: 370-379
Pope et al., Psychology Learning & Teaching 2007; 6 114-120
Gluting J et al., CARE College ADHD Response Evaluation Manual. Wilmington, DE: Wide Range Press; 2002
Pryor JH et al., The American freshman: national norms 2010. Higher Education Research Institute at UCLA; 2011.

Screening for ADHD in Adults

- World Health Organization (WHO) Adult Self Report Scale (Available in many languages)
  - 6- and 18- question versions, available for free at http://www.hcp.med.harvard.edu/ncs/asrs.php
- Developmental screen: Did you have difficulty with these problems before you entered puberty?
- Impairment screen: Are these symptoms causing difficulty in your life right now?
- Positive result → full psychiatric assessment for ADHD

CADDRA Guidelines Steering Committee. *Canadian ADHD Practice Guidelines.* http://www.caddra.ca/joomla/index.php?Itemid=70

Some Diagnostic Recommendations in College Students

- ≥4 Symptoms of inattention and/or hyperactivity/impulsivity Clusters; present and cause impairment currently.
- Onset prior to 12 yo AND contribute to impairments in multiple areas across lifespan.
- Seek 3rd party corroboration of Symptoms, impairment AND corroboration that impairment best accounted for by ADHD rather than another disorder or context.

McGough JJ, Barkley RA. Diagnostic controversies in adult attention deficit hyperactivity disorder. Am J Psychiatry 2004:161:1948-1956.

Considerations in Assessment of ADHD in College Students

- Observation at interview: may not manifest behavior
- Rating scales: useful for diagnostic confirmation
- Psychological/neuropsychological testing
  - Not diagnostic, but evidentiary
  - Useful for IQ estimation, learning disabilities or strategies
- Malingering
- Assessment of Physical Health (helpful to communicate with PCP).

Murphy K, Barkley RA. J Atten Disord 1996;1:147-161
Sullivan, BK et al., Appl Neuropsychol 2007;14:189-207
Rabiner DL et al., J Atten Disord 2009;13:259-270
Green P et al., . J Forensic Neuropsychol 2002 ;2:97-124
Suhr J et al. Arch Clin Neuropsychol 2008;23:521-530
Sollman MJ et al. Psychol Assess 2010:22:325-335
Booksh RL et al. J Atten Disord 2010;13:325-338
Jasinski LJ et al., Clin Neuropsychol 2011;25:1415-1428

Theories of Neural Networks in ADHD

- **The frontal-striatal circuit:** Associated with deficits in response suppression, freedom from distraction, working memory, organization, and planning, known as the **"cool" or "what"** EF network
- **The frontal-cerebellar circuit:** Associated with motor coordination deficits, and problems with the timing and timeliness of behavior, known as the "**when**" EF network
- **The frontal-limbic circuit:** Associated with symptoms of emotional dyscontrol, motivation deficits, hyperactivity/ impulsivity, and proneness to aggression, known as the **"hot" or "why"** EF network

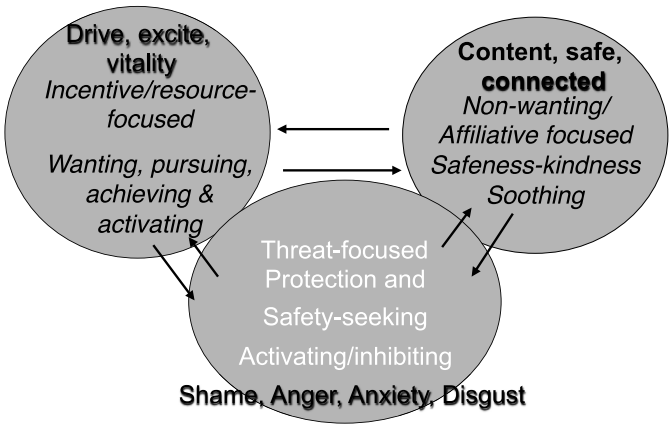
1. Nigg, J. T., & Casey, B. (2005). An integrative theory of attention-deficit/hyperactivity disorder based on the cognitive and affective neurosciences. Development and Psychology, 17, 785-806.
2. Castellanos, X., Sonuga-Barke, E., Milham, M., & Tannock, R. (2006). Characterizing cognition in ADHD: Beyond executive dysfunction. Trends in Cognitive Science, 10, 117-123.
3. Sagvolden, T., Johansen, E. B., Aase, H., & Russell, V. A. (2005). A dynamic developmental theory of attentiondeficit/hyperactivity disorder (ADHD) predominantly hyperactive-impulsive and combined subtypes. Behavioral and Brain Sciences, 28, 397-408.

College Students & ADHD: Academics

- Lower GPAs & More Academic Probation
- Perception of Academic Functioning:
  - *Less confident; more likely need to reread; difficulties finishing timed tests; work harder to receive good grades.*
- More problems using study aids, tests strategies, time management.
- Overall effort (in terms of hours) similar.

Heiligenstein E et al., J Am Coll Health 1999;47:181-185.
Blase SL et al., J Atten Disord 2009;13:297-309.
Advokat C et al., J Atten Disord 2011;15:656-666.
Shaw-Zirt B et al., J Atten Disord 2005;8:109-120.

How do we regulate affect?



P. Gilbert. Defense and safety: their function in social behavior and psychopathology
Br. J. Clin. Psychol., 32 (1993), pp. 131–154

College Students & ADHD: Social Functioning

- Limited data
- Poor Social Adjustment
- Less Developed Social Skills
- Lower Self-esteem
- Expressed concerns @ social relationships
- Didn't perceive self struggling
- Men with inattentive subtype more difficulties
- More aggression in romantic relationships

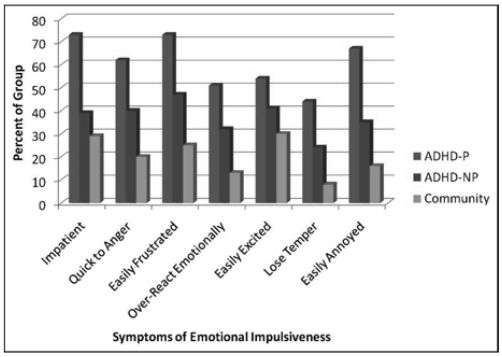
Heiligenstein E et al., J Am Coll Health 1999;47:181-185.
Blase SL et al., J Atten Disord 2009;13:297-309.
Shaw-Zirt B et al., J Atten Disord 2005;8:109-120.
Canu WH et al., J Atten Disord 2003;6:123-133.
Therialt SW et al., Violence Against Women 2001;7:1464-1489.

College Students & ADHD: Psychological Functioning

- Inconsistent results
- Some studies show little, if any differences.
- Others show greater emotional difficulties, distress, depression.
- Most students with ADHD do not report significant difficulties relative to peers.

Heiligenstein E et al., J Am Coll Health 1999;47:181-185.
Blase SL et al., J Atten Disord 2009;13:297-309.
Weyandt LL et al., Dev Neuropsychol 1998;14:643-656.
Wilmshurst L et al., J Atten Disord 2011;15:11-17.
Richards TL et al., J Coll Student Devel 1999;40:299-304.
Richards TL et al., J Atten Disord 2002;6:25-38.

Emotional Impulsivity in ADHD children followed to adulthood



ADHD-P = Persistent ADHD, ADHD-NP = Nonpersistent ADHD
From Barkley, R., Murphy, K. & Fischer, M. (2008). ADHD in Adults: What the Science Says. New York: Guilford

College Students & ADHD: Substance Use

- Most data shows increased use of:
- Tobacco: Self Medicating?
- ETOH
- Marijuana (2.5x more likely use past year)
- Other Drugs (6x more likely use past year)
- Doesn't appear due to Conduct Disorder

Blase SL et al., J Atten Disord 2009;13:297-309.
Upadhyaya HP et al., J Child Adolesc Psychopharmacol 2005;15:799-809.
Meaux, JB et al., J of Psych Men Health Nurs 16, 248–256.
Baker L et al., J Atten Disord 2012;16:255-263.
Conner BT, Lochman JE. Clin Psychol: Sci Pract 2010;17:337-349.
Wasserstein J. J Clin Psychol 2005;61:535-547.
Barkley RA et al. JAACAP 1990;29:546-557.
Rooney M et al., J Atten Disord 2012;16:221-234.

College Students, ADHD & Alcohol:

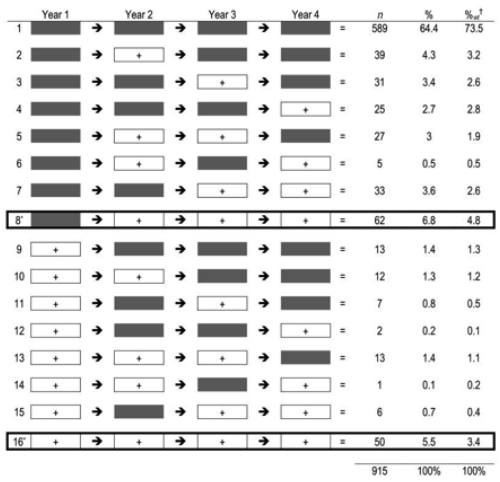
- Feels less in control of drinking; trouble stopping;
- Treatment with stimulants reported more problematic drinking vs. not treated;
- "triple vulnerability"
  1. *ADHD increases Risk of ETOH Use*
  2. *Developmental Stage (18-24 yrs)*
  3. *Context of College: Social life, expectations, away from home for first extended time*

Rooney M et al., J Atten Disord 2012;16:221-234
Upadhyaya HP et al., J Child Adolesc Psychopharmacol 2005;15:799-809

Misuse of ADHD Prescription

- 45% reported misusing medication for ADHD; M=F
- Alternative route of administration (27.9%)
- Higher dose than prescribed (62.8%)
- Mixing with drugs/alcohol to feel intoxicated (23.3%)
- Giving away and/or selling their medication (48.8%)
- Prescription for Amphetamine (69%) or MPH (31%)
- Prescribed
  - *extended release capsules (68%)*
  - *immediate release tablets (32%)*

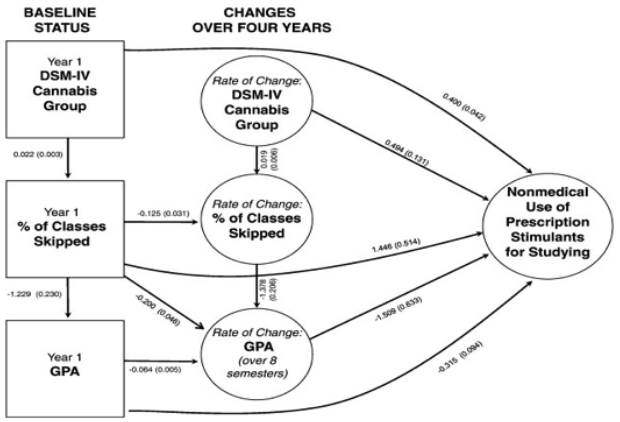
Jardin B et al., Journal of American College Health 2011 59(5): 373-377



Patterns of nonmedical use of prescription stimulants across four years of study

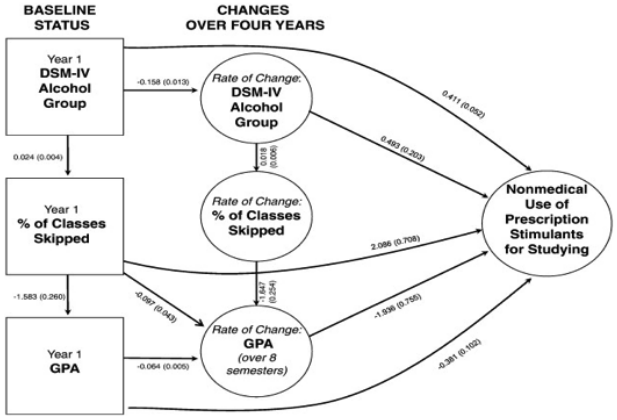
Aria AA et al., J Atten Disord. 2011 July; 15(5): 347–356

Cannabis Use Predicts Nonmedical Use of Prescription Stimulants for Studying



Arria , AM et al. Addictive Behaviors 2013 38 (3):1643 - 1650

Alcohol Use Predicts Nonmedical Use of Prescription Stimulants for Studying



Arria , AM et al. Addictive Behaviors 2013 38 (3):1643 - 1650

Caffeine and Illicit/prescription Stimulants for Cognitive Enhancement.

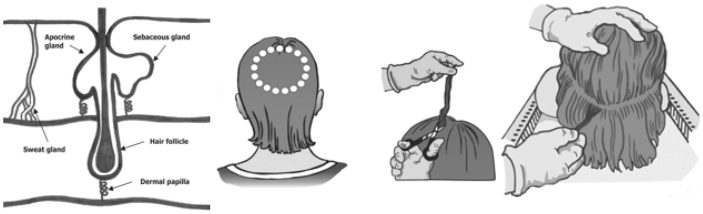
- Dimensions: medical, ethical and legal
- 44% there is a difference between caffeine and illicit/prescription stimulants for CE, 28% did not differentiate, 28% could not decide.
- 39% stated that there is a moral difference, 56% answered that there is no moral difference.

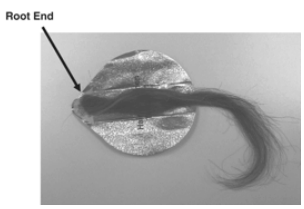
Franke AG, Lieb K, Hildt E. PLoS One. 2012;7(6):e40047

Urine Toxicology

Substance	Half-life (hrs)	Detection After Last Use (days)
Amphetamines	10-15	1-2
Barbiturates	20-96	3-14
Benzodazepines	20-90	2-9
Cocaine	0.8-6	0.2-4
Methaqualone	20-60	7-14
Opiates	2-4	1-2
Phenocyclodine	7-16	2-8
Cannabinoids	10-40	2-8 (acute) 14-42 (chronic)

AACAP Practice Parameter For The Assessment And Treatment Of Children And Adolescents With Substance Use Disorders 2004





Gail Audrey Ann Cooper. Hair testing is taking root *Ann Clin Biochem November 2011 48:516—530;*

Treatment of ADHD in College Students: Medications

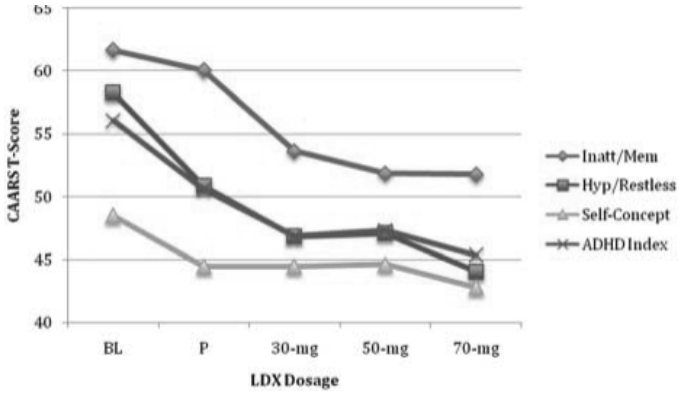
- How to measure response?
  - *Rating Scales or Anchor Points (functioning)*
- How to ensure safe storage?
- Sources of Information?
  - *Patient or Patient Plus*
- Dosing to cover schedule from AM thru PM
- Combining Immediate Release and Extended Delivery Stimulants
- Regular Schedule vs. “as needed”
- Adapting Dosing to Various Contexts

Medications FDA Approved for Treatment of ADHD

Medication	Usual Starting Dose	FDA Approved Daily Dose	Off-Label Max per Day*
Methylphenidate Preparations			
Short-acting			
MPH	5 mg bid	60 mg	>50 kg; 100 mg
Dex-MPH	2.5 mg bid	20 mg	50 mg
MPH	5 mg bid	60 mg	>50 kg; 100 mg
Intermediate-acting			
MPH SR	10 mg qd	60 mg	>50 kg; 100 mg
MPH ER	10 mg qd	60 mg	>50 kg; 100 mg
MPH CD	10 mg 1d	60 mg	>50 kg; 100 mg
MPH LA	20 mg 1d	60 mg	>50 kg; 100 mg
Long-acting			
Dex-MPH-XR	5 mg qd	60 mg	50 mg
MTS*	10 mg qd	30 mg	Not yet known
OROS-MPH	18 mg qd	72 mg	108 mg
Amphetamine Preparations			
Short-acting			
D-amphetamine or MAS	2.5-5 mg qd or bid	40 mg	>50kg; 60 mg
Long-acting			
MAS XR	10 mg qd	30 mg	>50kg; 60 mg
LDX	30 mg qd	70 mg	Not yet known
Dexedrine Spansule	5-10 mg qd or bid	40 mg	>50kg; 60 mg
Atomoxetine	< 70 kg: 0.5 mg/kg/day for 4 days; then 1 mg/kg/day for 4 days; then 1.2 mg/kg/day	Lesser of 1.4 mg/kg/ day or 100 mg	Lesser of 1.8 mg/kg/day or 100 mg
Guanfacine XR	1 mg	4 mg	Not yet known
Clonidine XR	0.1 mg	0.4 mg	Not yet known

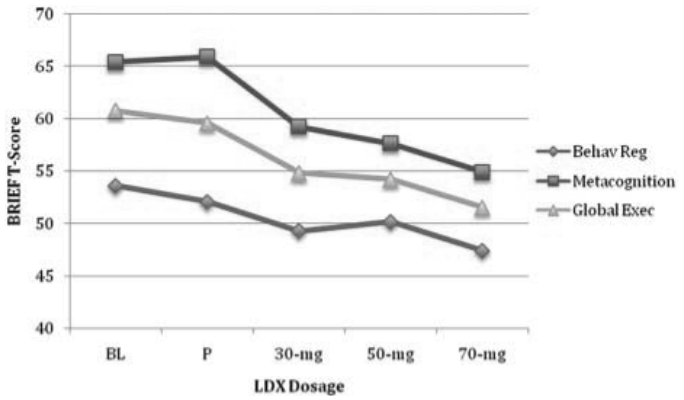
MAS=mixed amphetamine salts; MTS=methylphenidate transdermal system; LDX=lisdexamphetamine.
AACAP ADHD Practice Parameters. *JAACAP*. 2007;46:894-921. *recommended max daily dose.

A lot better but not well…



Dupaul GJ et al., J Atten Disord. 2012 Apr;16(3):202-20

A lot better but not well…



Dupaul GJ et al., J Atten Disord. 2012 Apr;16(3):202-20

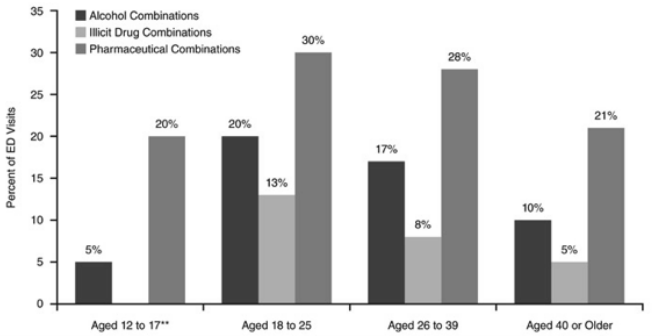
Pharmacokinetic Profiles of Medications for ADHD

- Single Camel Hump
  - *Ritalin, Focalin, Adderall, Dexedrine tablet*
- Double Camel Hump
  - *Adderall XR, Focalin XR, Ritalin LA*
- Ascending
  - *Concerta (22:78), Metadate CD (30:70), Daytrana, Vyvanse, Dexedrine Spansule*
- Flat
  - *Ritalin SR, Methylin ER*

Stimulants – Additional Considerations

- Dietary caffeine: recommend decrease in consumption to avoid over-stimulation
- Nicotine: similar caution
- Alcohol: toxic interactions not usually seen at mild/ moderate doses, but normal response to alcohol may be altered
- Decongestants (e.g. pseudoephedrine): should reduce dosage or stop stimulant for duration of use
- Diet: should be adjusted to avoid significant weight loss [i.e. not good diet medications!]
- Sleep is Necessary

Emergency Department Visits Involving Energy Drink Combinations* 2004 to 2009



* Visits involving energy drinks only are not shown. Because each visit may involve multiple drugs, the percentages may not add to the total.
** The percentage for illicit drug combinations was suppressed for visits made by patients aged 12 to 17 because of low statistical precision.
Source: 2004 to 2009 SAMHSA Drug Abuse Warning Network (DAWN).

Treatment of ADHD in College Students: Psychosocial Treatment

- No Empirical Studies in college students
- CBT
- Meta-Cognitive Therapy
- Mindfulness
- Coaching

Ramsay JR, Rostain AL. J Coll Student Psychother 2006;21:3-20
Safren SA et al. Behav Res Ther 2005;43:831-842
Solanto MV et al., Am J Psychiatry 2011;167:958-968
Swartz SL et al., Psychol Sch 2005;42:647-656
Parker DR et al., J Atten Disord 2011

Treatment of ADHD in College Students: Academic Accommodations

- Examples: Additional time for assignments and tests; distraction-reduced test settings;
- 60% not offered adequate accommodations;
- 55% with access to accommodations reported not using;
- < 1/3 of students with ADHD enrolled in foreign language courses used accommodations;
- Why? "not wanting" or "unnecessary" or "unaware it's available"
- No studies in college students about effect of accommodations.

Wolf L et al., Ann NY Acad Sci 2006;931:385-395
Sparks RL et al., J Learn Disabil 2004;37:169-178
Chew BL et al., J Atten Disord 2009;13:271-276

ADHD Subtypes & Academic Style: How best to engage?

- ADHD, combined type: Learning that is game like, competitive and leading to public recognition.
- ADHD, inattentive type: Strategies that facilitate cooperative learning and feedback.
- ADHD compared with LD: Those with ADHD showed more difficulty with time management, concentration, selection of main idea and test taking strategies.

Carlson CL et al., J of Learning Disabilities. (2002) 35:104-113.
Reaser A et al., Psychology in the Schools. (2007) 44: 627-638.

Executive Functions: "Oh Mighty ISIS"

- Initiate ~ getting started
- Sustain ~ sticking to it
- Inhibit ~ just this
- Switch ~ flowing well

"Getting and keeping your act together."

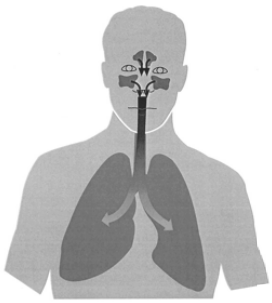
Adapted from Martha B. Denckla, M.D.

Strategies for Improving Executive Control Include:

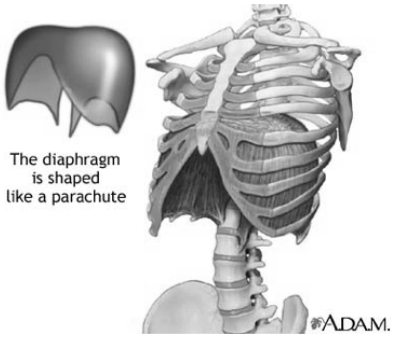
- Mindfulness Practices
- Externalizing Higher-Level Executive Processes
- Reducing Distracting Stimuli
- Amplifying Relevant Stimuli
- Addressing Executive Function Deficits
  - *Working Memory*
  - *Delay Aversion*

Fleming AP, McMahon RJ. Developmental Context and Treatment Principles for ADHD Among College Students. Clin Child Fam Psychol Rev (2012) 15: 303-329.

The Breath…



Slow, Long, Even, Deep, Smooth and Nasal



1. **Time**
2. **Texture**
3. **Space**
4. **Rest**

Strategies for Addressing Deficits in Motivation Include:

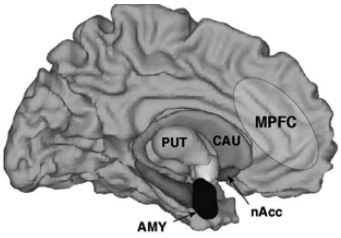
- Motivational Interviewing
- Structuring Contextual Factors
- Establishing External Reinforcement Contingencies
- Pros/Cons Working Towards Long-term Rewards
- Addressing Temporal Processing Deficits

Fleming AP, McMahon RJ. Developmental Context and Treatment Principles for ADHD Among College Students. Clin Child Fam Psychol Rev (2012) 15: 303-329.

Choice is Desirable

"Try not. Do. Or do not. There is no try." Yoda

Medial Left Hemisphere



Choice Opportunity

↑Reward Experience (↑Striatum)

↑ Self Relevance (↑Medial PFC)

Choice (Threat Context)

↑Cognitive Control of Emotion (↑Medial PFC)

↓Negative Affect (↓AMYGDALA)

Leotti LA et al., "Born to choose: the origins and value of the need for control" Trends in Cognitive Sciences, October 2010, Vol. 14, No. 10 457-463

Effective Communication Enhances Adherence

- Styles
  - Follow
  - Direct
  - Guide
- Skills
  - Asking
  - Listening
  - Informing

College Academic Specific Skills

- Time Management
  - *Review each syllabus and mapping out semester*
  - *Join Study Groups*
- Selecting Main Ideas
  - *RAP: R-read a paragraph; A-ask what the main ideas are; P-put ideas in own words*
- Test-Taking Strategies

Schumaker, J. B., et al., (1984). The paraphrasing strategy. Univ of Kansas
Allsopp, DH et al., (2005) Learning Disabilities Res & Prac, 20, 103–118

Cultivating Healthy Functioning in College Students with ADHD

- Sleep
  - *DFA, Restless sleep, Periodic leg mvts, sleep-disordered breathing; SE of Stimulants; SUD*
  - *Sleep Hygiene; CBT-Insomnia; Melatonin;*
- Physical Activity
  - *Regular vigorous activity improves EF, with or without Stimulants.*

Gau, SS et al., (2007) Sleep, 30, 195–201.
Medina, JA et al. (2010) Attention Deficit and Hyperactivity Disorders, 2, 49–58
Singleton, R. A., Jr, & Wolfson, A. R. (2009) J Stud Alcohol Drugs, 70, 355–363

Treatment Planning & Risk Management

"If it's not written, it may not have happened"

Document

1. **Clinical assessment and diagnosis**
2. **Clinical judgment which is the basis for the treatment recommendations**
3. **Communication sessions with patient (and family?) about impression(s) & recommendations**
4. **Ongoing Process of informed consent**

"Never worry alone!!!"
Taught to me by Ron Schouten, MD, JD

Management of the Complex Adult Patient with ADHD

Craig Surman, MD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

Managing Complex Challenges in Adults with ADHD: With Focus on Self-Regulation

Craig B.H. Surman, MD

Adult ADHD Research Program
Massachusetts General Hospital
Harvard Medical School

Lifetime Disclosures

Speaking / Education

- McNeil, Janssen, Janssen-Ortho, Novartis, Shire and Reed/ MGH Academy (funded by multiple companies)

Consulting

- McNeil, Nutricia, Takeda, Shire, Somaxon

Research Support, MGH Adult ADHD Program

- National Institutes of Health, Abbot, Cephalon, Hilda and Preston Davis Foundation, Eli Lilly, Magceutics, J & J / McNeil, Merck, Nordic Naturals, Nutricia, Pamlab, Pfizer, Organon, Shire, and Takeda

Dr Surman also receives royalties from:

Springer (Humana) for:
ADHD in Adults:
A Practical Guide to Evaluation and Management

&

Penguin (Berkeley) for:
FAST MINDS:
How To Thrive If You Have ADHD
(or think you might)

Typical Concern in Simple ADHD

"I have trouble getting around to, sticking with and finishing things"

DSM-IV ADHD in Adults

1) 6+ inattentive +/- impulsive / hyperactive symptoms:
2) Some related symptoms caused impairment since before age 7
   - onset by age 12, 4 current symptoms
   - = similar phenotype
3) Impairment in 2 or more settings
   - (school, work, home)
4) Clinically significant impairment
   - (social, academic, occupational)
5) Not explained by another disorder (other compromise of brain function)

American Psychiatric Association. *DSM-IV*. 4th ed. Arlington, Va: APA; 1994.[5]

No ADHD without related Impairment

Evaluate the burden of symptoms
- Does it show up differently in roles or contexts?
- Is it an effort to compensate for?

Consider impairment relative to potential
- How would individual function if symptoms resolved?

Is there mismatch with role/environment?
- Would change in role or environment remedy?

Is concern exaggerated?
- "workaholic" "perfectionistic" or fearful expectations vs. a burden limiting ability to self-actualize / thrive

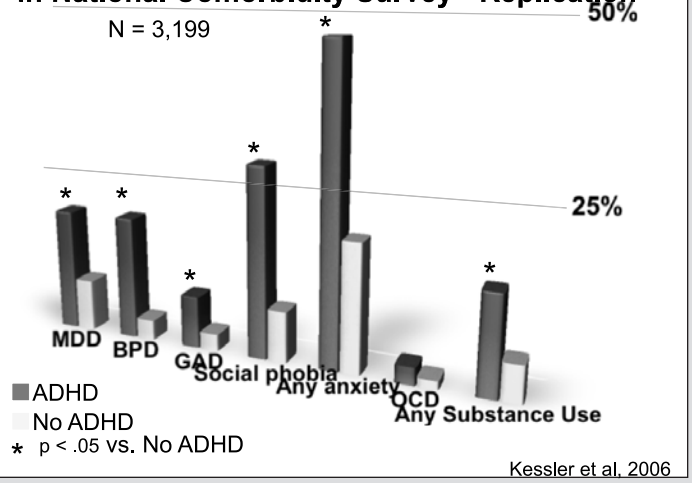
Accommodate, don't Enhance

Identification of ADHD in Complex Presentations

Typical Concern in Comorbid ADHD

"I do not feel or function like I used to - I don't feel like myself"

12 Month Comorbidity in 18-44 Year Old Adults in National Comorbidity Survey - Replication



Kessler et al. 2006

Identifying ADHD with Comorbidity

Identify all conditions compromising function
- Comprehensive evaluation - 3rd party helps
- Neuropsychological evaluation of learning/processing
- Frequent visits/ team treatment - get to know them!!

Learn their "States" vs. "Traits"

Symptoms of ADHD overlap with other disorders
- Resolution of comorbidity may reveal ADHD

Timecourse helps differentiate
- ADHD starts earlier than most disorders
- ADHD symptoms persistent, context highlights (eg: school vs. vacation)

Differential Diagnosis example: Bipolar Disorder

Overlap:

Core symptoms:

distractibility, motor hyperactivity, talkativeness

Associated traits:

irritability, low frustration tolerance

Differences (it is a mood disorder!):

- impairing mood, hypersexuality, impaired judgement, grandiosity

Similar rates in child and adult ADHD?

(eg: Biederman, Am J Psych 2002 and Psych Res 2004)

Characterize Any Mental Compromise eg: Anxiety

- Understand what preoccupies the patient + how often - is it a distraction source?
- Concern / obsessive behavior may be compensatory
- Anxious ADHD children: lower impulsivity, worse inattention, poorer working memory

Greater school, spare-time, interpersonal problems (Newcorn et al 2001; Barkley, ADHD Handbook 2006, Biederman J et al, 1993)

Conditions not to miss: Potential Contraindications to ADHD Pharmacotherapy*

- Cardiac disorder (by cardiac exam, history)
  - Structural heart defect, arrhythmia
  - Family history of sudden early death
- Untreated hypertension
- Recent substance use disorder
- History of psychosis or mania
- Narrow angle glaucoma
- Seizure or Tic disorder
- Recent MAOI use

*consultation, treatment, and/or monitoring may allow safe ADHD management

Self-Regulation 'Executive' Challenges Beyond the Core Symptoms of ADHD:

Control of Engagement across roles and over time

Typical Complaint:

"I don't do the right things

at the right time or keep healthy routines"

(Occurs in other disorders)

Executive Function Deficits (broad category of disorganization)

Neuropsychologically Defined:

EFD in 31% of ADHD vs. 16% of non-ADHD

ADHD+EFD: lower education, occupation, and socioeconomic status than non-ADHD

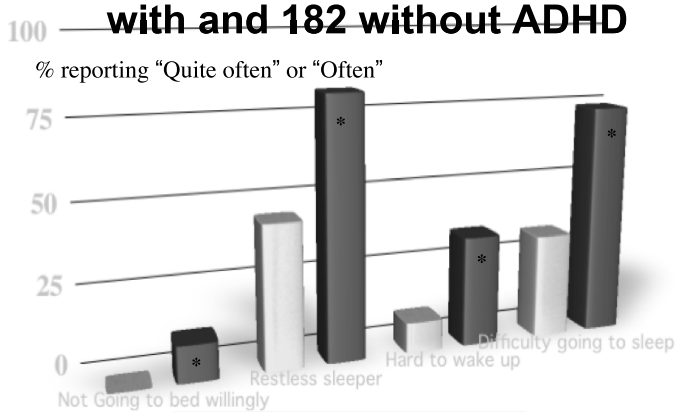
Control+EFD more likely to have repeated a grade

Behaviorally defined

eg. BRIEF-A, Barkley scales - more ecological

Biederman et al, Am J Psychiatry 2006

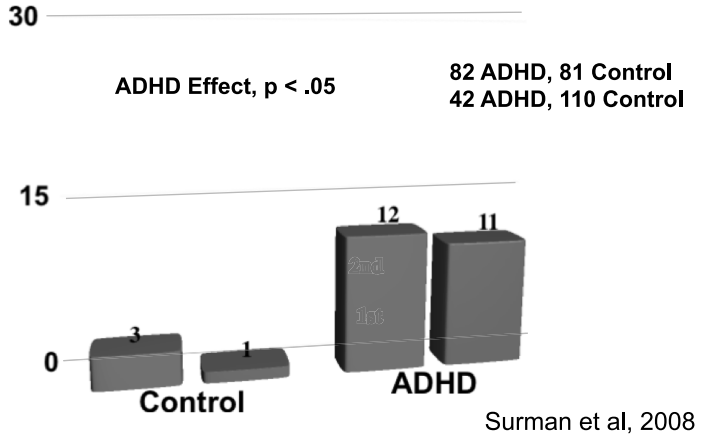
Sleep Dysfunction in 182 Adults with and 182 without ADHD



*p<0.01; Not accounted for by Axis I comorbidity

Surman et al, 2009

Exacerbation of Comorbidity: Lifetime Bulimia Nervosa in Two Female Cohorts



Surman et al, 2008

Deficient Emotional Self Regulation (DESR) Items

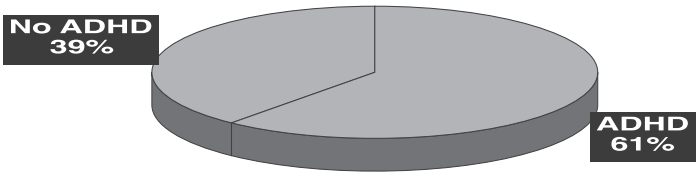
1. Quick to get angry or become upset
2. Easily Frustrated
3. Over-react emotionally
4. Easily excited by activities going on around me
5. Lose my temper
6. Argue with others
7. Am touchy or easily annoyed by others
8. Am angry or resentful

DESR in ADHD = > 95th percentile score of controls

Surman et al, American Journal Psychiatry, 2011

Study Subjects with DESR:

> 95th %ile inventory item frequency



(p < 0.001 ADHD vs non-ADHD)

Article

Deficient Emotional Self-Regulation and Adult Attention Deficit Hyperactivity Disorder: A Family Risk Analysis

Craig B.H. Surman, M.D.
Joseph Biederman, M.D.
Thomas Spencer, M.D.
Dayna Yorks, B.A.
Carolyn A. Miller, B.A.
Carter R. Petty, M.S.
Stephen V. Faraone, Ph.D.

Objective: A growing body of research suggests that deficient emotional self-regulation (DESR) is prevalent and morbid among patients with attention deficit hyperactivity disorder (ADHD). Family studies provide a method of clarifying the co-occurrence of clinical features, but no family studies have yet addressed ADHD and DESR.

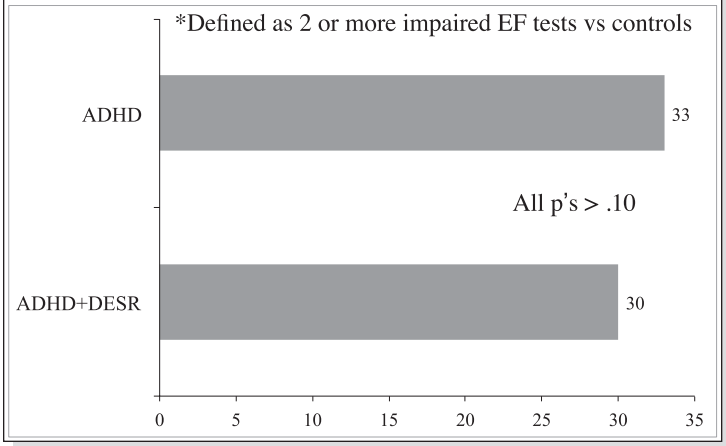
Method: Participants were 83 probands with and without ADHD and 128 siblings. All were assessed for axis I DSM-IV conditions with structured diagnostic interviews. The authors defined DESR in adult probands and siblings using items from the Barkley Current Behavior Scale. Analyses tested hypotheses about the familial relationship between ADHD and DESR.

Results: Siblings of ADHD probands were at elevated risk of having ADHD, irrespective of the presence or absence of DESR in the proband. The risk for DESR was elevated in siblings of ADHD plus DESR probands but not in siblings of ADHD probands. ADHD and DESR cosegregated in siblings. The risk for other psychiatric disorders was similar in siblings of the ADHD proband groups.

Conclusions: The pattern of inheritance of ADHD with DESR preliminarily suggests that DESR may be a familial subtype of ADHD. Our data suggest that DESR is not an expression of other axis I DSM-IV disorders or of nonfamilial environmental factors. The authors cannot exclude contribution of non-axis-I DSM-IV disorders to risk for DESR and cannot determine whether the cosegregation of ADHD in DESR within families is a result of genes or familial environmental risk factors. Further investigation of DESR and its correlates and treatment both in and outside the context of ADHD is warranted.

(Am J Psychiatry 2011; 168:617–623)

Rates of Executive Function Disorder* in ADHD Adults with / without DESR



Treatment Options

Simple ADHD

vs.

ADHD + Executive Problems

vs.

Comorbid Mental Disorders

Tailor Treatment to Challenges

ADHD is compounded by:

- **Axis I,II,III, IV comorbidity,**
- **limited ability to form habits, routines**
- **cognitive challenges (eg. dyslexia, time sense,**
- **planning ability, prioritizing, pace, memory)**
- **mismatched cognitive faculties**
- **lack of goals, motivation, purpose**
- **low self-monitoring**
- **low interpersonal efficacy**

Opposite of above are strengths for adaptation

Anticipating Treatment Effects

Medication robustly treats core ADHD:

- often improves engagement in the moment - the salience of tasks

Eg: better able to get around to, stick with, and finish tasks but still not doing the right task the right way at the right time

Skill training requires ability to:

- do “homework”
- form new habits / routines

Environmental accommodations feasible where:

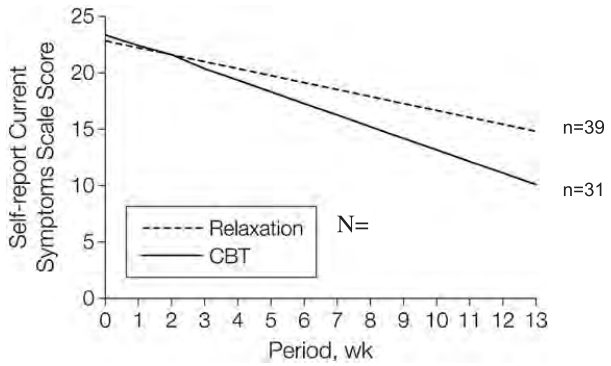
- skills enough for core role (eg. job description)
- format of activities can be adapted to match abilities

Treatable Factors

↑ Self-regulation skills
self-care; executive; emotional
Environmental Accommodation

↓ ADHD symptoms
Other limits to adaptive adjustment
comorbidity; negative self-talk

Self-report Current Symptoms Scale Score
Mixed Effects Analysis



Safren, S. A. et al. JAMA 2010;304:875-880.

JAMA

MGH CBT Modules

- 3 core modules
  - Psychoeducation about ADHD and training in organizing and planning
    - use of planner and task list
    - problem-solving training (generating alternatives, picking best solution)
    - Breaking task into steps
      - "Not getting started? First step is too big"
  - Skills to reduce distractibility
    - "Out of sight out of mind"; writing down thought distractions
  - Changing automatic thoughts
    - Blame ADHD, not you; Rational vs. emotional thought patterns
- Optional modules
  - Skills against procrastination
  - Including family member for support
- Review and relapse prevention

Safren et al, Mastering Your Adult ADHD, Oxford University Press

Metacognitive Group Therapy for Adult ADHD

- Group CBT vs Supportive Psychotherapy (N = 88)
  - 56% of subjects on medication
- Response greater for Group CBT
  (odds ratio=5.41; 95% CI=1.77–16.55)
- Modular treatment (12 weeks)
- Metacognitive therapy uses CBT principles to target
  - Time management
  - Organization and planning
  - Reducing depressed/Anxious Cognition

Solanto et al, *Am J Psychiatry 2010; 167:958–968).*

Metacognitive Group Therapy

- Session 1: CBT introduction, expectations, overview
- Sessions 2-6: Time and Task Management *Skills*
  - Breaking overwhelming tasks into manageable parts
  - Contingent rewards and Visualizing long-term rewards
  - Time awareness, Scheduling and Prioritizing
  - CBT for negative automatic thoughts
- Sessions 7-9: Organization Implementation / Maintenance
- Sessions 10-11: *Planning* with Flow Charting
- Session 12: Summarize Progress / Strategies / Future Goals
- Two Hour Sessions
  - Address Cognitive, Situational, Emotional Challenges in Homework
  - New topic with in session example and homework assignment
  - Cognitive strategies linked with problematic cues
    - "If I am having trouble getting started, then the first step is too big"
    - For distractions: "Out of sight, out of mind"

Solanto et al, *Am J Psychiatry 2010; 167:958–968).*

Regulatory Pattern: Sleep

- ADHD medication can help engage plan
- Use principles to create plan for change:
  - Identify critical choice moments + best plan
    - eg. when to wind down, start bedtime routine
  - Steer around pitfalls:
    - eg. sleep environment (screens dark !)
    - ; no-new-projects time
  - Create reward
    - (eg. reading in bed)
  - Foster accountability
    - (eg. spouse expectation, call friend)

Environmental Accommodation

Standard School Accommodations
- Copy of class notes, extra time and quiet for tests

Create structure:
- use natural accountability (? group work; mentoring; reward schedules)
- stimulation (adapt work to interests)
- reminder systems (calendars with alarms)

Match optimal work style and pattern
- sedentary vs. on the road, breaks, variety of projects

Outsource to "peripheral brains" - devices + people
- planning, prioritization, decisions
- schedule management
- capturing information (eg. recording pens; alarms to head for class)

Maximize interest, decrease distraction, outsource challenges, maintain accountability

Treatment of Comorbid ADHD

? Prioritize treatment of impairing comorbidity

Mild anxiety / mood distress (HAM A/D < 15) more amenable to ADHD treatment

Frame ADHD management as longer term goal

? Choose first-line comorbidity treatment or one that may also treat ADHD?

Caution: hypomania/mania, psychosis, substance abuse

ADHD medication may exacerbate comorbidity

mood, anxiety side effects occur

different agent or administration pattern may eliminate sleep or physical side effects - less often mood or "personality" effects

Stimulant Monotherapy for ADHD + MDD?

Methylphenidate IR treatment of adults with ADHD +/- psychiatric comorbidity

47 patients aged 18-59 years

Open; avg dose 0.5 mg/kg/day for 7 wks

Greater improvement in ADHD symptoms in patients without comorbidities

Less response in depressed patients

(BDI self report >/=18) in particular

Sobanski et al, 2006; Germany

ADHD+MDD - Treatment Options

? Target shared neurochemistry

- Desipramine may treat both
  - – Controlled study for ADHD in adults (Wilens et al, 1996)
- Buproprion may treat both
  - – Controlled studies in ADHD (Wilens et al, 2001 + 2005)
  - – Small open label study in ADHD+MDD adolescents (Daviss et al, 2001)
- Less evidence for Venlafexine
  - – Small open label studies in ADHD+MDD adults (Adler et al, 1995, Findling et al,1996

? Use first-line MDD treatment

- ?use least anticholinergic agents?

CBT / Other psychotherapy may be indicated

Treatment of ADHD + Bipolar Disorder

Mixed amphetamine salts

4 week, double blind crossover study

5 mg BID in 30 patients on divalproex for mania/ hypomania with ≥ 50% improvement in YMRS

ADHD benefit with MAS, not divalproex, mood ws stable (Scheffer et al, Am J Psych, 2005)

Buproprion

6 week, open label study

Up to 200 mg BID in 36 stabilized bipolar adults

Well tolerated, significant ADHD improvement (Wilens, Biol Psych, 2003)

Treatment of ADHD + Bipolar Disorder

ADHD medication can activate agitated or psychotic states - weigh risk carefully

Stabilize mood first

Use caution in ADHD medication dosing

- Start lower, increase slower
- ? Long acting stimulant better ?
- Re-assess mood frequently
- If mood worsens, restabilize, consider alternate agent

AACAP Practice Parameters

Treating ADHD may prevent SUD pre adult
Misuse is common
Ideal SUD patient:
- robust narrative of ADHD impairment
- solidly in early recovery
- seeking treatment for healthy reasons

Use nonstimulants in active SUD or higher risk
- Stimulants and nonstimulants do not appear to worsen SUD

Extended-release stimulants = lower street value
- but all can be misused

Don't prescribe unless you feel comfortable
(See Wilens et al., Am Jour Psych 2006 & JAACAP:2011)

Staying Grounded with Executive Challenges

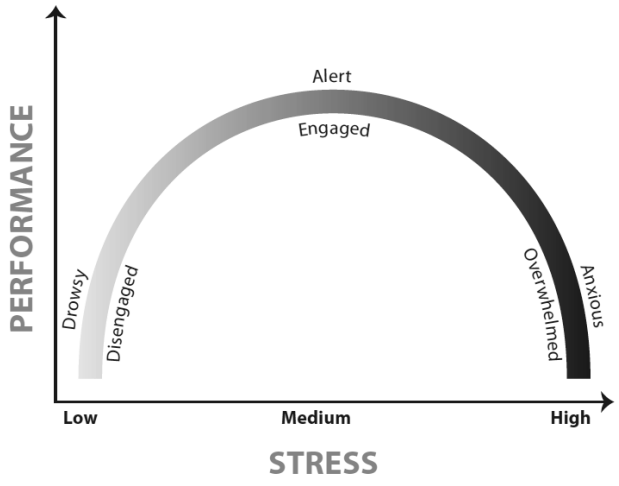
The Prefrontal Checklist

Clarity + Salience of efforts
? Are steps + goals clear, motivating?

Internal Distraction
? Is mental, physical state compromising ?
(stress, preoccupying ideas like unplanned tasks, feelings)

External Distraction
? Is the environment unsettling?
(low structure, sounds, reminders of other tasks)

See: FAST MINDS Surman, Bilkey + Weintraub



Rx effects on DESR Unclear

Atomoxetine
n=529; 170 with WRAADS Emotional Dysregulation (ED)
ED improved to same extent as ADHD
ED predicted CAARS treatment response
(Reimherr et al, 2005)

OROS-mph, double-blind placebo controlled studies
1) n=41: 16 ADHD+ED 25% had 50% lower WRAADS
18 ADHD+ED+ODD 50% " "
5 ADHD alone 49% " "
(Reimherr et al, 2007)
2) n=87: No change in BRIEF-A Emotional subscale
for "clinically improved" group (≥ 30% improved, CGI 1/2)
(Biederman et al, 2007)

Lisdexamfetamine trial
- WRAADS emotion effects not significant
(Adler et al, under review)

Help For DESR

Unconscious factors

- **Optimize top-down control**
- **Minimize bottom-up emotional tone**

Conscious factors

- **Practice alternative thoughts/actions**
- **Mental grounding / distraction**

Chain Analysis for DESR Moments

Some DESR moments are predictable

- **Consider what is different about:**
  - **state of mind (calm? stressed?)**
  - **challenges (decisions? transitions?)**
  - **health of mind (has nutrients it needs?)**
  - **the back of the mind**
    (unsettled concerns, upcoming challenge)

Avoid DESR "Scenes"

Find a natural, least-effort approach to avoiding DESR "scenes" in the daily "movie"

- **Can you avoid the DESR scene?**
- **Can you script alternative:**
  - **Behavior?**
  - **Mental focus (distract, change "mission")?**
  - **Response? (plan an "opposite action")**
- **What props will help? (reminder)**
- **What supporting cast will help?**
- **Make sure you rehearse!**

Cognitive/Dialectical Behavior Therapy?

DBT (emotion regulation training) helps borderline personality disorder, binge eating disorder, opioid dependence and treatment-resistant depression.

- **Understanding Emotions (CBT/DBT skill):** In this session, the therapist will introduce the idea of emotion regulation. The therapist will discuss how to label emotions as well as the function of emotions.
- **Mindfulness:** concept of mindfulness; observe and describe emotions without reacting.
- **Reducing Vulnerability to Negative Emotions:** Plan to improve self-care as needed, engaging in pleasant activities - plan for areas of improvement.

- **Opposite Action and Acceptance**: educate that specific actions are linked with emotions (e.g., anxiety pulls for avoidance, anger pulls for approach); idea of using the opposite action and acceptance to decrease suffering.
- **Presentation of Cognitive Model (CBT skill):** cognitive model between thoughts, behaviors and emotions. participant asked to monitor situations and their associated thoughts as a homework assignment.
- **Danger Zones / Trigger Thoughts (CBT skill—Anger Management):** situations that tend to elicit strong emotions and trigger thoughts immediately preceding emotional dysregulation.
- **Development of Rational Responses (CBT skill):** rational responses to combat trigger thoughts in danger zones.
- **Relapse Prevention (CBT skill):** reviewing skills and developing a plan for continued skills use

Conclusions

Attention to Emotion in ADHD Will Help:

- **Appreciation of dimensions of function**
- **Efficient seperation of DESR from other conditions**
- **Mainstream support for self-regulation problems**
- **Understand the neurobiology of self-regulation**

Summary

No ADHD without impairment

Identify and prioritize comorbidity

Identify self-regulation challenges

(organizational, mood, sleep, emotion control)

Change “default” behavior pattern by:

- Improved ability to engage (medication !)
- Changing environment to complement patient
- Practice new habits at key moments
- Maintaining accountability

Evaluate challenges + best supports regularly

Surman (ed): ADHD in Adults, A Practical Guide … (in press)
Surman, Bilkey & Weintraub: FASTMINDS … (in press)

Attention Deficit Hyperactivity Disorder Across the Life Span

SATURDAY MARCH 16, 2013

Saturday, March 16, 2013

7:30AM – 8:00AM	**Continental Breakfast**
8:00AM – 9:00AM	**ADHD and Mania** Janet Wozniak, MD
9:00AM – 10:00AM	**Comorbidity of ADHD with Substance Abuse and Associated Risk Management Issues,*** Timothy E. Wilens, MD
10:00AM – 10:15AM	Coffee Break
10:15AM – 11:15AM	**CBT & Psychosocial Treatments in ADHD** Aude Henin, PhD
11:15AM – 12:15PM	**ADHD, Tics and Tourette's Disorder** Barbara J. Coffey, MD, MS
12:15PM – 1:45PM	**Lunch Break (On Your Own)**
1:45PM – 2:15PM	**Driving and Working Impairments in ADHD** Ronna Fried, EdD
2:15PM – 2:45PM	**Management of ADHD in the Context of Autism Spectrum Disorders** Gagan Joshi, MD
2:45PM – 3:00PM	**Coffee Break**
3:00PM – 3:45PM	**Neuroimaging of ADHD** Eve Valera, PhD
3:45PM – 4:30PM	**Diagnostic Assessment Approaches to Adult ADHD** Craig Surman, MD
4:30PM – 5:15PM	**Cardiovascular Risk in the Management of ADHD*** Paul Hammerness, MD
5:15PM – 6:30PM	**Dinner (On Your Own)**

ADHD and Mania

Janet Wozniak, MD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

Pediatric Bipolar Disorder and ADHD

Janet Wozniak, M.D.

Director, Pediatric Bipolar Disorder Research Program

Associate Professor Psychiatry

Massachusetts General Hospital

Harvard Medical School

Disclosures of Potential Conflicts 2011-2012 Janet Wozniak MD

Source	Research Funding	Advisor/ Consultant	Employee	Speaker	Books, Intellectual Property	In-kind Services (example: travel)	Stock or Equity > $10,000	Honorarium or expenses for this presentation or meeting
Merck/Schering-Plough	XX							
McNeil	XX							
Shire	XX							

In the past, she has received research support, consultation fees or speaker's fees from: Eli Lilly, Janssen, Johnson and Johnson, McNeil, Pfizer, Shire. She is also the author of the book, *Is Your Child Bipolar,* published May 2008, Bantam Books.

Disclosures of Potential Conflicts 2011-2012 Janet Wozniak MD spouse John Winkelman MD PhD

Source	Research Funding	Advisor/ Consultant	Employee	Speaker	Books, Intellectual Property	In-kind Services (example: travel)	Stock or Equity > $10,000	Honorarium or expenses for this presentation or meeting
GlaxoSmithKline	XX							
Sunovian		XX						
Pfizer		XX						
UCB		XX						
Zeo Inc		XX						

In the past, he has received research support, consultation fees or speaker's fees from: Axon Labs, Boehringer-Ingelheim, Covance, Cephalon, Eli Lilly, GlaxoSmithKline, Impax, Jazz Pharmaceuticals, King, Luitpold, Novartis, Neurogen, Novadel Pharma, Pfizer, Sanofi-Aventis, Sepracor, Takeda, UCB (Schwarz) Pharma, Wyeth, Zeo.

THE NEW ENGLAND JOURNAL of MEDICINE

Perspective

MAY 20, 2010

Pediatric Mental Health Care Dysfunction Disorder?

Erik Parens, Ph.D., Josephine Johnston, L.L.B., M.B.H.L., and Gabrielle A. Carlson, M.D.

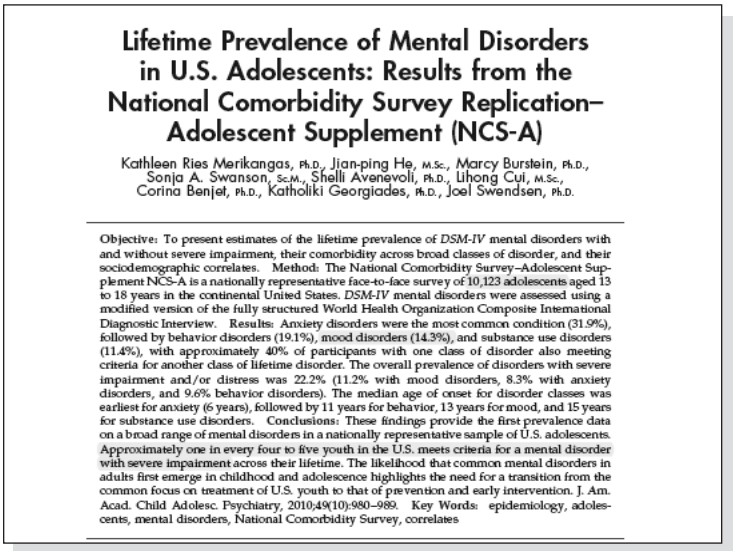
In February, the American Psychiatric Association released draft revisions for the next iteration of its diagnostic manual (the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [DSM-V]).

One of the draft's most talked-about features is a new diagnostic category for children: temper dysregulation disorder with dysphoria (TDD). The addition has been praised by some as a verdict on one of the hottest questions in child psychiatry: Is the dramatic increase in the number of children with a diagnosis of bipolar disorder appropriate? The answer appears to be no. But the creation of this new category raises another question: Will the TDD diagnosis advance what everyone agrees should be the ultimate goal of psychiatric classification — helping troubled children to flourish? Sadly, the answer to the second question is also no, unless we get serious about reforming pediatric mental health care.

The hallmark of bipolar disorder in adults is a manic episode, a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally increased goal-directed activity or energy, accompanying symptoms, and lasting at least 1 week. [illegible] a small but influential group of child psychiatrists [illegible] that most children with this disorder do not have discrete episodes of mania but rather have chronic and very severe nonelated mood as manifested by severe aggressive outbursts alternating between elevated and severe moods in a day. Between the mid-1

as reported by Moreno and colleagues,[1] the number of children with a diagnosis of bipolar disorder visiting outpatient clinics increased by a factor of 40. These children, some preschoolers, were primarily being treated with mood stabilizers and a new generation of antipsychotic drugs.

No one disputes that these



Lifetime Prevalence of Mental Disorders in U.S. Adolescents: Results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A)

Kathleen Ries Merikangas, Ph.D., Jian-ping He, M.Sc., Marcy Burstein, Ph.D., Sonja A. Swanson, Sc.M., Shelli Avenevoli, Ph.D., Lihong Cui, M.Sc., Corina Benjet, Ph.D., Katholiki Georgiades, Ph.D., Joel Swendsen, Ph.D.

Objective: To present estimates of the lifetime prevalence of *DSM-IV* mental disorders with and without severe impairment, their comorbidity across broad classes of disorder, and their sociodemographic correlates. **Method:** The National Comorbidity Survey–Adolescent Supplement NCS-A is a nationally representative face-to-face survey of 10,123 adolescents aged 13 to 18 years in the continental United States. *DSM-IV* mental disorders were assessed using a modified version of the fully structured World Health Organization Composite International Diagnostic Interview. **Results:** Anxiety disorders were the most common condition (31.9%), followed by behavior disorders (19.1%), mood disorders (14.3%), and substance use disorders (11.4%), with approximately 40% of participants with one class of disorder also meeting criteria for another class of lifetime disorder. The overall prevalence of disorders with severe impairment and/or distress was 22.2% (11.2% with mood disorders, 8.3% with anxiety disorders, and 9.6% behavior disorders). The median age of onset for disorder classes was earliest for anxiety (6 years), followed by 11 years for behavior, 13 years for mood, and 15 years for substance use disorders. **Conclusions:** These findings provide the first prevalence data on a broad range of mental disorders in a nationally representative sample of U.S. adolescents. Approximately one in every four to five youth in the U.S. meets criteria for a mental disorder with severe impairment across their lifetime. The likelihood that common mental disorders in adults first emerge in childhood and adolescence highlights the need for a transition from the common focus on treatment of U.S. youth to that of prevention and early intervention. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(10):980–989. **Key Words:** epidemiology, adolescents, mental disorders, National Comorbidity Survey, correlates

Merikangas, et al, National Comorbidity Survey Replication-Adolescent Supplement, 2010

TABLE 2 Lifetime Prevalence of *DSM-IV* Disorders by Sex and Age Group and Severe Impairment in the National Comorbidity Survey–Adolescent Supplement (NCS-A)

	DSM-IV Disorder													
	Sex				Age								Adolescents with Severe Impairment	
	Female		Male		13-14 y		15-16 y		17-18 y		Total			
DSM-IV Disorder	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE	%	SE
Mood disorders														
Major depressive disorder or dysthymia	15.9	1.3	7.7	0.8	8.4	1.3	12.6	1.3	15.4	1.4	11.7	0.9	8.7	0.8
Bipolar I or II	3.3	0.4	2.6	0.3	1.9	0.3	3.1	0.3	4.3	0.7	2.9	0.3	2.6	0.2
Any mood disorder	18.3	1.4	10.5	1.1	10.5	1.3	15.5	1.4	18.1	1.6	14.3	1.0	11.2	1.0
Anxiety disorders														
Agoraphobia	3.4	0.4	1.4	0.3	2.5	0.4	2.5	0.4	2.0	0.5	2.4	0.2	—	—
Generalized anxiety disorder	3.0	0.6	1.5	0.3	1.0	0.3	2.8	0.6	3.0	0.5	2.2	0.3	0.9	0.2
Social phobia	11.2	0.7	7.0	0.5	7.7	0.6	9.7	0.7	10.1	1.0	9.1	0.4	1.3	0.2
Specific phobia	22.1	1.1	16.7	0.9	21.6	1.6	18.3	1.0	17.7	1.3	19.3	0.8	0.6	0.1
Panic disorder	2.6	0.3	2.0	0.3	1.8	0.4	2.3	0.3	3.3	0.7	2.3	0.2	—	—
Posttraumatic stress disorder	8.0	0.7	2.3	0.4	3.7	0.5	5.1	0.5	7.0	0.8	5.0	0.3	1.5	0.2
Separation anxiety disorder	9.0	0.6	6.3	0.5	7.8	0.6	8.0	0.7	6.7	0.8	7.6	0.3	0.6	0.1
Any anxiety disorder	38.0	1.4	26.1	0.8	31.4	1.9	32.1	1.0	32.3	1.7	31.9	0.8	8.3	0.4
Behavior disorders														
Attention deficit hyperactivity disorder	4.2	0.5	13.0	1.0	8.8	0.9	8.6	0.8	9.0	1.1	8.7	0.6	4.2	0.4
Oppositional defiant disorder	11.3	0.9	13.9	1.2	12.0	1.2	12.6	1.3	13.6	1.4	12.6	0.9	6.5	0.7
Conduct disorder	5.8	1.1	7.9	1.2	4.4	1.2	7.5	1.2	9.6	1.3	6.8	0.9	2.2	0.4
Any behavior disorder	15.5	1.2	23.5	1.6	18.2	1.5	19.5	1.7	21.9	1.8	19.6	1.2	9.6	0.8

Changes to the Bipolar Diagnosis in DSM-5

A change to **criterion A for Mania** and Hypomania to require in addition to changes in mood

changes in energy and activity

ie “a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy”

Changes to the Bipolar Diagnosis in DSM-5

Removal of the old 'mixed episode' entirely and replacing it with a '***mixed specifier'*** involving the presence of 3 non-overlapping symptoms from the opposite pole that can be applied to episodes of mania, hypomania or depression...and even to depressions experienced by those with a lifetime dx of unipolar disorder.

FOR example: 2-3 manic or hypomanic symptoms occurring for at least 2-3 days simultaneously with a fully syndromal episode of depression

Used to be ‘mixed’ meant simultaneous presence of fully manic and fully depressive syndrome nearly every day for at least one week.

How to use the mixed specifier:

- Full criteria for a manic or hypomanic episode with at least ***3 depressive symptoms*** nearly every day:
  - Subjective depression
  - Worry
  - Self reproach/guilt
  - Negative evaluation of self
  - Hopelessness
  - Suicidal ideation or behavior
  - Anhedonia
  - Fatigue
  - Psychomotor retardation

How to use the mixed specifier:

- Full criteria for a major depressive episode with at least ***3 concurrent hypomanic*** symptoms:
  - Elevated mood
  - Decreased need for sleep
  - Goal directed activity
  - Increased energy and visible hyperactivity
  - Grandiosity
  - Accelerated speech
  - Racing thoughts

Bipolar NOS

- Will include 3 categories:
  - Subsyndromal
  - Other specified
  - Unspecified due to insufficient information

The New Temper Tantrum Disorder
Will the new diagnostic manual for psychiatrists go too far in labeling kids dysfunctional?
By David Dobbs|Posted Friday, Dec. 7, 2012, at 1:12 PM ET

Disruptive Mood Dysregulation Disorder DMDD Criteria

A. The disorder is characterized by severe recurrent *temper outbursts* that are grossly out of proportion in intensity or duration to the situation.

1. The temper outbursts are manifest verbally and/or behaviorally, such as in the form of verbal rages or physical aggression towards people or property.
2. The temper outbursts are inconsistent with developmental level.

B. *Frequency*: The temper outbursts occur, on average, three or more times per week.

C. *Mood between temper outbursts:*

1. Nearly every day, most of the day, the mood between temper outbursts is persistently irritable or angry.
2. The irritable or angry mood is observable by others (e.g., parents, teachers, peers).

D. *Duration*: Criteria A-C have been present for 12 or more months. Throughout that time, the person has not had 3 or more consecutive months when they were without the symptoms of Criteria A-C.

E. Criterion A or C is present in at least two settings (at home, at school, or with peers) and must be severe in at least in one setting.

F. The diagnosis should not be made for the first time before age 6 or after age 18.

G. The onset of Criteria A through E is before age 10 years.

Disruptive Mood Dysregulation Disorder DMDD Criteria

A. The disorder is characterized by severe recurrent *temper outbursts* that are grossly out of proportion in intensity or duration to the situation.

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B. *Frequency*: The temper outbursts occur, on average, three or more times per week.

Disruptive Mood Dysregulation Disorder DMDD Criteria

C. *Mood between temper outbursts:*

1. Nearly every day, most of the day, the mood between temper outbursts is persistently irritable or angry.
2. The irritable or angry mood is observable by others (e.g., parents, teachers, peers).

Disruptive Mood Dysregulation Disorder DMDD Criteria

D. *Duration*: Criteria A-C have been present for 12 or more months. Throughout that time, the person has not had 3 or more consecutive months when they were without the symptoms of Criteria A-C.

E. Criterion A or C is present in at least two settings (at home, at school, or with peers) and must be severe in at least in one setting.

F. The diagnosis should not be made for the first time before age 6 or after age 18.

G. The onset of Criteria A through E is before age 10 years.

DMDD Exclusionary Criteria

H. There has never been **a distinct period lasting more than one day** during which abnormally **elevated or expansive** mood was present most of the day, **and** the abnormally elevated or expansive mood was accompanied by the onset, or worsening, of **three of the "B" criteria** of mania (i.e., grandiosity or inflated self-esteem, decreased need for sleep, pressured speech, flight of ideas, distractibility, increase in goal directed activity, or excessive involvement in activities with a high potential for painful consequences; see pp. XX). Abnormally elevated mood should be differentiated from developmentally appropriate mood elevation, such as occurs in the context of a highly positive event or its anticipation.

I. The behaviors do not occur exclusively during an episode of **Major Depressive Disorder** and are not better accounted for by another mental disorder (e.g., **Autism Spectrum Disorder, Posttraumatic Stress Disorder, Separation Anxiety Disorder, Dysthymic Disorder**). (Note: This diagnosis **cannot co-exist with Oppositional Defiant Disorder or Bipolar Disorder**, though it can co-exist with Attention Deficit/ Hyperactivity Disorder, Conduct Disorder, and Substance Use Disorders. Individuals meeting criteria for both Disruptive Mood Dysregulation Disorder and Oppositional Defiant Disorder should only be given the diagnosis of Disruptive Mood Dysregulation Disorder. **If an individual has ever experienced a manic or hypomanic episode, the diagnosis of Disruptive Mood Dysregulation Disorder should not be assigned.)** The symptoms are not due to the effects of a drug or to a general medical or neurological condition.

American Psychiatric Association's
Diagnostic Statistical Manual, Fifth Edition, or
DSM-5
Published May 2013

DSM-5 Workgroup Rationale
Reduce the number of bipolar diagnoses

[The increase in pediatric BPD diagnoses] could be seen as reflecting appropriate diagnosis coming after a time of persistent under-diagnosis.

However, this increase coincided with a time period during which some child psychiatry researchers and practitioners adopted new conventions in assigning the diagnosis of BD to children.

These conventions would be expected to broaden the phenotype of pediatric BD, beyond the explicit boundaries of DSM-IV BD.

American Psychiatric Association's
Diagnostic Statistical Manual, Fifth Edition, or
DSM-5
Published May 2013

Since 2001, the rate of bipolar-disorder diagnosis among children and teens has jumped more than 4,000 percent (times 40).

Bipolar disorder often gets treated with combinations of antipsychotic and mood-stabilizing drugs (lithium and Risperdal, for instance) that have strong side effects.

Carries a “huge” stigma and attendant effect on self-image.

The new diagnosis could theoretically also lead to a reduction in the number of kids getting "medicated" for bipolar disorder unnecessarily and an increase in kids getting more “appropriate” interventions.

American Psychiatric Association's
Diagnostic Statistical Manual, Fifth Edition, or
DSM-5
Published May 2013

DSM-5 Workgroup Rationale

Pediatric bipolar disorder often presents with irritability and ‘chronicity,’ so this provides another (?less stigmatizing) diagnosis to use in highly irritable youth.

American Psychiatric Association's
Diagnostic Statistical Manual, Fifth Edition, or
DSM-5
Published May 2013

Started out as:
temper dysregulation disorder with dysphoria

Based on Leibenluft's SMD Severe Mood Dysregulation
which includes 'chronic hyperarousal symptoms eg insomnia, agitation, distractibility, racing thoughts, FOI, pressured speech, intrusiveness

DSM-5 Workgroup Rationale

- Since the Web site posting of this document in 2010, two important revisions have been made. The first is that, in response to concerns expressed by the community, the name of the disorder was changed from Temper Dysregulation Disorder to Disruptive Mood Dysregulation Disorder.
- The second relates to the fact that most of the children who meet criteria for Disruptive Mood Dysregulation Disorder will also meet criteria for Oppositional Defiant Disorder, since the two disorders have overlapping symptoms. However, only a minority of youth with Oppositional Defiant Disorder will meet criteria for Disruptive Mood Dysregulation Disorder, because the latter is considerably more severe than the former.

American Psychiatric Association's
Diagnostic Statistical Manual, Fifth Edition, or
DSM-5
Published May 2013

critics say:

•May turn temper tantrums into a mental disorder
•Does not 'stem the tide' on bipolar diagnoses
•APA makes money from the new DSM edition
•Psychiatry wants to appear that it is 'making progress'
•Occurs at same time that it is easier to diagnose a mixed state

Focus on Childhood and Adolescent Mental Health

Examining the Proposed Disruptive Mood Dysregulation Disorder Diagnosis in Children in the Longitudinal Assessment of Manic Symptoms Study

David Axelson, MD; Robert L. Findling, MD, MBA; Mary A. Fristad, PhD, ABPP; Robert A. Kowatch, MD, PhD; Eric A. Youngstrom, PhD; Sarah McCue Horwitz, PhD; L. Eugene Arnold, MD; Thomas W. Frazier, PhD; Neal Ryan, MD; Christine Demeter, MA; Mary Kay Gill, MSN; Jessica C. Hauser-Harrington, PhD; Judith Depew; Shawn M. Kennedy, MA; Brittany A. Gron, BS; Brieana M. Rowles, MA; and Boris Birmaher, MD

ABSTRACT

Objective: To examine the proposed disruptive mood dysregulation disorder (DMDD) diagnosis in a child psychiatric outpatient population. Evaluation of DMDD included 4 domains: clinical phenomenology, delimitation from other diagnoses, longitudinal stability, and association with parental psychiatric disorders.

Method: Data were obtained from 706 children aged 6–12 years who participated in the Longitudinal Assessment of Manic Symptoms (LAMS) study. Sample was accrued from November 2005 to November 2008. *DSM-IV* criteria were used, and assessments, which included diagnostic, symptomatic, and functional measures, were performed at intake and at 12 and 24 months of follow-up. For the current post hoc analyses, a retrospective diagnosis of DMDD was constructed using items from the K-SADS-PL, a version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children, which resulted in criteria closely matching the proposed *DSM-5* criteria for DMDD.

Results: At intake, 26% of participants met the operational DMDD criteria. DMDD+ vs DMDD− participants had higher rates of oppositional defiant disorder (relative risk [RR] = 3.9; *P* < .0001) and conduct disorder (RR = 4.5; *P* < .0001). On multivariate analysis, DMDD+ participants had higher rates of and more severe symptoms of oppositional defiant disorder (rate and symptom severity *P* values < .0001) and conduct disorder (rate, *P* < .0001; symptom severity, *P* = .01), but did not differ in the rates of mood, anxiety, or attention-deficit/hyperactivity disorders or in severity of inattentive, hyperactive, manic, depressive, or anxiety symptoms. Most of the participants with oppositional defiant disorder (58%) or conduct disorder (61%) met DMDD criteria, but those who were DMDD+ vs DMDD− did not differ in diagnostic comorbidity, symptom severity, or functional impairment. Over 2-year follow-up, 40% of the LAMS sample met DMDD criteria at least once, but 53% of these participants met criteria at only 1 assessment. DMDD was not associated with new-onset of mood or anxiety disorders or with parental psychiatric history.

Conclusions: In this clinical sample, DMDD could not be delimited from oppositional defiant disorder and conduct disorder, had limited diagnostic stability, and was not associated with current, future-onset, or parental history of mood or anxiety disorders. These findings raise concerns about the diagnostic utility of DMDD in clinical populations.

J Clin Psychiatry 2012;73(10):1342–1350

Irritable mood and temper outbursts are common in youth referred for psychiatric treatment.[1,2] They are also the core features of the proposed diagnosis disruptive mood dysregulation disorder (DMDD) in *DSM-5*.[3] DMDD is characterized primarily by frequent, severe, recurrent temper outbursts and chronically irritable and/or angry mood, both of which must be present for at least a year. The *DSM-5* Work Groups raised concerns that many youth with severe, nonepisodic irritable mood are inappropriately diagnosed with bipolar disorder.[4] The DMDD diagnosis was constructed to capture the phenomenology of youth with severe, chronic irritability, with the goal of reducing the chance that youth with this phenotype would receive a bipolar diagnosis.

The *DSM-5* Work Groups note that there is currently relatively limited research to support the DMDD diagnosis.[4] Most available studies focus on an overlapping but not identical construct called severe *mood dysregulation* (SMD). SMD includes the core criteria of DMDD, but also requires symptoms of chronic hyperarousal such as insomnia, agitation, distractibility, racing thoughts, flight of ideas, pressured speech, and intrusiveness.[5] Published research on SMD has primarily been from a carefully phenotyped cohort of 146 youth referred to the National Institute of Mental Health (NIMH) Intramural Program.[6] The youth with SMD were predominantly male (66%) and had high lifetime rates of attention-deficit/hyperactivity disorder (ADHD; 85%), oppositional defiant disorder (86%), and anxiety disorders (58%). About 16% met lifetime criteria for major depressive disorder (MDD). The youth with SMD were shown to be different from youth with a specified phenotype of bipolar I disorder (requiring distinct episodes of manic symptoms, including either elated mood or grandiosity) on a number of domains, including lower familial rates of bipolar disorder, lower onset rates of manic and hypomanic episodes over prospective follow-up, and differences on several neuropsychological domains and measures of brain structure and functioning.[6]

Other studies relevant to the SMD/DMDD phenotype have been post hoc analyses of large datasets in which a

Examining the Proposed Disruptive Mood Dysregulation Disorder Diagnosis in Children in the Longitudinal Assessment of Manic Symptoms Study

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J Clin Psychiatry 2012;73(10):1342–1350

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DMDD inadequately studied and untested?

- LAMS assessed 706 children age 6-12, baseline and followup 12 and 24 months later
- 26% met criteria for DMDD. They had more ADHD, ODD and CD, and more severe impairment for these, than non-DMDDs
- 53% met criteria at 12 months, only 19% at all three assessments.
- DMDD at intake did not predict bipolar
- “Common, transient, difficult to distinguish from ODD and CD”

Axelson, JClin Psych 2012

Pediatric Bipolar Disorder Persistence

Child Bipolar I Disorder Prospective Continuity With Adult Bipolar I Disorder; Characteristics of Second and Third Episodes; Predictors of 8-Year Outcome

Barbara Geller, MD; Rebecca Tillman, MS; Kristine Bolhofner, BS; Betsy Zimerman, MA
Arch Gen Psychiatry. 2008;65(10):1125-1133

Conclusions: In grown-up subjects with child BP-I, the 44.4% frequency of manic episodes was 13 to 44 times higher than population prevalences, strongly supporting continuity.

Persistence of Pediatric Bipolar Disorder

Four-Year Longitudinal Course of Children and Adolescents With Bipolar Spectrum Disorders: The Course and Outcome of Bipolar Youth (COBY) Study

Birmaher B, Axelson D, Goldstein B, Strober M, Gill MK, Hunt J, Houck P, Ha W, Iyengar S, Kim E, Yen S, Hower H, Esposito-Smythers C, Goldstein T, Ryan N, Keller M.Am J Psychiatry. 2009 Jul;166(7):795-804.

N=214 Bipolar I and N=169 Bipolar II and NOS, followed for 4 years with the Longitudinal Interview Follow Up Evaluation

Recurrences common
Symptomatic on average for 60% of the follow-up period.
40% had symptoms during 75% of the followup period.
25% of BPD II and 38% of BPD NOS converted to BPI

Persistence of Pediatric Bipolar Disorder

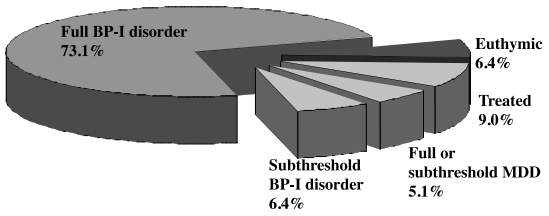
HIGH LEVEL OF PERSISTENCE OF PEDIATRIC BIPOLAR-I DISORDER FROM CHILDHOOD ONTO ADOLESCENT YEARS: A FOUR YEAR PROSPECTIVE LONGITUDINAL FOLLOW-UP STUDY
Wozniak, Petty, Schreck, Moses, Faraone, Biederman

78 of 105 youth with Bipolar I disorder followed up after 3.6 years

- Baseline age 10.5 years, 76% male
- Age of onset bipolar disorder 4.9 years
- Duration of BPD at baseline 7.6 years

Persistence of DSM-IV BP-I in youth at 4-year Follow-up

(N=78/105)



Only 5 were euthymic without treatment

Pediatric-Onset Bipolar Disorder

- ADHD plus BPD has been neglected at both ends of the life cycle due to skepticism regarding pediatric onset bipolar disorder and continuity of ADHD into adulthood
- Clinical and research skepticism leads to a reluctance to diagnose and study the condition

Differential Diagnosis with ADHD

- Overlapping symptoms include:
  a) Distractibility
  b) Physical hyperactivity
  c) Talkativeness

The first scientific article to systematically document the comorbidity between ADHD and Bipolar Disorder

Attention-Deficit Hyperactivity Disorder and Juvenile Mania: An Overlooked Comorbidity?

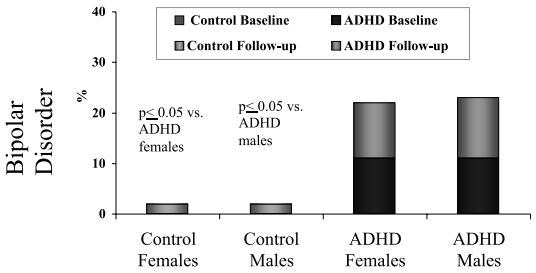
JOSEPH BIEDERMAN, M.D., STEPHEN FARAONE, PH.D., ERIC MICK, B.A., JANET WOZNIAK, M.D., LISA CHEN, B.A., CHERYL OUELLETTE, B.A., ABBE MARRS, B.A., PHOEBE MOORE, B.A., JENNIFER GARCIA, B.A., DOUGLAS MENNIN, B.A., AND ELISE LELON, M.ED.

ABSTRACT

Objective: To evaluate the psychiatric, cognitive, and functional correlates of attention-deficit hyperactivity disorder (ADHD) children with and without comorbid bipolar disorder (BPD). **Method:** *DSM-III-R* structured diagnostic interviews and blind raters were used to examine psychiatric diagnoses at baseline and 4-year follow-up in ADHD and control children. In addition, subjects were evaluated for cognitive, academic, social, school, and family functioning. **Results:** BPD was diagnosed in 11% of ADHD children at baseline and in an additional 12% at 4-year follow-up. These rates were significantly higher than those of controls at each assessment. ADHD children with comorbid BPD at either baseline or follow-up assessment had significantly higher rates of additional psychopathology, psychiatric hospitalization, and severely impaired psychosocial functioning than other ADHD children. The clinical picture of bipolarity was mostly irritable and mixed. ADHD children with comorbid BPD also had a very severe symptomatic picture of ADHD as well as prototypical correlates of the disorder. Comorbidity between ADHD and BPD was not due to symptom overlap. ADHD children who developed BPD at the 4-year follow-up had higher initial rates of comorbidity, more symptoms of ADHD, worse scores on the CBCL, and a greater family history of mood disorder compared with non-BPD, ADHD children. **Conclusions:** The results extend previous results documenting that children with ADHD are at increased risk of developing BPD with its associated severe morbidity, dysfunction, and incapacitation. *J. Am. Acad. Child Adolesc. Psychiatry*, 1996, 35(8):997–1008. **Key Words:** bipolar disorder, attention-deficit hyperactivity disorder, comorbidity.

J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 35:8, AUGUST 1996

Bipolar Disorder in Girls and Boys with and without ADHD



Biederman et al. J Affect Disord. 1997; 44:177-188
Biederman et al. Biological Psychiatry 2003; 53: 952-960

One of the most cited articles in the history of the Journal

Mania-Like Symptoms Suggestive of Childhood-Onset Bipolar Disorder in Clinically Referred Children

JANET WOZNIAK, M.D., JOSEPH BIEDERMAN, M.D., KATHLEEN KIELY, B.A., J. STUART ABLON, B.A., STEPHEN V. FARAONE, PH.D., ELIZABETH MUNDY, B.A., AND DOUGLAS MENNIN, B.A.

ABSTRACT

Objective: To examine the prevalence, characteristics, and correlates of mania among referred children aged 12 or younger. Many case reports challenge the widely accepted belief that childhood-onset mania is rare. Sources of diagnostic confusion include the variable developmental expression of mania and its symptomatic overlap with attention-deficit hyperactivity disorder (ADHD). **Method:** The authors compared 43 children aged 12 years or younger who satisfied criteria for mania, 164 ADHD children without mania, and 84 non-ADHD control children. **Results:** The clinical picture was fully compatible with the *DSM-III-R* diagnosis of mania in 16% ($n = 43$) of referred children. All but one of the children meeting criteria for mania also met criteria for ADHD. Compared with ADHD children without mania, manic children had significantly higher rates of major depression, psychosis, multiple anxiety disorders, conduct disorder, and oppositional defiant disorder as well as evidence of significantly more impaired psychosocial functioning. In addition, 21% ($n = 9$) of manic children had had at least one previous psychiatric hospitalization. **Conclusions:** Mania may be relatively common among psychiatrically referred children. The clinical picture of childhood-onset mania is very severe and frequently comorbid with ADHD and other psychiatric disorders. Because of the high comorbidity with ADHD, more work is needed to clarify whether these children have ADHD, bipolar disorder, or both. *J. Am. Acad. Child Adolesc. Psychiatry*, 1995, 34, 7:867–876. **Key Words:** bipolar disorder, attention-deficit hyperactivity disorder, comorbidity, children.

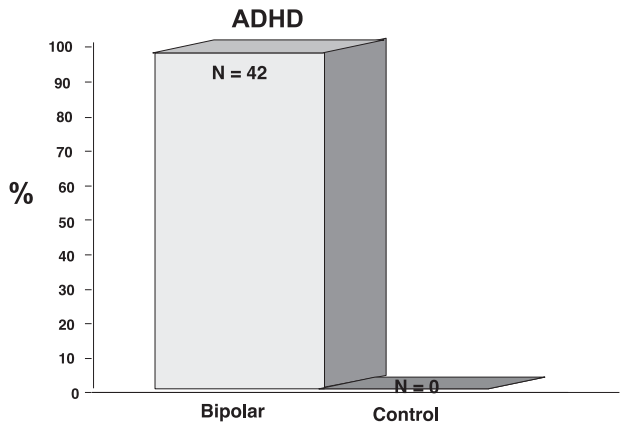
MGH Juvenile Mood Disorders Study First Cohort Study

(Wozniak & Biederman, 1995)

- Subjects
  - Prepubertal Mania (N=43)
  - 16% of 262 referals < 12 year
  - mean age 7.9 years

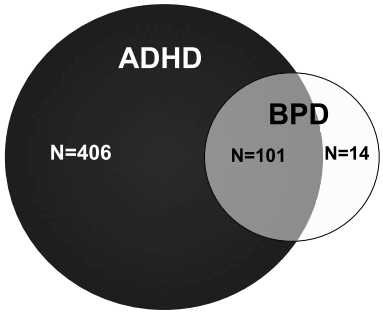
Prepubertal Bipolar Disorder

Wozniak & Biederman, et al., 1995



2004 MGH Study of Pediatric BPD

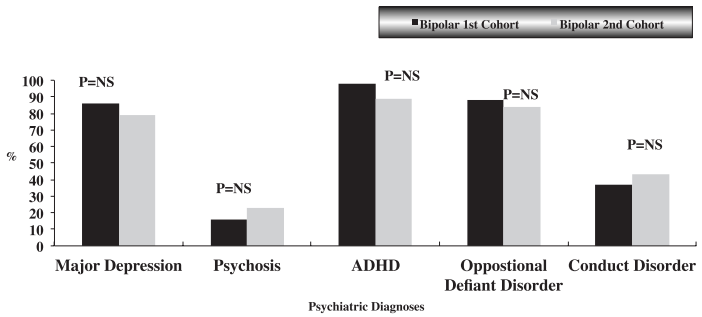
Diagnostic Overlap of BPD and ADHD [Second Cohort]



Biederman, JAD 2004

2004 MGH Study of Pediatric BPD

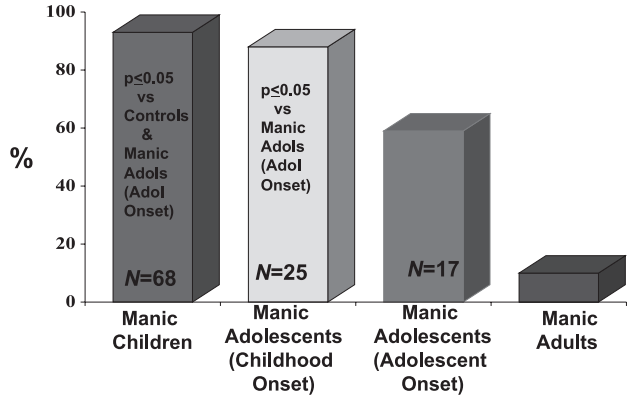
Comorbid Disorders by Bipolar Cohort



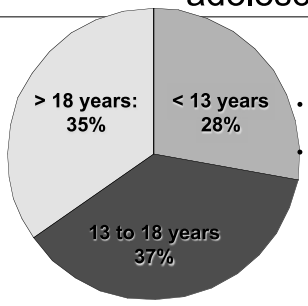
Is Comorbidity with ADHD A Marker for Juvenile Onset Mania?

Faraone, Biederman & Wozniak, et al, 1996

Rates of ADHD



Most bipolar adults in STEP-BD (N=983) reported onset in childhood or adolescence



- About 65% of adults with onset < 18
- Almost a third with onset <13

Perlis, Miyahara, Marangell, Wisniewski, Ostacher, DelBello, Bowden, Sachs, Nierenberg, Biol Psych 2004;55:875-881

Bipolar Disorder and ADHD

Because both BPD and ADHD disorders are known to be familial, one useful approach to understand their relationship is the use of family aggregation data

(Pauls, 1999)

Using family genetic data, we investigated the relationship between ADHD and bipolar disorder in children and adolescents in a familial risk analysis study

Family Study Methodology

"Family studies have consistently found a higher rate of bipolar disorder among the relatives of early onset bipolar disorder patients than in relatives of later-onset cases, which supports the notion of a larger genetic contribution to the early-onset cases."

Faraone, Glatt, Tsuang *The Genetics of Pediatric Onset Bipolar Disorder* Biol Psych 2003

Risk of Bipolarity in First Degree Relatives

Adult bipolar probands 2.4-3.9%
- Andreasen 1987

Adolescent bipolar probands 8.6%
- Strober 1992

Prepubertal bipolar probands 30%
- Strober 1992

Conclusion: Early onset bipolar disorder presents with a *more severe* **genetic diathesis**

Bipolar Disorder and ADHD

Competing hypotheses:

1) BPD and ADHD represent variable expressivity of the same underlying risk factor

(high rates of ADHD would be present in relatives of probands with BPD and high rates of BPD would be present in relatives of probands with ADHD)

Bipolar Disorder and ADHD

Competing hypotheses:

1)BPD and ADHD represent variable expressivity of the same underlying risk factor

2) BPD and ADHD are independently transmitted

(high rates of BPD would be present in relatives of probands of with BPD and high rates of ADHD would be present in relatives of probands with ADHD)

Bipolar Disorder and ADHD

Competing hypotheses:

1)BPD and ADHD represent variable expressivity of the same underlying risk factor

2) BPD and ADHD are independently transmitted

3) BPD and ADHD represent a genetic subtype

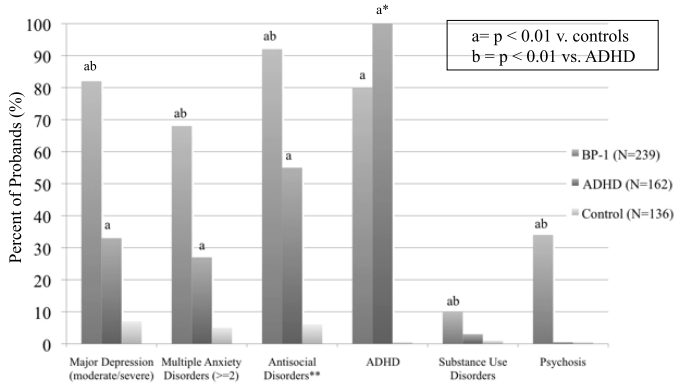
(the combined condition BPD+ADHD would be present in relatives of probands with the combined condition)

Meta-Analysis of Controlled Family Studies of Pediatric Bipolar Disorder:
Familiality in BP-I Probands vs Controls

Study	BP-I probands (N)	FAMILIALITY	
		BP-I	CONTROLS
Kutcher 1991	N=23	15%	1%
Wozniak 1995	N=16	13%	3%
Faraone 1997	N=15	16%	3%
Geller 2006	N=95	28%	4%
Wozniak 2010	N=157	18%	5%

Wozniak J Clin Psych, 2012

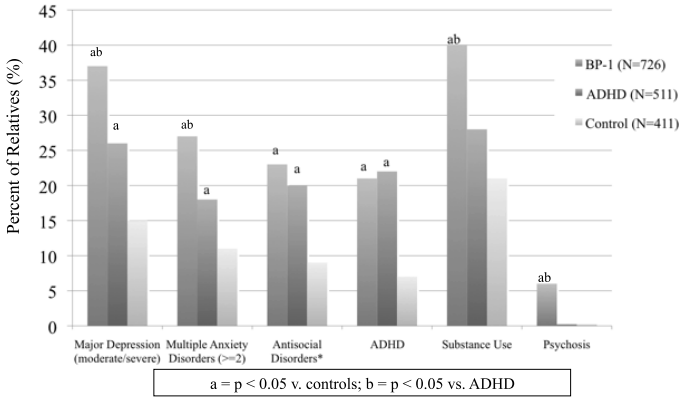
Rate of psychiatric disorders in pediatric bipolar disorder, attention deficit hyperactivity disorder (ADHD), and control probands



*By definition all probands in this sample have ADHD.
**Includes antisocial disorder, conduct disorder, oppositional defiant disorder

Wozniak J Clin Psych, 2012

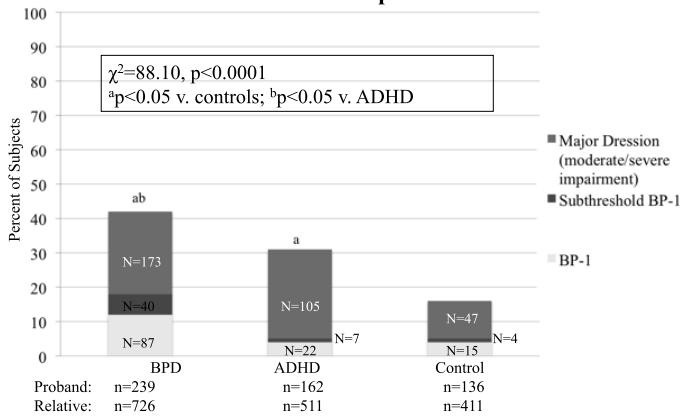
Rate of psychiatric disorders in first-degree relatives of pediatric bipolar disorder, attention deficit hyperactivity disorder (ADHD), and control probands



*Includes antisocial disorder, conduct disorder, oppositional defiant disorder

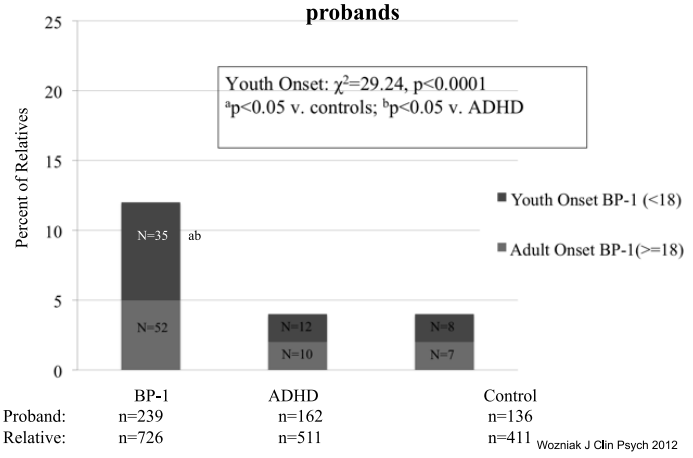
Wozniak J Clin Psych 2012

Risk for mood disorders in first degree relatives of pediatric bipolar disorder, attention deficit hyperactivity disorder (ADHD) and control probands



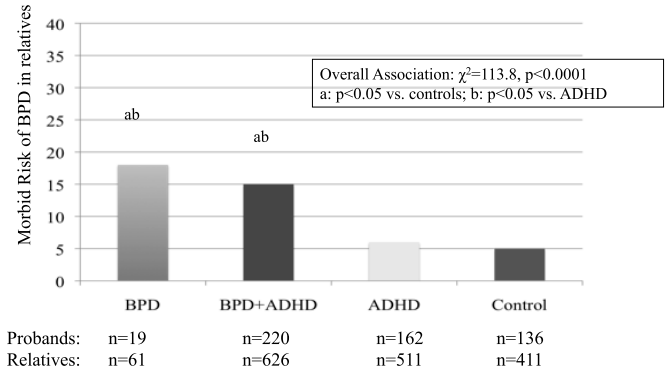
Wozniak J Clin Psych, 2012

Characteristics of first degree relatives of pediatric bipolar disorder, attention deficit hyperactivity disorder (ADHD) and control probands



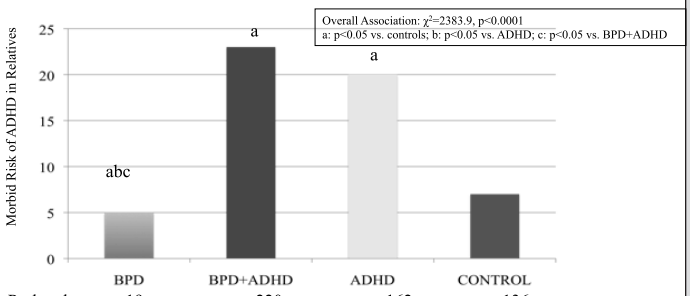
Wozniak J Clin Psych 2012

Morbid Risk of Bipolar Disorder in First Degree Relatives of Youth with Bipolar Disorder, Bipolar+ADHD, ADHD, and Controls



*No significant difference in risk between relatives of those in the BPD alone group vs. those in the BPD+ADHD group

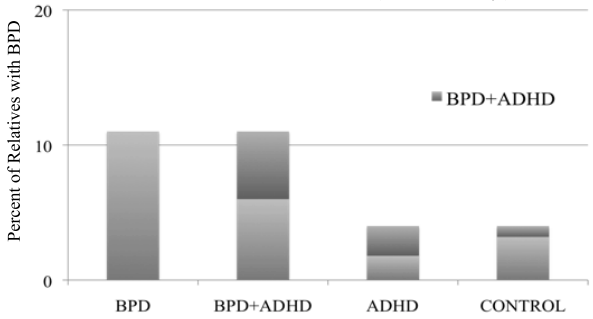
Morbid Risk of ADHD in First Degree Relatives of Youth with Bipolar Disorder, Bipolar+ADHD, ADHD, and Controls



	BPD	BPD+ADHD	ADHD	CONTROL
Probands:	n=19	n=220	n=162	n=136
Relatives:	n=61	n=626	n=511	n=411

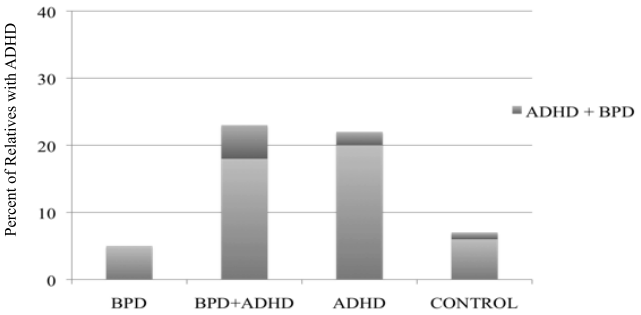
- Cosegregation
  - Among relatives of the BPD+ADHD probands
    - 46% (n=33) of the 71 relatives with BPD, also had ADHD
    - 20% (n=111) of the 555 relatives without BPD, had ADHD
    - X^2=24.92, p<0.001
  - Among relatives of the BPD only probands
    - 0 of the 7 relatives with BPD also had ADHD
    - 6% (n=3) of the 54 relatives without BPD, had ADHD
    - X^2=0.41, p=0.69

Percent of First Degree Relatives with Bipolar Disorder in Youth with Bipolar Disorder, Bipolar+ADHD, ADHD, and Controls (Familiality)



	BPD	BPD+ADHD	ADHD	CONTROL
Probands:	n=19	n=220	n=162	n=136
Relatives:	n=61	n=626	n=511	n=411

Percent of First Degree Relatives with ADHD in Youth with Bipolar Disorder, Bipolar+ADHD, ADHD, and Controls with ADHD (Familiality)



Probands:	n=19	n=220	n=162	n=136
Relatives:	n=61	n=626	n=511	n=411

From: Examining the Comorbidity Between Attention Deficit Hyperactivity Disorder and Bipolar I Disorder: A Meta-Analysis of Family Genetic Studies

Meta-Analysis of the Relative Risk of ADHD Among Relatives of Bipolar I Probands

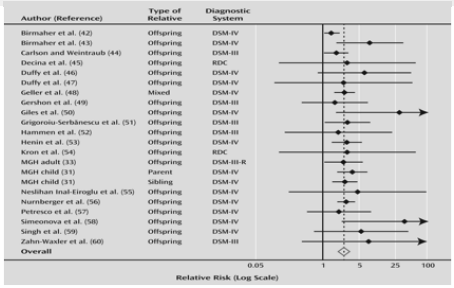


Figure Legend:

Meta-Analysis of the Relative Risk of ADHD Among Relatives of Bipolar I Probands[53] For each comparison, the dot is the relative risk and the horizontal line is the 95% confidence interval (95% CI). The center of the diamond at the bottom is the weighted relative risk across all studies, and the width of the diamond is its 95% CI. MGH=reanalysis of child and adult proband studies from Massachusetts General Hospital Pediatric Psychopharmacology Program (see Method section).

Am J Psychiatry. 2012;169(12):1256-1266. doi:10.1176/appi.ajp.2012.12010087

From: Examining the Comorbidity Between Attention Deficit Hyperactivity Disorder and Bipolar I Disorder: A Meta-Analysis of Family Genetic Studies

Meta-Analysis of the Relative Risk of Bipolar I Disorder Among Relatives of ADHD Probands

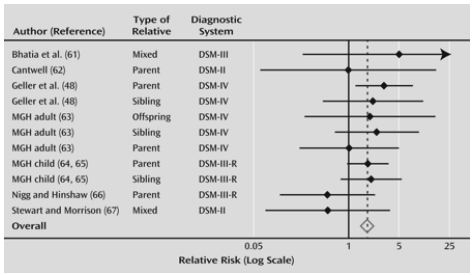


Figure Legend:

Meta-Analysis of the Relative Risk of Bipolar I Disorder Among Relatives of ADHD Probands[68] For each comparison, the dot is the relative risk and the horizontal line is the 95% confidence interval (95% CI). The center of the diamond at the bottom is the weighted relative risk across all studies, and the width of the diamond is its 95% CI. MGH=reanalysis of child and adult proband studies from Massachusetts General Hospital Pediatric Psychopharmacology Program (see Method section).

Am J Psychiatry. 2012;169(12):1256-1266. doi:10.1176/appi.ajp.2012.12010087

Bipolar Disorder and ADHD

CONCLUSIONS

Family history can be an external validator in cases of complicated comorbidity.

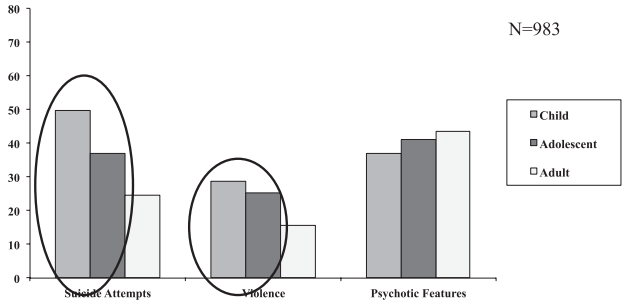
BPD+ADHD follow a pattern consistent with genetic cosegregation, suggesting a genetic subtype

Why is appropriate diagnosis important?
Because it leads to the best evidence based treatment

Treatment Risk versus Benefit includes *the risk of not treating* with attendant:

- Suicide attempts and completed suicide
- Substance Abuse and Addiction
- Reckless Behavior with Arrest
- Other consequences of hypersexuality and dangerous impulsivity

Bipolar adults with childhood and adolescent onset had more lifetime suicide attempts and violence



Perlis, Miyahara, Marangell, Wisniewski, Ostacher, DelBello, Bowden, Sachs, Nierenberg, Biol Psych 2004;55:875-881

Comorbidity of ADHD with Substance Abuse and Associated Risk Management Issues

Timothy E. Wilens, MD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

Comorbidity of ADHD with Substance Abuse and Associated Risk Management Issues

Timothy E. Wilens, M.D.
Director, Center for Addiction Medicine &
Senior Staff in Child Psychiatry

Massachusetts General Hospital
Harvard Medical School

Disclosures*

Dr. Wilens has served as a consultant, speaker, or has received grant support from the following

- NIH (NIDA, NIMH)
- Euthymics
- Shire
- Published Straight Talk About Psychiatric Medications for Kids (Guilford Press)

- The medications discussed in this presentation may not be FDA approved for the disorder(s) being discussed, dosing, age groups, or in context with substance use disorders.

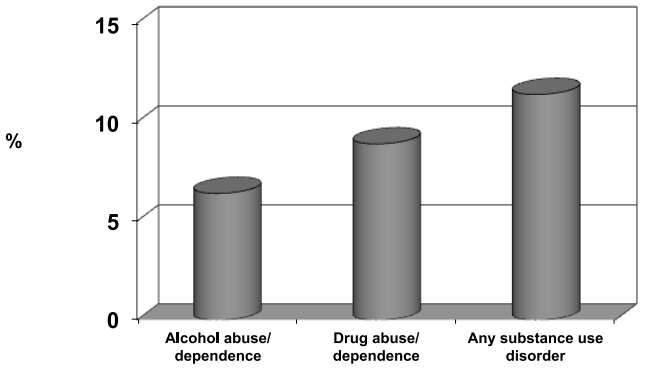
*** Past 3 years**

ADHD Overview

- Most common presenting neurobehavioral disorder in childhood
- Epidemiology: Worldwide 6-9% of children and adolescents; 4-5% of adults
- Chronic course characterized by inattention/ distraction, impulsivity, and hyperactivity
- Associated with impairment in multiple domains
- Nonpharmacological and pharmacological agents effective for treatment

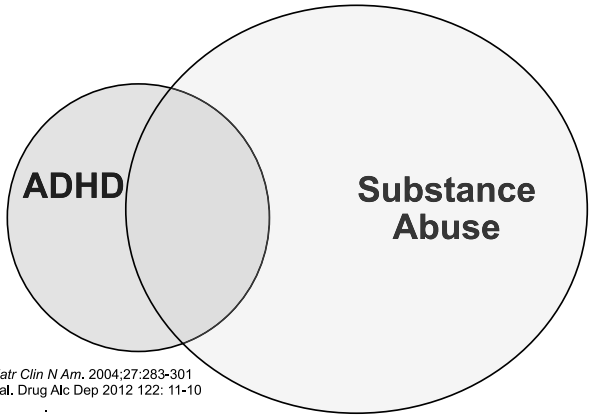
(Wilens and Spencer, ADHD Across the Lifespan, *Postgraduate Medicine*: 2010)

Lifetime Prevalence of DSM-IV Substance Use Disorders in the National Comorbidity Survey-Adolescent (NCS-A)



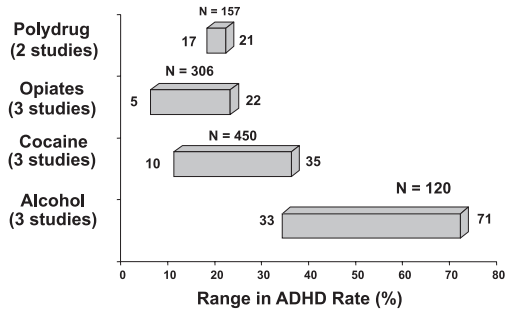
Merikangas et al. J.Am.Acad.Child Adolesc.Psychiatry, 2010;49(10):980-989

Overlap between ADHD and Substance Abuse (SUD)



Wilens T. *Psychiatr Clin N Am.* 2004;27:283-301
van Emmerick et al. Drug Alc Dep 2012 122: 11-10

ADHD + Substance Abuse: Illustrative Overlap in Adults With Substance Abuse



Overall, 23% of adults with substance abuse have ADHD (N=29 studies)*.

Wilens T. *Psychiatr Clin N Am.* 2004;27:283-301; *van Emmerick et al. Drug Alc Dep 2012 122: 11-19

Childhood ADHD is Related to Future Cigarette and SUD

Likelihood (Odds Ratio; OR) to Develop SUD

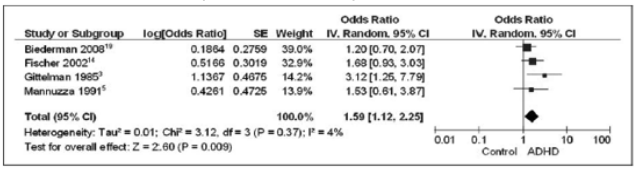


FIGURE 4 Meta-analysis of attention-deficit/hyperactivity disorder (ADHD) and psychoactive substance use disorder. Note: Results from a meta-analysis comparing ADHD versus control subjects for psychoactive substance use disorder. CI = confidence interval.

Likelihood (Odds Ratio; OR) to develop Cigarette Smoking

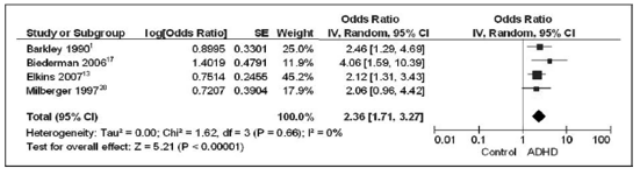
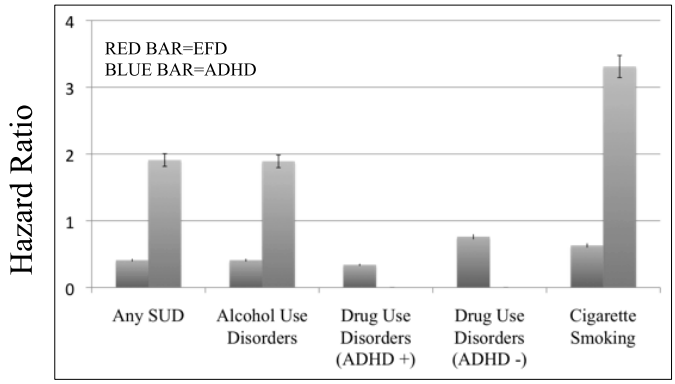


FIGURE 6 Meta-analysis of attention-deficit/hyperactivity disorder (ADHD) and nicotine use. Note: Results from a meta-analysis comparing ADHD versus control subjects for nicotine use. CI = confidence interval.

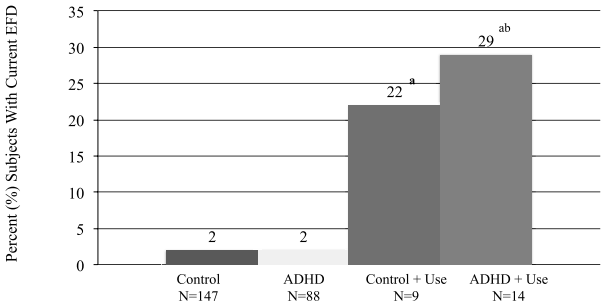
Charach et al. JAACAP 2011 50(1)9-21

Executive Function Deficits in Midadolescence Do Not Predict SUD 5 Years Later (N=412)



(Wilens et al. *J Am Acad Child Adolesc Psych* 2011 50: 141-149)

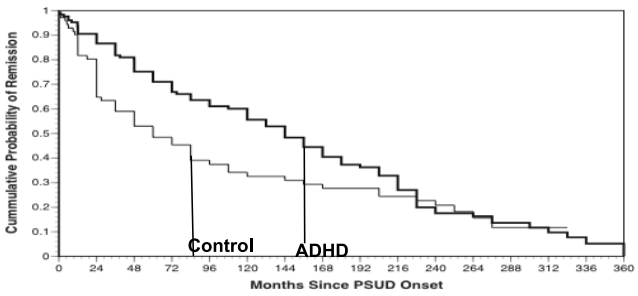
However, Cigarette Smoking Increase the Likelihood of Subsequent Executive Functioning Deficits in Transitional Aged Youth



(Wilens et al. *J Am Acad Child Adolesc Psych* 2011 50: 141-149)

Pairwise Comparisons:
[a] $p < 0.05$ vs. Controls; [b] $p < 0.05$ vs. ADHD; [c] $p < 0.05$ vs. both ADHD and Use

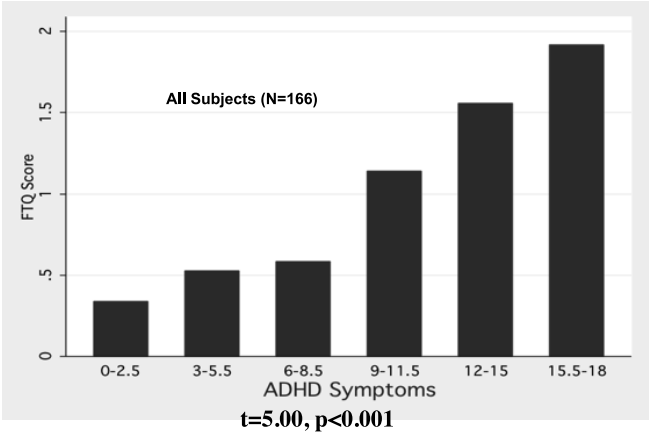
Rate of Remission from Psychoactive Substance Use Disorders (PSUD) in ADHD and Non-ADHD Control Adults



BOLD line indicates ADHD adults, THIIN line indicates non-ADHD Control Adults.
See Table 2 for statistically significant predictors of remission.

(Wilens et al. Am J Add:1998)

ADHD Symptoms are Directly Related to Higher Smoking Scores

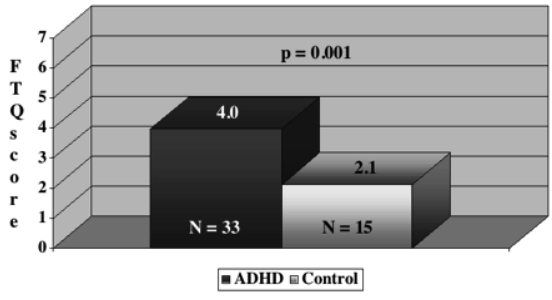


t=5.00, p<0.001

(Wilens, Vitulano, Upadhyaya et al. *Journal of Pediatrics* 2008; 153: 414-419)

Smoking Severity is Greater in ADHD

FTQ Score for Smokers

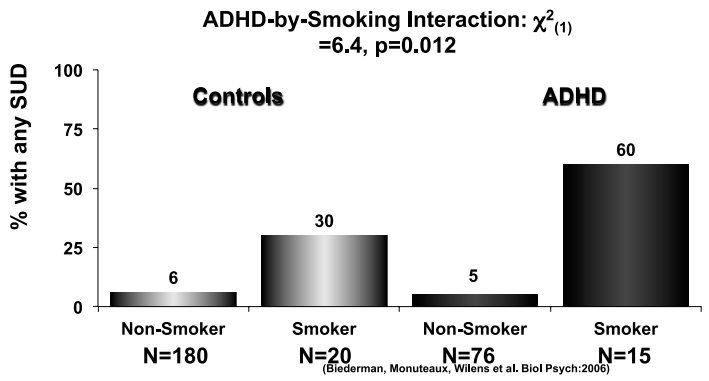


Age: Mean=19.6, Range 15-25

FTQ denotes Fagerstrom Tolerance Questionnaire

(Wilens, Vitulano, Upadhyaya et al. *Journal of Pediatrics* 2008; 153: 414-419)

Smoking and Subsequent Substance Use Disorders in Youth with and without ADHD



(Biederman, Monuteaux, Wilens et al. Biol Psych:2006)

Course of SUD Associated with ADHD

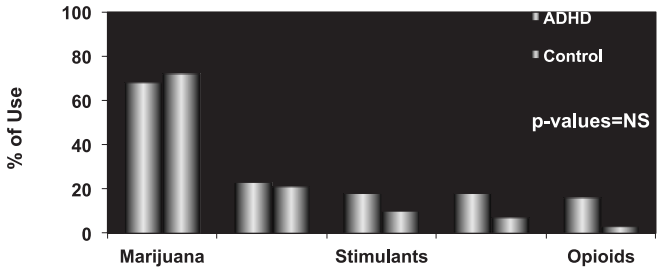
- Lower retention in SUD treatment
- Longer course of SUD
- More severe SUD
- Higher rates of other psychiatric comorbidities (e.g. conduct/antisocial disorders)
- Less remission from SUD

(Carroll and Rounsaville, Comp Psych 1993: 34:75-82; Schubiner et al J Clin Psych:2000:61:244-251 Levin et al. Drug Alc Dep 1998; 52:15-25; Levin et al. 2004; Wilens et al. Am J Add 1998, 2004)

What Links ADHD and Substance Abuse ?

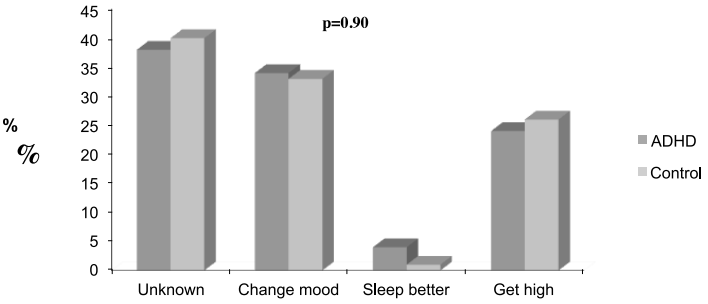
ADHD Adults Do Not Selectively Abuse Specific Drugs

Classes of Drugs Abused in Adults With a Drug Use Disorder



Biederman, Wilens & Mick *Am J Psychiatry.* 1995;152(11):1652-1658.

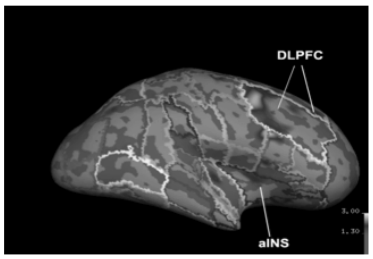
ADHD and Controls with Substance Use: Motivation for Drug Use



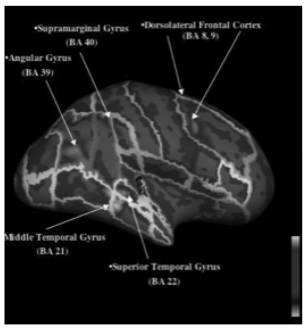
(Wilens et al. Am J Addictions: 2006)

Cortical Thinning Similarities between Cocaine Addiction and ADHD

Adult with Cocaine Addiction



Adult with ADHD



(Makris et al. Cerebral Cortex, 2006)

ARTICLES

nature neuroscience
2012; 15(6):920-7.

Adolescent impulsivity phenotypes characterized by distinct brain networks

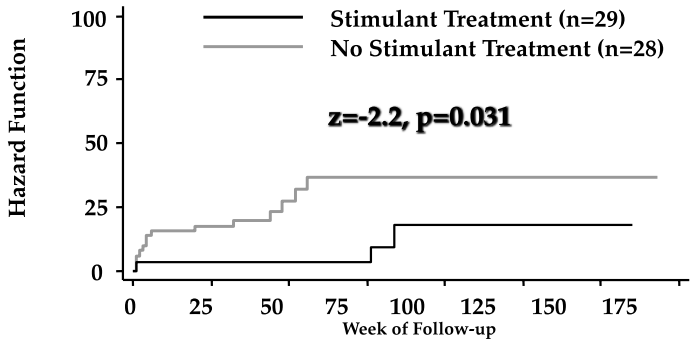
Robert Whelan[1,2], Patricia J Conrod[3,4], Jean-Baptiste Poline[5], Anbarasu Lourdusamy[3], Tobias Banaschewski[6], Gareth J Barker[3], Mark A Bellgrove[7], Christian Büchel[8], Mark Byrne[2], Tarrant D R Cummins[7], Mira Fauth-Bühler[9], Herta Flor[10], Jürgen Gallinat[11], Andreas Heinz[11], Bernd Ittermann[12], Karl Mann[9], Jean-Luc Martinot[13,14], Edmund C Lalor[2], Mark Lathrop[15], Eva Loth[3,16], Frauke Nees[10], Tomas Paus[17–19], Marcella Rietschel[20], Michael N Smolka[21,22], Rainer Spanagel[23], David N Stephens[24], Maren Struve[10], Benjamin Thyreau[5], Sabine Vollstaedt-Klein[9], Trevor W Robbins[25], Gunter Schumann[3,16], Hugh Garavan[1,2] & the IMAGEN Consortium[26]

The impulsive behavior that is often characteristic of adolescence may reflect underlying neurodevelopmental processes. Moreover, impulsivity is a multi-dimensional construct, and it is plausible that distinct brain networks contribute to its different cognitive, clinical and behavioral aspects. As these networks have not yet been described, we identified distinct cortical and subcortical networks underlying successful inhibitions and inhibition failures in a large sample (n = 1,896) of 14-year-old adolescents. Different networks were associated with drug use (n = 1,593) and attention-deficit hyperactivity disorder symptoms (n = 342). Hypofunctioning of a specific orbitofrontal cortical network was associated with likelihood of initiating drug use in early adolescence. Right inferior frontal activity was related to the speed of the inhibition process (n = 826) and use of illegal substances and associated with genetic variation in a norepinephrine transporter gene (n = 819). Our results indicate that both neural endophenotypes and genetic variation give rise to the various manifestations of impulsive behavior.

Prevention of Substance Abuse in ADHD Youths

Concurrent Stimulant Treatment and Smoking Initiation in ADHD Youth

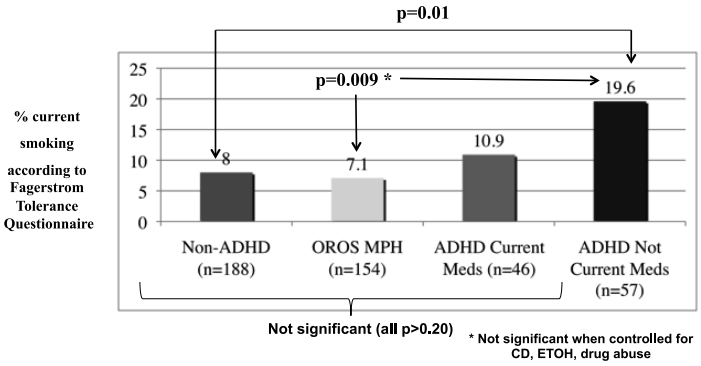
(Monteaux, Biederman, Wilens et al. J Clin Psych: 2007)



Prevention study of bupropion for cigarettes (Duration up to 6 years).

Primary outcome: Bupropion not effective. Secondary outcome- Stim treatment and outcome

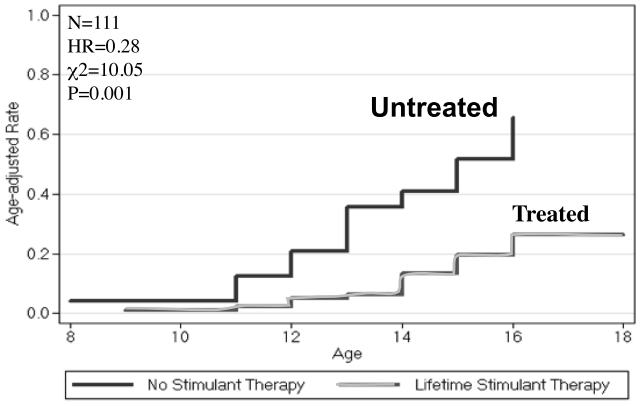
Smoking Outcomes (mean 10 mo [up to 24 mo]): Clinical Trial Subjects vs. Comparators



Hammerness P, et al. *J Pediatr 2012*

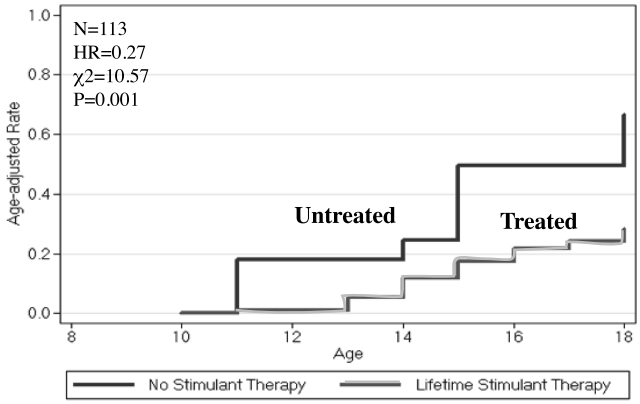
MGH Study of Adolescent Girls with ADHD: Stimulant Treatment Protects Against Subsequent Cigarette Smoking

(Wilens et al. Arch Ped Adoles Med, 2008)



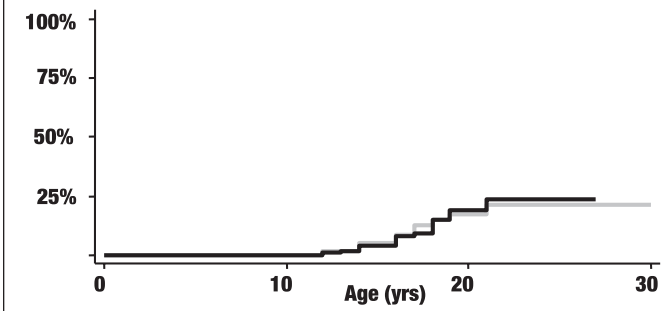
MGH Study of Adolescent Girls with ADHD: Stimulant Treatment Protects Against Subsequent Substance Use Disorder

(Wilens et al. Arch Ped Adoles Med, 2008)



Treatment of ADHD Does Not Impact Later Alcohol Dependence in Young Adults

(Biederman, Monateaux, Wilens et al, *Am J Psych*, 2008)



Note: These results are similar to those of Mannuzza et al. *Am J Psych*, 2008)

Cases

- Use of National Patient Register - looking for at least one diagnosis ADHD per ICD-9 or ICD-10 (data available for all inpatient psychiatric hospitalization since 1973 and all outpatient diagnoses since 2001
- Cases are born no later than 1990
- Then they use Prescribed Drug Register for data on prescriptions (data from 2005 onward).

Controls

- 10 controls to each case (matched year of birth, sex, and geographic location)
- Stated they obtained them from general population sample

Criminality

- National Crimes Register (convictions since 1973)
- Register of Persons suspected of a crimes (Suspected even if not proven)

Also used

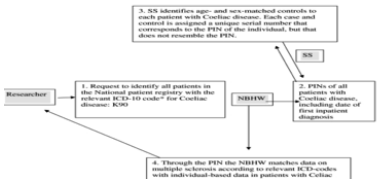
Migration, cause of death, and prison registers to account for migration/deaths/imprisonment.

They used "population-based registers in Sweden, with unique personal identification numbers, enabling accurate linkage."

Swedish health care and national health registers are dependent on the presence of a unique identifier

The personal identification numbers are unique identifiers in the Total Patient Register, includes data on name, place of residence, sex, age, civil status, immigration, relations etc.

Below is an example of how the personal identification number (PIN) would work in a research trial, in this case for celiac disease (image from paper [1]),



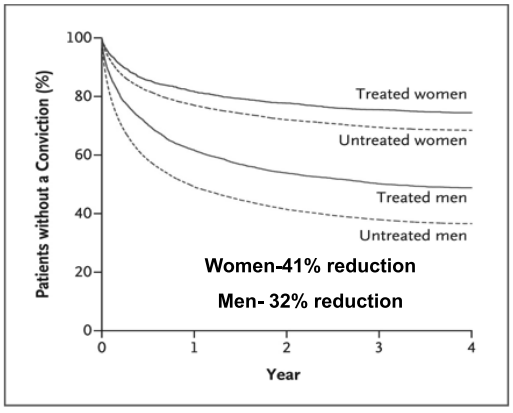
Medication for ADHD and Criminality

- Focus on drug arrests- a proxy drug/alcohol use disorders
- Swedish national registry of outpatients and inpatients with ADHD
- N = 25,656 ADHD
- 5 year followup
- About 50% of ADHD on medications.
- Approximately 40% of convictions related to drug offenses

(Lichtenstein et al. NEJM 2012: 367:2006-2014)

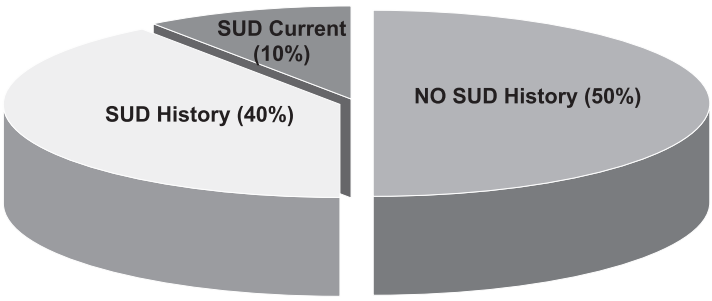
ADHD Medications Reduce Drug and Other Related Criminality

(Lichtenstein et al. NEJM 2012: 367:2006-2014)



Swedish national registers (N= 25,656 with ADHD-about 50% on medications. Approximately 40% of convictions related to drug offenses (Tx OR=0.6). No difference in type of ADHD medication (stimulants, nonstimulants) or level of crime.

SUD in ADHD Adults Presenting for Treatment



ADHD ADULTS

(SUD rates from Wilens et al. Am J Add:1998)

For every complex problem, there is a simple solution

And it is wrong

George Bernard Shaw

Double-Blind Studies Using Stimulants to Treat Current Substance Abusers with ADHD

5 Studies:

- **1 study in adolescent substance abusers administered Pemoline**
- **2 studies in adult cocaine abusers administered IR or SR MPH**
- **1 study in adult methadone maintenance patients administered SR MPH or SR-Bupropion**
- **1 study in adults with briefly abstinent amphetamine abusers given OROS MPH**

♦ **Efficacy (vs placebo)**

- **No overall improvement in SUD (trend to improvement in one)**
- **Two studies suggest benefit in reducing ADHD symptoms on some measures but not others**

♦ **Safety**

- **No serious adverse events**
- **No worsening of SUD**
- **No evidence of diversion**

Schubiner et al., *Exp Clin Psychopharmacol*. 2002;10(3):286-94; Riggs, et al. *JAACAP*. 2004; 43(4): 420-430; Levin, et al. 2006 a,b; Konstenius M et al. *Drug and Alcohol Dependence* 2010: 108:130-3)

NIDA Clinical Trial Network: Controlled Cigarette Cessation Study of OROS MPH in Adult Cigarette Smokers with ADHD

Methods

- N=252 adults (126/arm); 6 sites, > 1/2 pack per day smoking
- OROS MPH dose of 72 mg/day
- Brief weekly individual "Smoke Free CBT"
- Nicotine patch: 21 mg/day; target quit date end of week 4

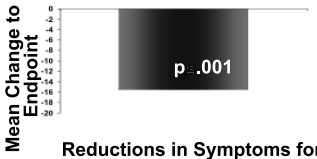
Outcome: OROS MPH vs Placebo

- Improved ADHD ($p<0.0001$)
- No change in cigarette cessation (primary)
  - No worsening of cigarette smoking
  - Trend to fewer cigarettes in OROS MPH group
  - (More severe cases had improvement in cigarette use [secondary])
- Predictable adverse effects; no clin. significant CV effects

(Winhusen et al. J Clin Psych 2010; Covey et al. Nic Tob Res: 2011)

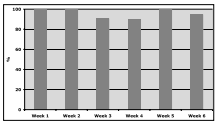
Lack of Improvement in SUD in Adults With ADHD+Mixed Substance Abuse (N=32) Treated Openly with Bupropion SR

ADHD



Reductions in Symptoms for Baseline to Endpoint (LOCF)

Substance Use (Self Report)



(Wilens et al. J Att Rel Dis [2010]:1(3):25-35)

NIDA Clinical Trial Network: Controlled Study of OROS MPH + CBT in Adolescents with ADHD and Mixed SUD

Methods

- 16 week randomized study in mixed SUD (no opioid or meth)
- N=150 /arm (11 sites); OROS MPH dose = 72 mg/day (>95% tolerated)
- Weekly individual CBT

Outcome

- Both groups improved in ADHD and in SUD
- OROS MPH vs Placebo:
  - No significant improvement in ADHD (investigator/parent)
  - No significant improvement in SUD (adolescent self report)
    - Trends to fewer (+) urines in OROS MPH group
- Predictable adverse effects and low abuse

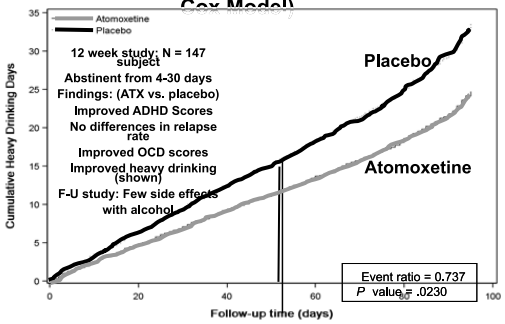
(Riggs et al. J Am Acad Child Adolesc Psych 50: 903-914: 2011)

Atomoxetine in Adolescent SUD and ADHD

Thurstone et al. J AM Acad Child Psych 2010: 49(6): 573-582

- **N= 70 adolescents with ADHD. All subjects had at least one active non-nicotine SUD.**
- **Design: 12 weeks of atomoxetine or placebo in addition to motivational interviewing/cognitive behavioral therapy.**
- **Results: There were no differences between ADHD scores or in use of substances between treatment groups that emerged during the study.**
- **Note: The authors speculated that the therapy may have contributed to a larger than expected placebo response.**

Atomoxetine vs Placebo in Recently Abstinent Adults with Alcohol Use Disorder: Recurrent Episodes of Heavy Drinking (Multiple Event Cox Model)



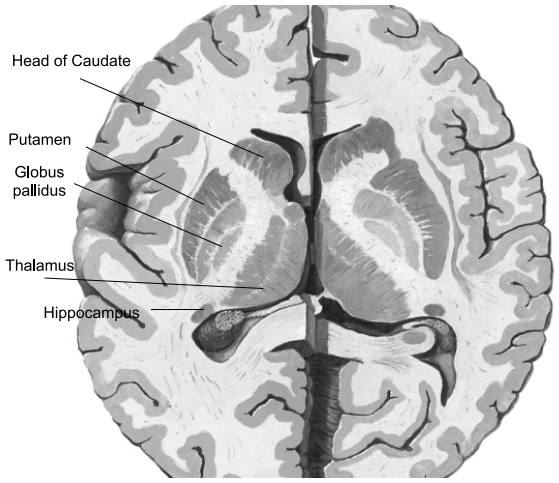
An event ratio of 0.737 indicates that, relative to patients treated with placebo, atomoxetine-treated patients experienced an approximately 26.3% greater reduction in the rate of heavy drinking. Separation between groups first occurred at day 55.

(Wilens et al. *Drug Alc Dep* 2009:96:145-154 2008; Adler et al. *Am J Addict* 2009:18: 393-401)

Stimulant Misuse and Diversion

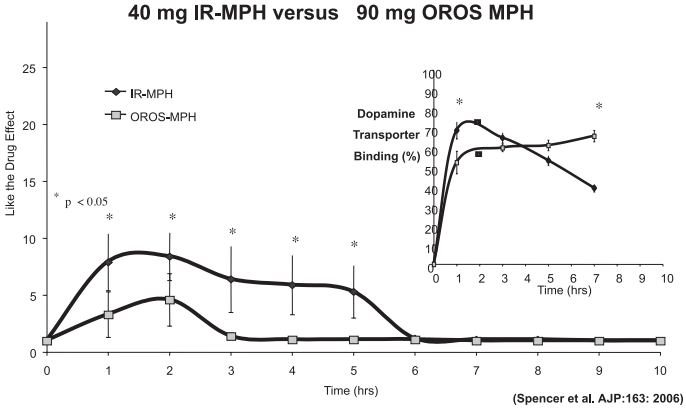
- **N=22 Studies (N>113,000 participants); mostly survey studies in college students (80%)**
- **10-20% prevalence of non medical use of stimulants**
- **65-85% of stimulants diverted from "friends"**
  - **Majority *not* "scamming" local docs**
  - **Not seen as potentially dangerous**
- **Motivation typically for concentration and alertness more so than getting "high"**
- **Appears to be occurring in substance (ab)users during academic decline**
- **Increased risk of SUD in stimulant misusers (not causal)**

(McCabe and Teeter, Addiction; 2005; Arria et al. Sub Abuse:2007; Wilens et al. JAACAP: 2006, 2008)



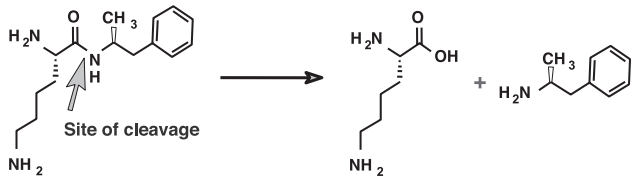
Stimulant Preparation Linked to Dopamine Transporter Binding and Likeability

40 mg IR-MPH versus 90 mg OROS MPH



(Spencer et al. AJP:163: 2006)

Lisdexamfetamine Chemistry



Prodrug stimulant: L-lysine covalently linked to d-amphetamine
May have lower abuse liability compared to IR d-amphetamine

(Jasinski et al. Psychopharmacology, 2008)

ADHD + SUD: Clinical Recommendations

- Non-pharmacologic approaches
  - For ADHD: Cognitive-remediation, self-help, group and individual psychotherapy (e.g. cognitive-behavioral therapy)
  - Family Tx for adolescents and young adults Non-stimulants:
- Consider non-stimulants for current substance abusers or those that are recently abstinent
- Atomoxetine
  - Lacks abuse liability
  - Useful in comorbid cases
  - Efficacy data in abstinent alcohol + ADHD (for both ADHD and SUD)
  - No AEs with alcohol or THC
- Bupropion
  - No known interactions with alcohol or THC
  - Efficacy in cigarette cessation & mood disorders
- Guanfacine, clonidine, modafinil, tricyclics-untested but potentially useful

Wilens TE. *Psychiatr Clin North Am*. 2004;27(2):283-301; Wilens & Morrison *Curr Opinions 2011; 24: 280-285*.; Riggs PD, et al. *J Am Acad Child Adolesc Psychiatry*. 1998;37(3):331-2; 50: Riggs et al. *J Am Acad Child Adolesc Psychiatry* 903-914:2011; Schubiner H. *CNS Drugs*. 2005;19(8): 643-55.; Wilson JJ, Levin FR. *J Child Adolesc Psychopharmacol*. 2005;15: 751-763.; Mariani JJ, Levin FR. *Adv Psychiatry*. 2006).

SUD in ADHD:
Clinical Recommendations Prior to Treatment

- Stimulants:
  - Use in substance-abusing patients is complex and controversial
  - If possible, include family members or close nonsubstance-abusing friends involved in the treatment plan
  - Use extended-release formulations of stimulants (e.g. lisdexamfetamine, OROS MPH, d-MPH XR, MPH-LA, MAS XR or MPH SR, MTS/patch)

Wilens TE. *Psychiatr Clin North Am*. 2004;27(2):283-301; Wilens & Morrison *Curr Opinions 2011; 24: 280-285*.; Riggs PD, et al. *J Am Acad Child Adolesc Psychiatry*. 1998;37(3):331-2; 50: Riggs et al. *J Am Acad Child Adolesc Psychiatry* 903-914:2011; Schubiner H. *CNS Drugs*. 2005;19(8):643-55.; Wilson JJ, Levin FR. *J Child Adolesc Psychopharmacol*. 2005;15: 751-763.; Mariani JJ, Levin FR. *Adv Psychiatry*. 2006).

Conclusions

- ADHD is a risk factor for SUD
- ADHD-SUD link both neurobiologically and environmentally mediated
- Protective effects into adolescence appear operant with treatment of ADHD
- Treatment of comorbid individuals requires management of both SUD and ADHD
- Risk/diversion of stimulants an issue-particularly in transitional aged youth (e.g. 16-25 yo)

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MGH Website on Addictions

www.addictionanswers.com

CBT & Psychosocial Treatments in ADHD

Aude Henin, PhD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

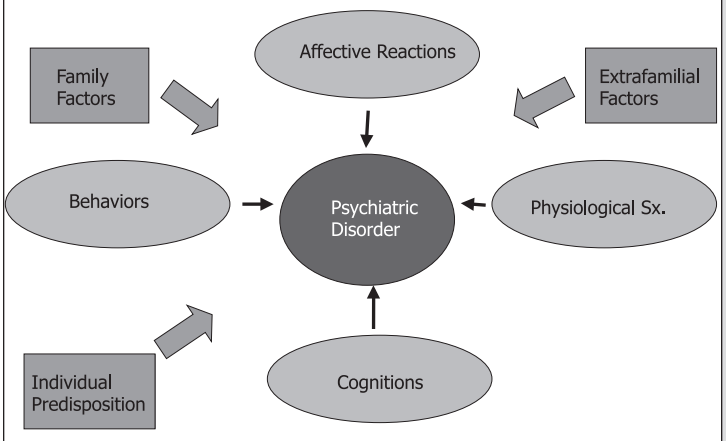
Cognitive-Behavioral Therapies for ADHD

Aude Henin, Ph.D.
Massachusetts General Hospital

Disclosures

Source	Consultant	Advisory Board	Stock of Equity > $10,000	Speakers Bureau	Research Support	Royalties	Honorarium for This Talk or Meeting	Expenses Related to THIS Talk or Meeting	Other Honorarium
Pfizer	X								
Concordant Rater Systems	X								
Oxford University Press						X			

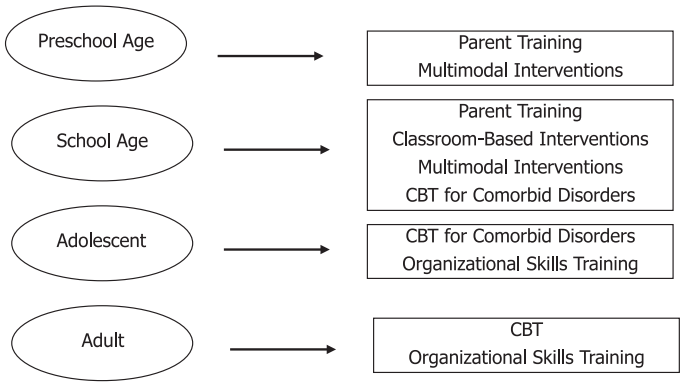
CBT Model



Common Aspects of BT/CBT Approaches

- Therapy is usually time-limited
- Emphasis on manualized, empirically-supported treatments
- Sessions are structured
- Therapist is active
- Therapist as “coach”, teacher
- Collaborative enterprise with patient
- Active practice of skills between sessions

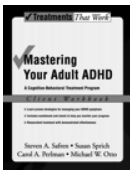
Developmental Perspective on CBT Interventions



Organizational Skills Training

CBT-ADHD Overview

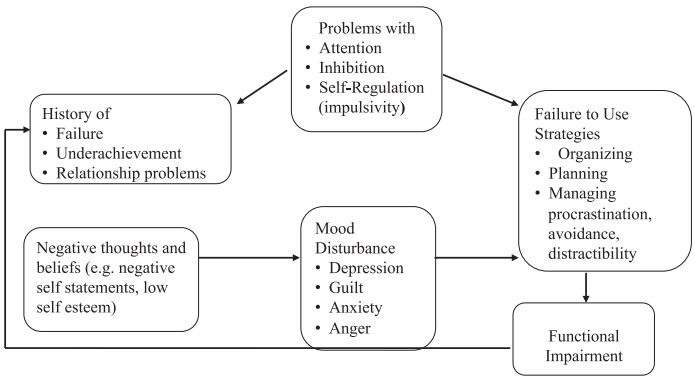
Modules: 12 sessions, each 50 minutes long



CORE MODULES
- Psychoeducation, Organizing and Planning
- Coping with Distractibility
- Cognitive Restructuring

OPTIONAL MODULES
- Procrastination
- Session with significant other

CBT Model of ADHD



Organizational Strategies

- Develop a system to manage tasks and appointments
- Using a calendar and task list
  - Write everything down
  - Keep all to-do's in one place
  - Use of reminders/alarms
  - Creating routines around to-do's
  - Using self-reinforcement/self-reward

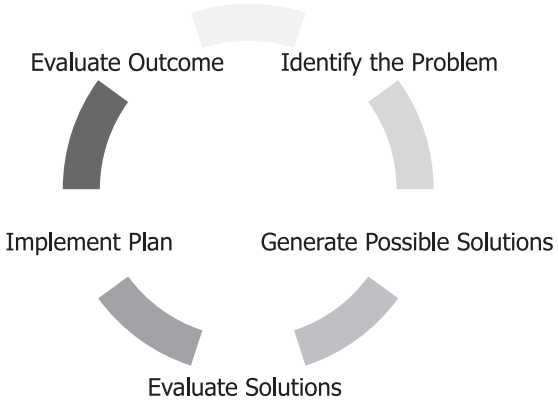
Organizational Systems

- Prioritizing Tasks
  - Use of A-B-C system
  - A=most important, do right now
  - B=less important, longer-term
  - C=least important, can wait
- Reduce tendency to start with fun, easier tasks

Organizational Systems

- Organizing objects:
  - Everything has a place; creating routines
  - Breaking large tasks into smaller ones
  - Setting up regular routines around organization
  - System must be easy, useable

Problem Solving Skills



Distraction Management

- Distractibility Delay
  - Measure attention span
  - Break down task to fit attention span
  - If distractions occur during this time, write them down and continue working
  - Review distractions after the task is completed
- Reducing Sources of Distraction
  - Identify common distractions
  - Use problem solving to decrease these

Cognitive Restructuring

Goals:

- Identify negative/distorted cognitions
- Develop alternate, more realistic/helpful ways of viewing the situations (coping thoughts)
- To develop

Cognitive Restructuring Worksheet

Situation	Thoughts	Emotion (0-10)	Challenge	Emotion (0-10)
Taking a test	I am going to fail! I can't do this.	Anxious (7) Hopeless (6)	I have to try my best. I studied hard for this test and I did well on the last 2 tests.	Anxious (3) Hopeful (3)
Doing Homework	I don't feel like doing it now. I'll do it later	Stressed (5) Bored (6)	I've got to get it done sometime and I won't want to do it later. Let me do a little now.	Focused (4) Stressed (3)

Managing Procrastination

- Identifying triggers for procrastination
  - Not sure where to start?
  - Anxiety about task?
  - Unhelpful cognitions?
- Use MI approach (short/long term pros & cons)
- Develop plan for coping with procrastination
  - Break down task into smallest component
  - Implement cognitive strategies
  - Link task to more frequent task (Premack principle)

Involvement of Significant Others

- Present CBT model of ADHD
- Discuss concerns and impact of ADHD on the family
- Discuss how to support patient in implementing skills
- Managing expectations

Managing Pitfalls and Problems in Treatment

- Motivation
- Difficulty doing Homework between sessions
- Frustration

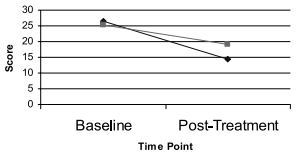
CBT Adults - Methods

- 86 men and women taking medications for ADHD who still had clinically significant (CGI of 3 or greater) symptoms
- 2 arms – random assignment
  - CBT
  - Relaxation with Educational Support (RES)
- Independent Assessor
  - ADHD Rating Scale
  - Clinical Global Impression (CGI)
  - Hamilton Anxiety and Depression Scales
- Self Report
  - Current Symptoms Scale
  - Beck Depression and Anxiety Inventory

Safren et al. 2010, JAMA

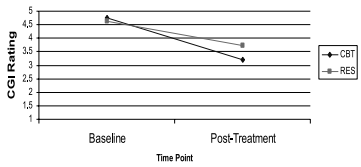
Results: Continuous Symptom Scores Baseline and Post-Treatment

IA Rated ADHD Rating Scale



CBT had significantly better IA-rated scores on the ADHD rating scale than those who were assigned to RES (magnitude −4.631; 95% CI, −8.30 to −0.963; *p*=.02)

IA Rated CGI



CBT had significantly better IA rated CGI scores than those who were assigned to RES (magnitude −0.0531; 95% confidence interval [CI], −1.01 to −0.05; *p*=.03)

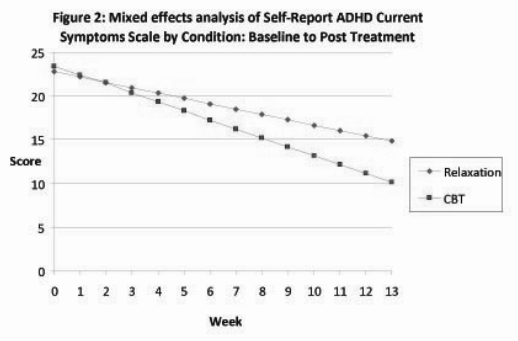
Safren et al. 2010, JAMA

Results: Categorical "responders"

- CBT had a greater number of CGI "responders" (2 point or greater reduction), OR = 3,80, 3.80; 95% CI, 1.50 to 9.59; *P*=.01
  - •CBT: 53%
  - •RES: 23%
- ADHD Rating Scale "responder" = 30% or greater reduction in symptoms (medication trial standard), OR = 4.29; 95% CI, 1.74 to 10.58; *P*=.002
  - •CBT: 67%
  - •RES: 33%

Safren et al. 2010, JAMA

Results: Session by Session Self-Report (CSS) Ratings



Within-subject longitudinal models: the slope of improvement (Figure 2) in the CBT condition was greater than that for the RES condition (ß = -0.407; p<.0001).

Safren et al. 2010, JAMA

Longitudinal Follow-up of those in CBT with partial or full response (a-priori)

- Slopes did not differ from zero indicating maintenance of gains
  - ADHD rating scale (=−0.12;95%CI,−0.41to 0.18;*P*=.41),
  - CGI (=0.01[95%CI, −0.03 to 0.05];*P*=.59)
  - self-report Current Symptoms Scale (=0.05 [95% CI, −0.04 to 0.15]; *P*=.26)

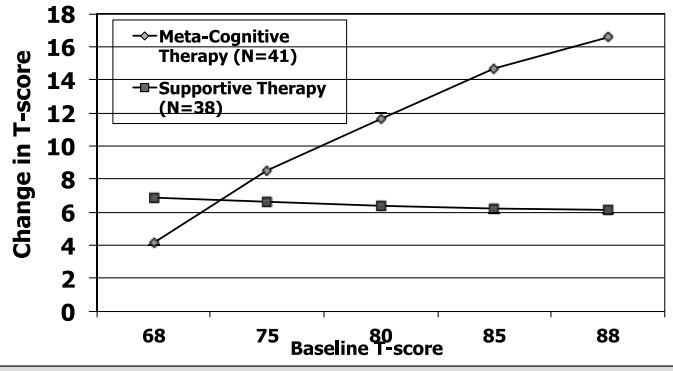
Safren et al. 2010, JAMA

- CBT superior to a time-matched control (Relaxation with educational support)
- Gains were maintained over follow up
- Effects specific to ADHD symptoms (e.g. both groups showed distress reductions)
- Future directions:
  - •Test with individuals unable or not willing to take medicines
  - •Pilot testing with adolescents (14-17) currently underway

Meta-Cognitive Therapy for Adult ADHD (Solanto et al., 2010)

- 12-session group therapy
- Focuses on:
  - Providing contingent self-reward
  - Dismantling complex tasks into manageable parts
  - Sustaining motivation towards distant goals
- Integrates traditional CBT techniques (e.g., cognitive restructuring)
- Uses self-instruction with a cognitive response to problems
- Uses support and modeling by therapist and group members

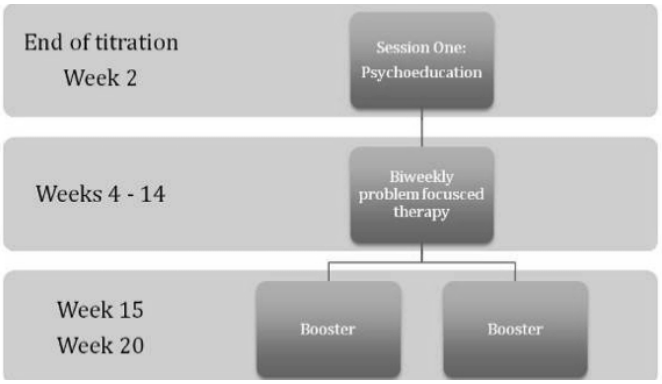
Results of Meta-Cognitive Therapy



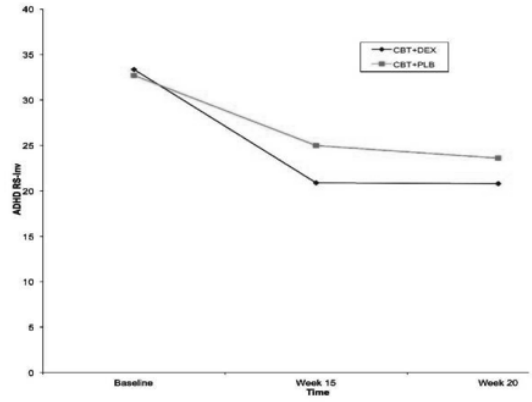
Randomized Trial of CBT for Adults with ADHD with and without Medication

- 23 participants randomized to CBT and Dextroamphetamine
- 25 participants randomized to CBT and placebo
- Patients and investigators blind to treatment assignment
- Two co-primary outcomes were used:
  - ADHD symptoms on the ADHD-RS-Inv
  - Sheehan Disability Scale (self-report)

CBT Treatment Modules

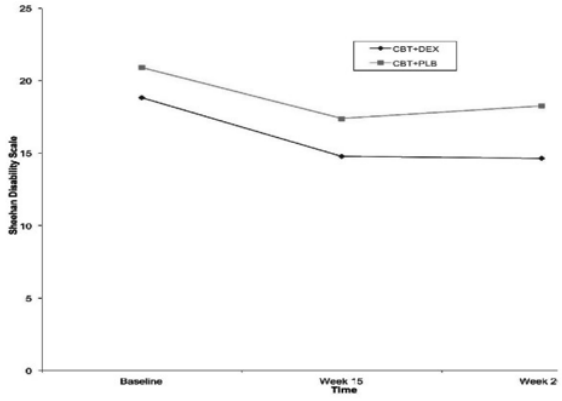


Results: ADHD RS-Inv (Weiss et al., 2012, BMC Psychiatry)



Results: Sheehan Disability Scale

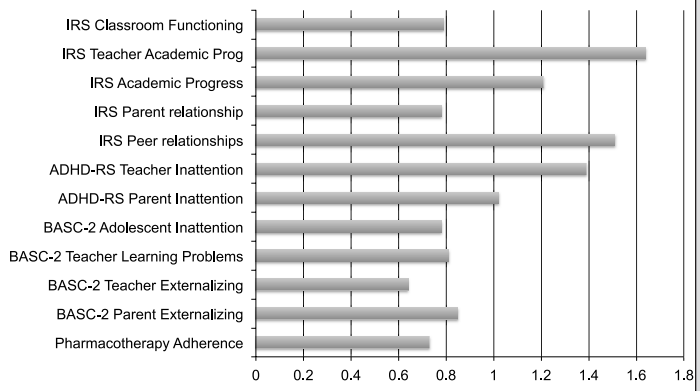
(Weiss et al., 2012, BMC Psychiatry)



CBT for Adolescents with ADHD

- 68 adolescents with ADHD and associated psychiatric comorbidities
- Downward extension of Safren et al. adult CBT protocol
- Outcome variables consisted of:
  - narrow band (ADHD) symptom
  - broadband (e.g., mood, anxiety, conduct) symptom measures
  - functioning measures

CBT for Adolescents with ADHD (Effect Sizes)



Antshel et al. 2012 J. Attention Disord

Organizational Skills Training for 3rd to 5th Graders (Abikoff et al. 2013 JCCP)

- Aim: To ameliorate organization, time management and planning
- Design:
  - 158 3rd-5th grade children with ADHD randomized to:
    - Organizational skills training (OST)
    - Non-skills, performance-based intervention (PATHKO)
    - Wait-list control condition (WL)

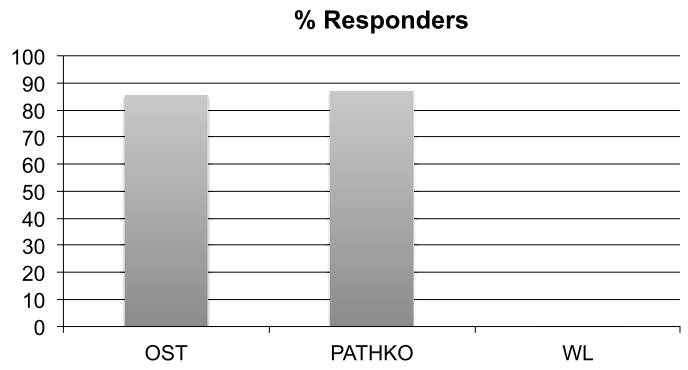
Structure of OST Intervention

- 20 individual sessions held over 10-12 weeks
- Parents included for last 10 mins of session
- Skills included:
  - Recording assignments and due dates
  - Organizing school papers/using checklists
  - Tracking time for task completion
  - Breaking tasks into steps
  - Use of skills to address “glitches” and maximize use of their “Mastermind”
- Work with parents/teachers to monitor/reward skill implementation

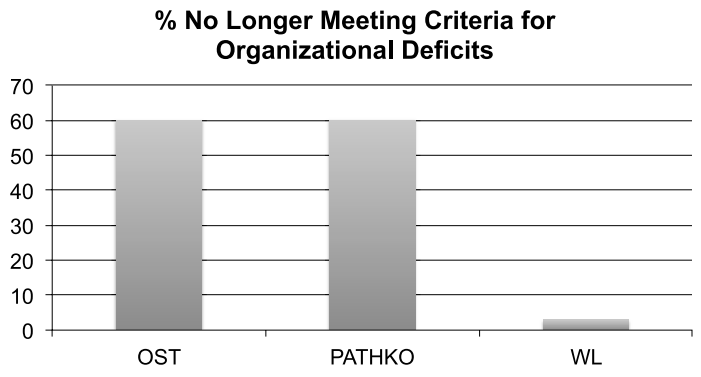
Structure of PATHKO Intervention

- 20 sessions held with parents (children come in briefly at the end)
- Focus is on motivating children
- Training parents and teachers to:
  - Establish specific individualized goals
  - Use “Daily Report Cards”
  - Prompt, monitor, praise/reward children for meeting goals
  - Use of token Economy System
  - Establish homework rules and structures

Post-Treatment Respons on CGI-I



Post-Treatment Clinically Meaningful Change



Results (Abikoff et al., 2013 JCCP)

- Children treated with OST (compared to WL) improved significantly in their home and school organization, time management, and planning
- There were few differences between OST and PATHKO at post-trmt
- OST was superior to PATHKO in parent ratings of organizational skills at post-trmt and 2 Yr follow up
- Though there was some decline, org skills remained improved over 2 yr FU

Parent Management Training Approaches

Behavioral Management Techniques

- Based on operant behavioral principles

  - Positive/negative reinforcement
  - Punishment
  - Contingent reinforcement
  - Extinction
  - Identifying antecedents to behaviors
  - Modeling

Rationale

- Children with ADHD have deficits in rule-governed behaviors
  - Parents may need to use more explicit, systematic ways of presenting and enforcing rules to address these deficits

Rationale

- Symptoms of ADHD contribute to impairment in the parent-child relationship
  - Parents may develop maladaptive parenting strategies to deal with behavioral difficulties
  - Modifying poor parenting practices may increase positive outcomes in children

Examples of PMT Approaches

- *Defiant Children* (Barkley, 1997)
- *The Incredible Years* (Webster-Stratton, 1992)
- *Parent-Child Interaction Therapy* (PCIT; Eyberg & Robinson, 1982)
- *Triple P-Positive Parenting Program* (Sanders et al., 2000)
- *New Forest Parenting Package* (NFPP: Sonuga-Barke et al., 2006)

PMT Strategies

- Review of information on ADHD and causes of non-compliant behaviors
- Rewarding prosocial behaviors (Catching your child being good)
  - Attending to positive behaviors
  - Praising positive behaviors
  - Child-centered play (PCIT)
  - Token Economy System (points; stickers)

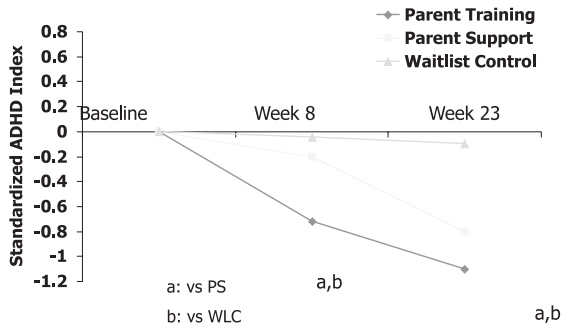
PMT Strategies (cont'd)

- Decreasing Unwanted Behaviors
  - Selecting Ignoring
  - Time-out for noncompliance
  - Giving effective commands
- School Daily Report Card
- Managing future misconduct/relapse prevention

PMT for Preschool Children (Sonuga-Barke et al., 2001)

- 78 3 year old children with ADHD randomized to:
  - Parent Training (n=30)
  - Parent Counseling and Support (n=28)
  - Waitlist Control (n=20)
- Assessed at post-treatment (8 weeks) and 23 week follow-up with the PACS and observational measure

Efficacy of PMT in Preschool Children: Changes in ADHD Symptoms



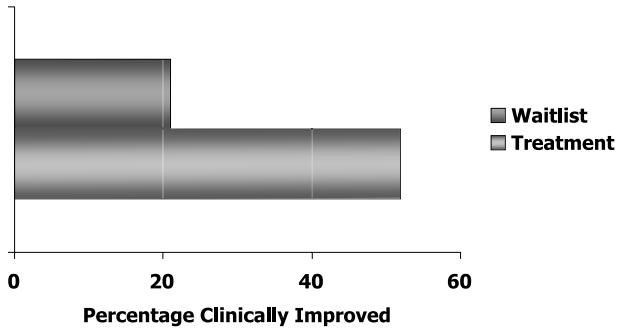
Sonuga-Barke et al., 2001; J Am Acad Child Adolesc Psychiatry; 40: 402-408

Follow-up Study of Efficacy of PMT

(Jones et al., 2008)

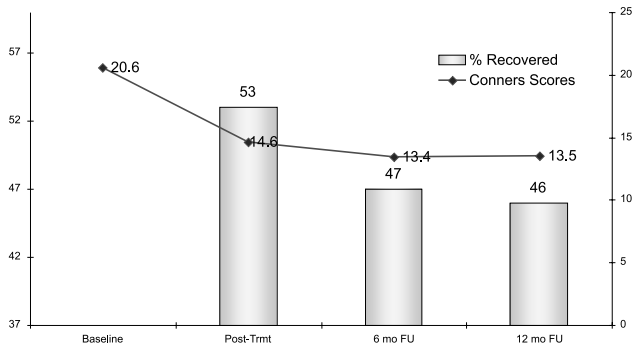
- 79 Families with children 3-5 years with signs of ADHD and conduct problems
- Randomized to *Incredible Years* PMT (n=50) or Waitlist (n=29)
- Followed up to 12 months post-treatment (n=50)

Post-Treatment Gains



Jones et al., 2008, Child: Care, Health, & Development, 33, 749-756.

12 Month Follow-up Data



Jones et al., 2008, Child: Care, Health, & Development, 33, 749-756.

Meta-analysis of Behavioral Treatments

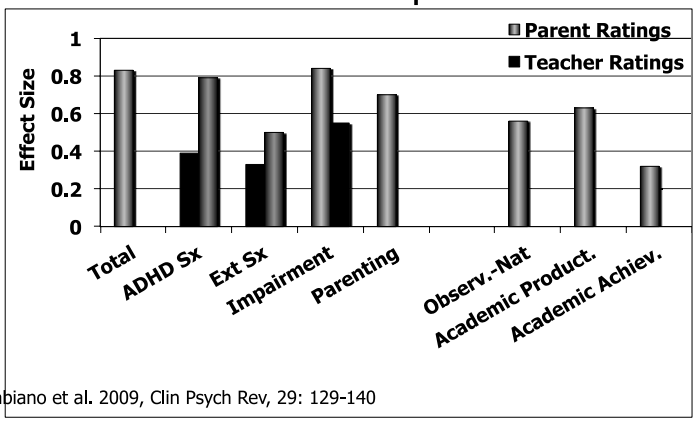
(Fabiano et al., 2009)

- 20 between-group studies of ADHD (N=523)
- 30 pre-post studies (N=1,077)
- 24 within-subject trmt studies (N=386)
- 44 single-case design studies (N=108)
- Studies of ODD/CD must have had at least 50% of sample with ADHD

Demographic & Study Characteristics

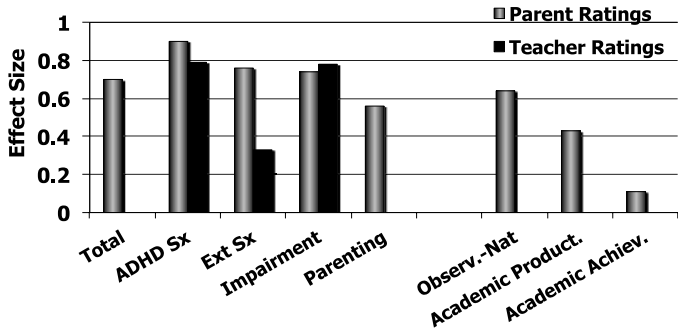
Category	Between-Group	Pre-Post
% Boys	78	82.5
Mean Age	7.1 (2.4)	8.2 (2.6)
% Caucasian	75	85
% ODD	42	62
% CD	9	33
Trmt		
Parent-Based	85	100
School-Based	26	40
Child-Based	35	37

Results of Meta-Analysis: Between-Group Studies



Fabiano et al. 2009, Clin Psych Rev, 29: 129-140

Results of Meta-Analysis: Pre-Post Studies



Fabiano et al. 2009, Clin Psych Rev, 29: 129-140

MTA Study

- 579 children from 6 sites
- Ages 7.0-9.9 at baseline (mean 8.5 ±.8 yrs)
- Dx of DSM-IV ADHD-Combined Type
- Randomized to:
  - Combined Med Mgmt+CBT
  - Med Mgmt
  - CBT
  - Community Care
- Participants assessed at Baseline, Post-Treatment (14 months), 24 months, 36 months, 6 years, 8 years

CBT in MTA Study

- Multicomponent Therapy
  - 27-session group parent training
  - 8 individual parent sessions
  - 8-week summer treatment program
  - 12 weeks classroom administered behavior therapy with half-time aide
  - 10 teacher consultation sessions

Summary of MTA Findings: 14 weeks

- Comb and MedMgt showed greater improvements in ADHD and ODD symptoms than Beh or CC participants.
- Comb but not MedMgt had better outcomes than Beh and CC for:
  - Internalizing symptoms
  - Teacher-rated social skills
  - Parent-child relations
  - Reading achievement

Summary of MTA Findings: 14 weeks (cont'd)

- Compared to Med Mgmt, Comb had greater improvements in:
  - Categorically defined success rates
  - Parent-child interaction
  - Better outcomes with 20% lower doses of methylphenidate
  - Parent and teacher satisfaction
- Comb and Behav had greater changes in:
  - Self-reported parenting behaviors
  - Homework problems

MTA Findings: Longer-Term Follow-up

- At 24 months:
  - Approximately half of the initial advantage of Comb and MedMgt had dissipated
- At 3-8 years:
  - No significant group differences in ADHD/ODD symptoms or functioning
  - Initial ADHD symptom trajectory was a strong predictor of outcome at 6 and 8 years
  - Overall maintenance of improvement in functioning relative to baseline
  - But, MTA group functioning less well than non-ADHD classmate sample

Conclusions

- Behavioral approaches are an efficacious alternative for children who cannot take medications
- Behavioral approaches are useful with preschoolers
- Medications are a first-line treatment for ADHD symptoms
- But behavioral treatments can promote other outcomes (e.g., improved parent-child relationships)

Conclusions

- CBT/Organizational skills training appears efficacious for older adolescents or adults with ADHD
- May be efficacious with children as well
- CBT can address comorbid conditions (ie, anxiety disorders; depression)

Finding a CBT Therapist

- Look for graduate training in a CBT program and/or CBT internship
- Association for Behavioral and Cognitive Therapies
  - www.abct.org
- European Association of Behaviour and Cognitive Therapies
  - www.eabct.com

ADHD, Tics and Tourette's Disorder

Barbara J. Coffey, MD, MS

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

Tics, Tourette's Disorder and ADHD
March 16, 2013

ADHD Across the Life Span

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Icahn School of Medicine at Mount Sinai
Chief, Tics and Tourette's Clinical and Research Program
New York, New York
Research Psychiatrist
Nathan Kline Institute for Psychiatric Research
Orangeburg, New York

Disclosures of Potential Conflicts (2012-2013)

Source	Research Funding	Advisor Consult	Employee	Speakers Bureau	Books, Intellectual Property	In-kind Services (example: travel)	Stock or Equity > $10,000
Boehringer Ingelheim	X						
Catalyst	X						
NIMH	X						
Otsuka	X						
TSA	X	X		X			
Shire	X						
Genco Sciences		X					

Disclosures of Potential Conflicts (Lifetime)

Source	Research Funding	Advisor Consult	Honoraria	Employee	Speakers Bureau	Books, Intellectual Property	In-kind Services (example: travel)	Stock or Equity > $10,000
American Academy of Child and Adolescent Psychiatry			X					
Bristol Myers Squibb	X							
Jazz Pharmaceuticals		X						
NINDS	X							
Novartis		X						
Pfizer	X							
Tourette Syndrome Association	X	X			X			
Eli Lilly	X	X						

Tics, Tourette's Disorder and ADHD

Learning Objectives:

At the end of the lecture, participants will be able to:

- Discuss the prevalence of tics and Tourette's Disorder and comorbid ADHD
- Discuss the impact of tics and Tourette's Disorder on the course and outcome of ADHD across the life cycle
- Cite relevant studies with clinical application including genomics, neuroimaging, psychopharmacology and behavioral science for this comorbid picture
- Construct a comprehensive treatment plan for patients with comorbid ADHD, tics and Tourette's Disorder

Epidemiology: Bi-Directional Overlap of ADHD and Tic Disorders

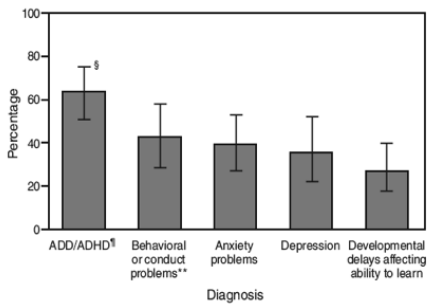
- 1) Rates of tic disorders are higher (10-30%) in children with Attention Deficit Hyperactivity Disorder (ADHD) than in children without ADHD (1-10%) *(Spencer, Biederman, Coffey et al., Arch Gen Psych; 1999, 56: 842-84)*
- 2) Rates of comorbid ADHD are high (50-75%) in clinically referred children with Tourette's Disorder (TD). (*Coffey, Biederman, et al. J Nerv Ment Dis; 2000;188:583-588; Freeman, TS International Data base Consortium; Eur Child Adolesc Psych 2007; 16 [suppl; 1]; 1/15-1/23*)
- 3) Rates of ADHD in a TD community sample were higher (8.3%) than ADHD population prevalence (3.9%) *(Apter et al, 1993)*

Tics and Tourette's Disorder: Epidemiology

(Scahill et al; Mor Mortal Weekly Report CDC; 2009)

- CDC Prevalence of Diagnosed TS in Youth age 6-17 in 2007 in US (National Study of Children's Health)
- 0.3-1% US
- 3x more common in boys than girls
- 2x more frequently diagnosed age 12-17 vs. 6-11

Prevalence of selected diagnoses among persons aged 6-17 years who have ever received a diagnosis of Tourette syndrome (TS),† by parent report (National Survey of Children's Health, United States, 2007)



- † Among children ever diagnosed with TS, 79% also had been diagnosed with at least one other selected diagnosis. Among children who currently have TS, 73% currently have at least one additional selected diagnosis.
- ¶ ADHD, by parent report.
- ** Such as oppositional defiant disorder or conduct disorder, by parent report.

TS Genome-wide Association Study results: **Findings in 1285 cases and 4964 controls: no markers achieved a genome wide threshold of significance (Scharf et al. Molecular Psychiatry; 2012)**

	Cases	*Controls*
N	1496	5249
Gender (% male)	79%	39%
Age at assessment, years (mean, s.d.)[a]	16.6±11.5	
Age of tic onset, years (mean, s.d.)[b]	6.0±2.8	
OCD (%)[c]	42%	
ADHD (%)[d]	61%	

Abbreviations: ADHD, attention-deficit hyperactivity disorder; GWAS, genome-wide association study; OCD, obsessive-compulsive disorder; TS, Tourette's syndrome.

[a] Based on 1247 cases with available data.

[b] Based on 1110 cases.

[c] Based on 1223 cases.

[d] Based on 1048 cases.

Genome-wide association study of Tourette syndrome (Scharf et al 2012)

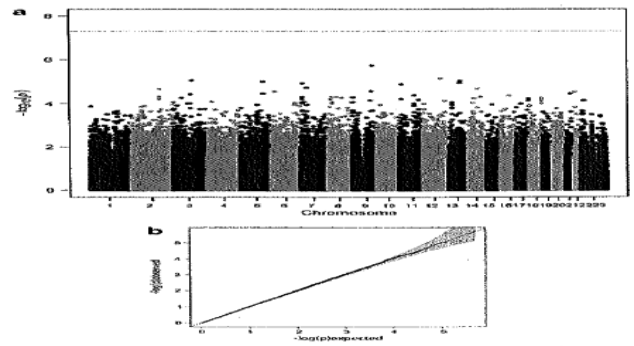


Figure 1. Results of the primary meta-analysis from the three European ancestry Tourette's syndrome (TS) populations. (**a**) Manhattan plot of all genotyped single-nucleotide polymorphisms (SNPs) for 1285 TS cases and 4964 controls from the EU, AJ and FC populations. Grey line indicates the genome-wide significance threshold of 5×10^{-8}. (**b**) Quantile–quantile plot of observed vs expected $-\log_{10}(p)$ values from the primary meta-analysis. The 95% confidence interval of expected values is indicated in grey. The genomic control λ value is 0.996. AJ, Ashkenazi Jews from the United States and Israel; EU, European ancestry, nonisolate cases from North America and Europe; FC, French Canadians from Quebec, Canada.

Tourette International Collaborative (TIC) Genetic Study

TIC Genetics
Tourette International Collaborative Genetics Study

TIC Genetics Team

- International team of experts in TD
  - 10 sites in USA (7 clinical); 6 sites in South Korea (5 clinical); 10 clinical sites in Europe
- All subjects consent for sharing repository
- Specific Aims: Recruitment of 1590 individuals with TD over 3 years with focus on families with 3 or more affected members, at least 5 per 9 recruitment sites per year
- Whole exome sequencing on 2 of the most distally related affected individuals from each of 5 families
- Search for rare coding mutations shared by affected individuals within families
- Then prioritize any genes for which rare, likely deleterious mutations are shared among affected individuals from more than one family

TIC Genetics Sites-USA (n=10)

Connecticut
Young Shin Kim
Robert King
Matthew State

Iowa
Samuel Kuperman

Indiana
Tatiana Foroud

Missouri
John Rice

New Jersey
Gary Heiman
Jay Tischfield

New York
Barbara Coffey
Dorothy Grice
Bennett Leventhal

Ohio
Donald Gilbert

Pennsylvania
Lawrence Brown

Washington State
Samuel Zinner

TIC Genetics Sites- Europe (n=10)

Denmark
- Kerstin von Plesssen

Germany
- Andrea Ludolph
- Hannah Metzger
- Alexander Münchau
- Veit Roessner

Netherlands
- Andrea Dietrich
- Pieter Hoekstra
- Athanasios Maras
- Jeroen H. Visser

Spain
- Pablo Mir Rivera
- Astrid Morer

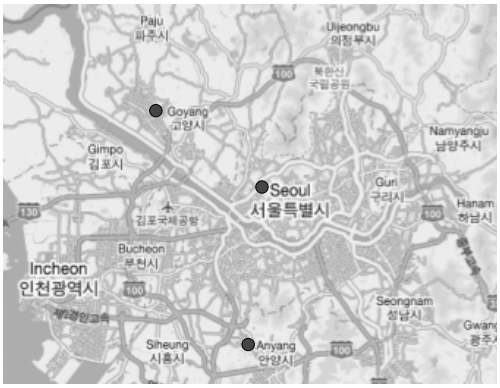
United Kingdom
- Tammy Hedderly
- Isobel Heyman

TIC Genetics Sites- South Korea (n=6)

Anyang
Hyun Ju Hong

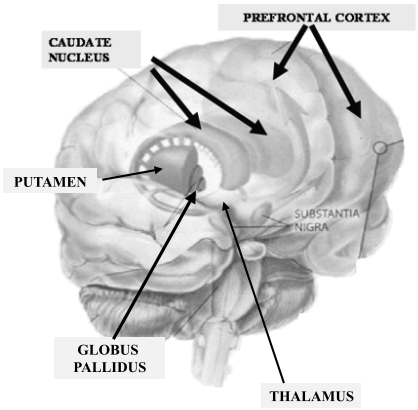
Goyang
Young-Key Kim
Jungeun Song

Seoul
Kyungjin Ahn
Keun-Ah Choen
Kyungun Jhung
Eun-Joo Kim
Yun-Joo Koh
Dong-Ho Song



TIC Genetics: Methods

- Recruit subjects and obtain informed consent
- Subjects complete self-report questionnaire
- Clinician reviews and verifies symptoms
- Clinician enters data into online Diagnostic summary system
- Blood samples drawn and sent to RUCDR for processing
- Genomic analyses (SNP arrays, whole exome)



Cortico-Striato-Pallido-Thalamic Circuit

TD and ADHD: Neurobiology

(Seidman et al; Biol Psychiatry; 2005; 57; 1263-1272; Sukhodolsky et al; Eur Child Adolesc Psychiatry 2007;16:1/51-1/59; Leckman et al; JCAP, 2010; 20 (4); 237-247; Dickstein et al; J Child Psych Psych; 2006: 47: 10. 1051-1062)

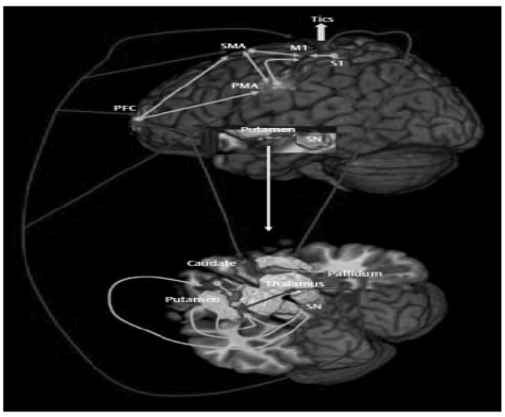
- Inhibition is a core deficit in both disorders
- Executive functions abnormalities in both thought to result from fronto-striatal and frontal-parietal network dysfunction
- ADHD: In youth, smaller volumes in DLPC, caudate, pallidum, corpus callosum and cerebellum (Seidman et al; 2005)
- ADHD: Across studies, significant patterns of frontal hypoactivity in ADHD, including ACC, DLPC, inferior prefrontal, and related regions: basal ganglia, thalamus and parietal cortex.

TD and ADHD: Neurobiology

(Seidman et al; Biol Psychiatry; 2005; 57; 1263-1272; Sukhodolsky et al; Eur Child Adolesc Psychiatry 2007;16:1/51-1/59; Leckman et al; JCAP, 2010; 20 (4); 237-247; Dickstein et al; J Child Psych Psych; 2006: 47: 10. 1051-1062)

- TD: Approximate 5% reduction in caudate volume reported in both children and adults with TD (Peterson et al; 2003).
- Inverse correlation between caudate volume in childhood and tic severity in early adulthood (Bloch et al; 2005)
- Cortical thinning in youth reported in sensory and motor areas, correlating with worst ever tic severity (Sowell et al; 2008).
- TD+ ADHD: CTSC misguided neural oscillations may result in BG disinhibition, worsened by frontal hypoactivity in ADHD. Since both TD and ADHD improve with time, may be due to increased myelinization of prefrontal regions.

FIGURE 4. Motor Circuits Hypothesized to Generate or Control Tics in Tourette's Syndrome[a]



Wang et al. 2011

Tourette's Disorder: Natural History and Course: Does it Remit or Persist? What About Comorbidity?

DSM IV-TR American Psychiatric Association (2000)

- Course: "…….The duration of the disorder is usually lifelong, though periods of remission lasting from weeks to years may occur……..."

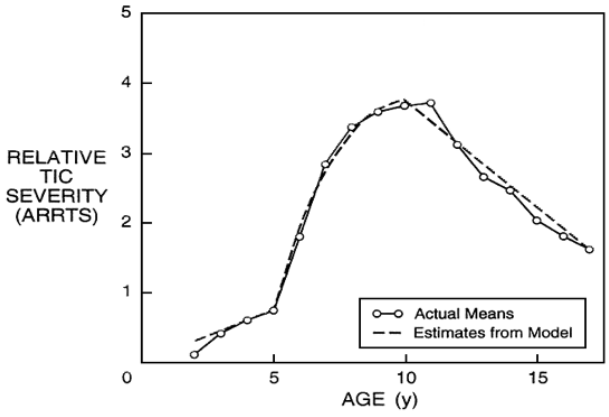
Tic severity:

- Research in the past decade suggests *peak severity occurs at about age 10-11 years* with improvement into adolescence (retrospective birth cohort design)

(Leckman et al. Pediatrics. 1998; Coffey et al. JNMD. 2004)

Time Course of Tic Severity Ratings

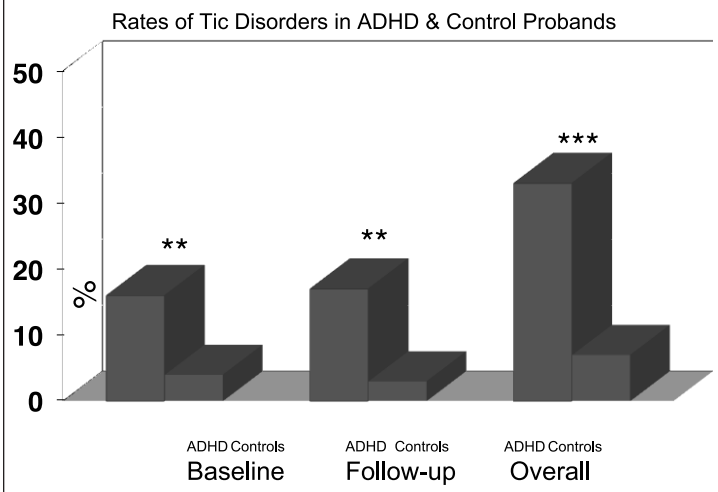
(Leckman, Zhang, et al. Pediatrics. 1998;102:14-19)

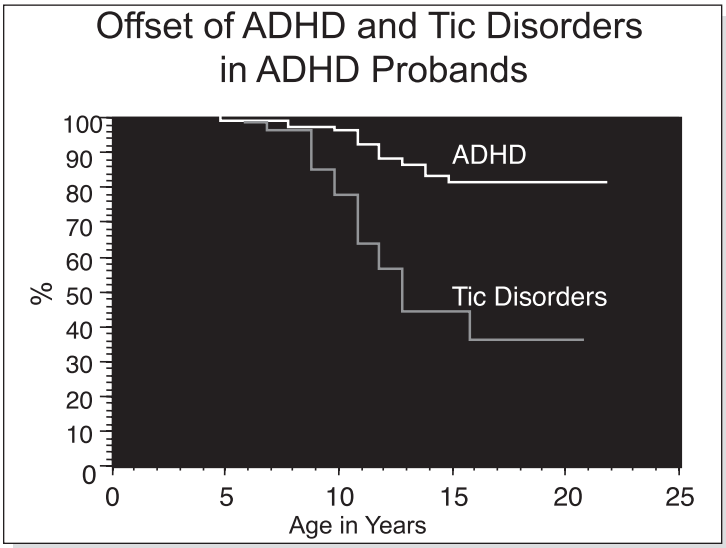


Course of ADHD and Tic Disorders: What Happens to Tics in the Context of ADHD Over Time?

(Spencer, Biederman, Coffey, et al. Arch Gen Psych 1999, 56: 842-847)

- Design: **Prospective ADHD follow-up**
- Objective: To evaluate the prevalence and impact of tic disorders at baseline and at follow-up on the course of ADHD.
- Methods: N=128 boys with ADHD; N=110 controls. Duration of follow-up: 4 years.
- Results:
- Proportion of ADHD youth with tics: 34%
- Remission rate for tics over 4 years: 65%
- Remission rate for ADHD: 20%
- Conclusion: Tic remission rate is independent of ADHD
- Tic disorders did not impact ADHD course





Informativeness of Structured Diagnostic Interviews in the Identification of Tourette's Disorder in Referred Youth

(*Coffey, B. et al.J. Nerv. Ment. Dis. 2000;Sep;188 (9):583-588)*

Clinical and Demographic Characteristics of Non-specialized and Specialized Clinic Patients with TD

	Non-specialized Clinic patients (N=92)		Specialized Clinic patients (N=103)		Overall Significance
	Mean	**SD**	**Mean**	**SD**	***p***
Current Age	10.8	3.23	10.8	3.62	0.89
SES	2.0	1.13	2.2	1.24	0.42
	N	**%**	**N**	**%**	***p***
Past GAS	47.9	7.50	48.6	7.57	0.54
Current GAS	51.3	7.32	51.9	6.52	0.55
% Male	82	90	81	80	0.06

Comorbidity: Disruptive Behavior Disorders

	Non-specialized Clinic Patients		Specialized Clinic Patients		Overall Significance
	(N = 92)		(N = 103)		
Diagnosis	**N**	**%**	**N**	**%**	***p***
ADHD	76	84	74	72	.053
Conduct Disorder	18	20	14	14	.25
Oppositional Defiant Disorder	63	69	58	57	.91
Any Disruptive Disorder	83	91	86	84	.14
***Pure TD (Non-comorbid)**	2	2	5	5	.31

Anxiety Disorders

	Non-specialized Clinic Patients		Specialized Clinic Patients		Overall Significance
	(N = 92)		(N = 103)		
Diagnosis	**N**	**%**	**N**	**%**	***p***
Panic Disorder	10	11	15	15	.45
Agoraphobia	21	23	27	26	.61
Social Phobia	15	16	5	5	.008
Simple Phobia	25	27	30	30	.73
OCD	19	21	37	36	.021
Separation Anxiety	22	24	39	39	.028
Multiple Anxiety Disorders (2+)	32	35	41	40	.47

Developmental Course of Tourette's Disorder and ADHD

Developmental Psychopathology of Children and Adolescents with Tourette Syndrome-Impact of ADHD
(Roessner et al. Eur Child Adolesc Psych; 2007; 16;1/24-1/25)

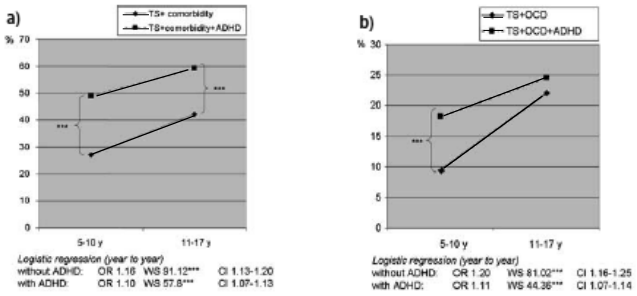
Design and Subjects: TS International Data Base Consortium

N=5060 patients in 67 tertiary centers in 27 countries:. Cross-sectional design; youth age 5-17 years

Findings:

1. Higher rate of comorbidity in TD+ADHD than TD-ADHD in children and adolescents
2. Rate of OCD was higher in TD+ADHD in children (age 5-10) but not adolescents (age 11-17).
3. But OCD developed more rapidly year to year in the TD-ADHD group

Year-wise changes of the rate of comorbidities in children and adolescents with TD versus TD+ADHD in (a) number of comorbidities and (b) obsessive compulsive disorder



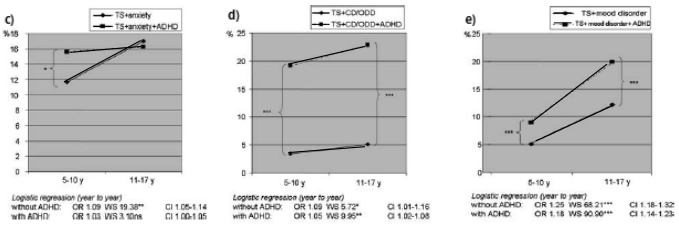
Roessner, Eur Child Adolesc Psychiatry, 2007

Developmental Course of Tourette's Disorder and ADHD
(Roessner et al. Eur Child Adolesc Psych; 2007; 16;1/24-1/25)

International Data Base Consortium. N=5060 patients in 67 tertiary centers in 27 countries: TS. Cross-sectional; youth age 5-17 years

1. Rate of comorbid ODD/CD was higher in youth with TD+ ADHD than TD-ADHD
2. Mood disorders were more frequent in children with TD+ ADHD, but the rate of increase was independent of ADHD
3. Anxiety disorders were slightly more frequent in TD+ ADHD in children, but not in adolescents; rate of anxiety disorders rose more rapidly in TD-ADHD

Year-wise changes of the rate of comorbidities in children and adolescents with TD versus TD+ADHD in (c) anxiety disorders, (d) conduct disorders/oppositional defiant disorder, (e) mood disorders



Roessner, Eur Child Adolesc Psychiatry, 2007

Tourette Syndrome in Youth with and without OCD and ADHD

(Lebowitz, E. Motlagh, M. Katsovich, L. King, R. Lombroso, Pgrantz, H. Line h. Bentley, M. Gibert, D. Singer, H. Coffey, B. TSSG, Kurlan, R. Leckman, J. Eur Child Adolesc Psych 2012; 21: 451-457)

- Design: Compared TS only with TS+ADHD and TS+OCD.
- N=158 youth. 53% TS+OCD, 39% TS+ADHD, 24% both
- Results: TS+OCD had more severe tics, more depression and anxiety, poorer global functioning
- TS+ADHD: same tic severity, but greater psychosocial stress, more externalizing behaviors, and poorer global functioning
- Conclusion: More research is needed on TS subtypes.

Table 1 Demographic and clinical characteristics for 158 children with tic disorders by sample of origin

	Study 1 [27] ($n = 76$)	Study 2 [28] ($n = 82$)
Age mean (SD)*	10.18 ± 1.8	11.2 ± 1.7
Male gender *N* (%)	77.6 (39 %)	73.1 (60 %)
Race (% Caucasian)	96.1 %	97 %
Parent education in years—mean (SD)	15.4 (2.5)	15.3 (2.8)
PANDAS percent (*N*)*	35.5 % (27)	51.2 % (42)
Clinical diagnosis—percent (*N*)		
OCD*	65.8 % (50)	42.6 % (35)
ADHD*	48.7 % (37)	29.2 % (24)
ODD	14.5 % (11)	13.4 % (11)
CD	2.6 % (2)	0 % (0)
General anxiety disorder	9.2 % (6)	7.3 % (6)
Separation anxiety	9.2 % (7)	18.2 % (15)
Specific phobia*	7.9 % (6)	23.1 % (19)
Major depression	9.2 % (7)	8.5 % (7)
Baseline severity measures—mean (SD)		
Yale Global Tic Severity Scale	17.8 (8.8)	16.8 (8.8)
Children's Yale-Brown Obsessive Compulsive Scale	7.9 (7.2)	8.7 (8.4)
Conners Abbreviated Symptom Questionnaire-Parent*	9.2 (7.5)	6.1 (5.6)
Children's Depression Inventory	5.5 (6.1)	2.0 (2.6)
Multidimensional Anxiety Scale for Children	46.4 (17.7)	47.2 (17.7)
Child Global Assessment Scale for Global Functioning-Clinician	77.0 (12.3)	73.5 (15.4)

PANDAS pediatric autoimmune disorders associated with streptococcal infections, *TD* tic disorder, *OCD* obsessive–compulsive disorder, *ODD* oppositional defiant disorder, *CD* conduct disorder

* $p < 0.05$

Lebowitz et al. 2012

Table 3 Binary logistic regression of anxiety disorders, oppositional defiant disorder, and depression in 158 youth with tic disorders as predicted by the presence of OCD or ADHD

	OCD			ADHD			H-L $\chi^2_{(2)}$	p
	β	Wald's $\chi^{2*}_{(1)}$	p	β	Wald's $\chi^2_{(1)}$	p		
Anxiety disorder	0.897	5.72	0.017	0.306	0.705	0.401	0.395	0.821
EXT	0.092	0.037	0.847	1.18	6.03	0.014	0.86	0.65
MDD	1.72	1.8	0.028	0.334	0.338	0.561	3.82	0.148

Anxiety disorder = at least one: separation anxiety, social phobia, specific phobia, agoraphobia, generalized anxiety, panic disorder

OCD obsessive compulsive disorder, *ADHD* attention deficit hyperactivity disorder, *EXT* externalizing disorder (i.e., oppositional defiant disorder and/or conduct disorder), *MDD* major depressive disorder; *H-L* χ^2 Hosmer and Lemeshow Chi-square goodness of fit

Lebowitz et al. 2012

Disentangling Effects of Tourette Syndrome and ADHD on Cognitive and Behavioral Phenotypes

(Rizzo, R. Curatolo, P. Gulisano, M. Virzi, M. Arpino, C. Robertson, M. Brain and Development; 2007; 29; 413-420)

- Design: N=80 youth, age 6-16 years, in 4 groups: TS only, ADHD only, TS+ADHD, controls.
- Results: All cases differed significantly from controls. TS only did not differ from controls in behavioral ratings or IQ.
- ADHD, with or without TS, was associated with more behavioral problems and lower IQ.
- No difference in affective and anxiety symptoms between three case groups, but differed from controls.
- TS patients were found to be more "delinquent" than controls.
- Conclusions: May be additive effect of ADHD and TS.

Table 2
Multidimensional Anxiety Scale for Children (MASC), Child Depression Inventory (CDI), and Child Behaviour Checklist (CBCL) scores in cases and controls

	TS-only	TS + ADHD	ADHD-only	Control	p value
CBCL anxious and depression scales	65.00 (3.00)	65.89 (2.80)	66.00 (2.60)	61.20 (2.89)	0.000
MASC	50.25[a] (15.05)	50.50[a] (13.39)	49.75[a] (7.75)	38.50 (5.65)	0.002
CDI	11.4[a] (1.60)	13.71[a] (1.70)	12.35[a] (1.95)	4.75 (0.95)	0.000

TS-only, Tourette syndrome-only; ADHD-only, attention deficit hyperactivity disorder-only; TS + ADHD, combined disorder Tourette syndrome + attention deficit hyperactivity disorder.
Mean values are shown with SD in parentheses.
p values denote the significant difference between each clinical group and the control group.
[a] Highly significant <.01.

Rizzo et al. 2007

Neuropsychological Functioning in Children with Tourette Syndrome with and without Attention Deficit Hyperactivity Disorder
(Sukhodolsky,D. Landeros-Weisenberger,A. Scahill L., Leckman, J. Schultz, R. JAACAP, Vol. 49 (11), November 2010; 1155-1164)

- Aim: Compare neuropsychological tests in children with TD, TD+ADHD, ADHD, and healthy controls
- Design: N=56 TD, 45 TD+ADHD, 64 ADHD, 71 HC
- Tests: CPT, Stroop, Beery VMI, Purdue Pegboard
- Results: TD children did not differ from HC on measures of response inhibition and VMI.
- ADHD children were impaired on all study measures.
- Boys with TD, but not girls, were impaired in dominant hand Purdue performance.
- TD+ADHD had no deficits on Stroop, VMI, and Purdue, but were impaired on sustained attention of CPT.
- Conclusion: Comorbid ADHD is associated with neuropsychological deficits in children with TD.

Neuropsychological Performance of Children with TD, Children with TD+ADHD, Children with ADHD, and Unaffected Controls

	TS		TS+ADHD		ADHD		Controls		Analysis		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	p	Significant Post Hoc Bonferroni Comparison
Conners' CPT											
Errors of omission (%)	4.55	3.70	6.78	6.28	5.79	6.32	3.15	3.82	$F_{(3,208)} = 5.08$	.002	TS+ADHD = ADHD < NC
Errors of commission (%)	53.35	22.65	55.90	22.46	58.38	18.73	49.74	18.57	$F_{(3,208)} = 1.90$	.131	
Reaction time (ms)	414.55	76.61	423.12	88.45	429.50	102.58	405.68	83.58	$F_{(3,208)} = 0.80$	.497	
RT variability (SE)	11.76	5.90	13.81	6.50	15.02	8.57	10.13	5.92	$F_{(3,208)} = 5.80$	.001	TS+ADHD = ADHD < NC
Stroop											
Golden Interference Score	168.57	77.25	171.63	75.57	180.41	77.11	140.91	62.34	$F_{(3,221)} = 3.90$	.01	ADHD < NC
Purdue											
Dominant raw score[a]	13.55	2.21	13.47	1.90	13.10	1.97	14.54	1.67	$F_{(3,231)} = 6.73$	.000	ADHD<NC
Nondominant raw score	12.53	1.89	12.64	1.97	12.19	2.24	13.27	1.64	$F_{(3,231)} = 3.62$	.014	ADHD<NC
Bimanual raw score	10.35	1.69	10.37	1.75	10.09	1.61	11.20	1.51	$F_{(3,231)} = 5.88$	.001	ADHD<NC
VMI											
Beery Standard Score	100.44	15.59	92.89	14.26	88.65	14.21	98.63	14.81	$F_{(3,224)} = 7.96$	.000	ADHD < NC = TS

Note: CPT = Continuous Performance Test; NC = normal controls; RT = reaction time; SE = standard error; VMI = Beery Visual Motor Integration Test.
[a]Significant diagnosis by gender interaction effect $F_{(1,120)} = 4.12$, $p < .05$ revealed that boys but not girls with TS-only were impaired in their dominant hand Purdue performance.

Sukhodolsky, JAACAP, 2010

Executive Function (EF) in Children with Tourette Syndrome and/or ADHD
(Harris, E. Schuerholz, L. Singer, H. Reader, M. Brown, J. Cox, C. Mohr, J. Chase, G. Denckla, M. Journal of International Neurospsychological Society; 1995; 1; 511-516)

- Design: Neuropsychological battery, including 10 EF tasks, administered to 10 children with TS only, 48 with ADHD only, and 32 with TS+ADHD.
- Results: All children had problems with timed CPT (TOVA).
  TS only had fewer EF impairment and higher perceptual organization scores than TS+ADHD or ADHD only.
- Conclusion: Problems in reaction time and timed response consistency are common to all three groups. Children with TS only have relatively fewer EF impairments.

Table 1. Mean (median) age and WISC–R FSIQ, and distribution of gender, for children with TS-only, ADHD-only, and TS+ADHD

	TS-only ($n = 10$)	ADHD-only ($n = 48$)	TS+ADHD ($n = 32$)
Age (yr)*	11.6 (11.6)	9.6 (9.9)	11.1 (11.2)
FSIQ**	111 (111.5)	117 (117.5)	103 (100.5)
Gender			
Girls	2	14	2
Boys	8	34	30

*$p < .01$ for differences among groups; ADHD-only significantly different from TS-only and TS+ADHD.
**$p < .01$ for differences among groups; ADHD-only significantly different from TS+ADHD.

Harris et al. 1995

Table 2. Quality of performance on tasks in the executive function test battery for children with TS-only, ADHD-only, or TS+ADHD

	Percent (N) with performance more than 1 SD worse than mean		
Variable name	TS-only ($n = 10$)	ADHD-only ($n = 48$)	TS+ADHD ($n = 32$)
TOVA			
Omission errors	33.3 (3)	50.0 (23)	54.8 (17)
Commission errors	33.3 (3)	39.1 (18)	35.5 (11)
Mean reaction time	77.8 (7)	78.3 (36)	87.1 (27)
Variability of reaction time	66.7 (6)	67.4 (31)	80.7 (25)
WCST			
Perseverative errors	11.1 (1)	10.6 (5)	22.6 (7)
Set breaks	44.4 (4)	42.5 (20)	35.5 (11)
Categories achieved	44.4 (4)	38.3 (18)	58.1 (18)
Category fluency	20.0 (2)	18.7 (9)	28.1 (9)
Letter fluency	10.0 (1)	22.9 (11)	18.7 (6)
ROCF			
Copy Organization	0.0 (0)	22.9 (11)	34.4 (11)

Harris et al. 1995

Psychosocial Outcome and Psychiatric Comorbidity in Older Adolescents with Tourette Syndrome
(*Gorman, D. Thompson, N. Plessen, K. Robertson, M. Leckman, J. and Peterson, B.; Br J Psych; 2010; 197; 36-44)*

- *Aim: To compare psychosocial outcome and lifetime comorbidity rates in older adolescents with TD and controls*
- *Design: N=65 with TD identified in childhood, and 65 matched community controls, assessed at age 18*
- *Results: Compared with controls, TD individuals had substantially lower CGAS scores and higher rates of ADHD, MDD, and CD ($p < 0.01$). In those with TD, poorer psychosocial outcomes were associated with greater ADHD, OCD and tic severity.*
- *Conclusion: Clinically referred youth with TD have impaired psychosocial outcome and high comorbidity rates in late adolescence.*

Comparison of lifetime psychiatric disorders in the Tourette syndrome group and community controls

	Tourette syndrome ($n=65$)	Controls ($n=65$)	Test statistic		Conditional logistic regression			
							Controlling for a lifetime diagnosis of ADHD	
	n (%)	n (%)	χ^2 (d.f. = 1)	P	OR (95% CI)	P	OR (95% CI)	P
Any psychiatric disorder (including OCD)[a,b]	61 (93.8)	–	–	–	–	–	–	–
Any psychiatric disorder except OCD	60 (92.3)	37 (56.9)	21.5	$<10^{-5}$	21.5 (2.9–161.1)	**<0.01**	9.3 (1.2–74.3)	**0.04**
ADHD	43 (66.2)	9 (13.8)	37.1	10^{-9}	7.3 (2.8–19.5)	10^{-4}	–	–
OCD[b]	25 (38.5)	–	–	–	–	–	–	–
Anxiety disorder (non-OCD)[c]	26 (40.0)	16 (24.6)	3.5	0.06	2.0 (0.8–4.8)	0.1	1.8 (0.6–5.0)	0.3
Learning disorder[d]	27 (41.5)	8 (12.3)	14.1	**<0.001**	7.9 (2.2–28.2)	**0.001**	3.5 (0.9–14.4)	0.08
Stuttering	8 (12.3)	5 (7.7)	0.8	0.4	2.2 (0.5–9.7)	0.3	3.0 (0.5–17.4)	0.2
Conduct disorder	15 (23.1)	2 (3.1)	11.4	**0.001**	7.8 (1.7–36.8)	**0.01**	3.7 (0.7–21.5)	0.1
Major depressive disorder	40 (61.5)	17 (26.2)	16.5	10^{-4}	4.2 (1.8–9.7)	**0.001**	3.6 (1.4–9.2)	**0.01**
Dysthymic disorder	7 (10.8)	3 (4.6)	1.7	0.2	3.8 (0.9–16.7)	0.08	3.0 (0.5–19.0)	0.2
Bipolar disorder	4 (6.2)	0 (0.0)	2.3[g]	0.1	–	–	–	–
Primary psychotic disorder[e]	5 (7.7)	0 (0.0)	3.3[g]	0.07	–	–	–	–
Substance use disorder[f]	9 (13.8)	6 (9.2)	0.7	0.4	1.7 (0.5–6.1)	0.4	0.7 (0.1–3.8)	0.7

Gorman, BJ Psych, 2010

Impact of Tic Disorders on ADHD Outcome Across the Life Cycle: Findings from a Large Group of Adults With and Without ADHD
(Spencer, Biederman, Faraone, Mick, Coffey, et al. Am J Psych 2001; 158: 611-617)

- Objective: To assess impact of presence of tic disorder on the course of ADHD in adults.
- Methods: Blinded, retrospective assessment by Structured Clinical Interview for DSM IV (SCID), supplemented with modules from the K-SADS-E covering childhood diagnoses.
- N=312 adults with ADHD; N=252 adult controls
- Results: Significantly ***greater proportion of adults with ADHD*** (12%) ***than those without ADHD (4%) had tic disorders***
- Tic disorders followed mostly a remitting course and had little impact on functional capacities.
- Conclusion: Adult findings confirm and extend previous findings in youth with ADHD, documenting that although individuals with ADHD are at greater risk for tic disorders, *the presence of tics has limited impact on ADHD outcome.*

Adults with Tourette Syndrome with and without Attention Deficit Hyperactivity Disorder
(Haddad, A. Umoh, B. Robertson, M. Acta Psychiatr Scand; 2009; 120; 299-307)

- Design: N=80 adults with TS only were compared to 64 with TS+ADHD in a clinical interview and standardized measures of depression, anxiety and OCD
- Results: No differences in tic severity. TS+ADHD had significantly more depression, anxiety, OCD and behavioral problems than TS only. Differences in ADHD family history.
- Conclusion: More overall behavioral problems and psychopathology in adults with TS+ADHD vs TS only is consistent with findings in children.
- ADHD treatment in childhood may prevent development of behavioral problems later in life.

Table 1. Measures of (a) clinical severity of TS and (b) psychopathology in the whole sample and in the TS-only and TS+ADHD groups. *n* varies due to missing data

	Whole group		TS-only		TS+ADHD		
	n	Mean (SD)	*n*	Mean (SD)	*n*	Mean (SD)	t (df)	*P*
(a) Measures of clinical severity of TS								
YGTSS	116	46.52 (20.01)	64	46.42 (18.16)	52	46.63 (22.43)	−0.056 (114)	0.955
DCI	111	61.46 (17.85)	60	59.15 (15.85)	51	64.18 (19.77)	−1.487 (1109)	0.140

		TS-only		TS+ADHD		
	Population norm (mean)	*n*	Mean (SD)	*n*	Mean (SD)	t (df)	*P*
(b) Measures of psychopathology							
BDI	5.0*	75	11.11 (9.35)	62	15.79 (10.21)	−2.799 (135)	0.006
STAI-trait	38.1†	72	47.68 (11.57)	60	52.60 (9.85)	−2.601 (130)	0.010
LDI	17.8‡	75	25.36 (14.67)	64	27.92 (12.61)	−1.094 (137)	0.276

*Metcalfe et al. (36)
†Spielberger et al. (37)
‡Snowdon et al. (38)

Haddad et al. 2009

Table 2. (a) TS phenomenology, (b) psychopathology and (c) behavioural difficulties in the TS-only and TS+ADHD groups. *n* varies due to missing data

	TS-only	TS+ADHD	χ^2	*P*
(a) TS phenomenology				
Coprolalia	18/79	23/63	3.214	0.073
Copropraxia	6/77	14/62	6.098	0.014
Echolalia	30/78	34/63	3.381	0.066
Echopraxia	24/79	29/63	3.671	0.055
Palilalia	20/76	24/63	2.209	NS
Palipraxia	13/76	14/61	0.731	NS
(b) Psychopathology				
OCD diagnosis	29/76	26/63	0.140	NS
Self-injurious behaviour	31/79	30/64	0.842	NS
(c) Behavioural difficulties				
Aggressive or attacks people	14/79	23/63	6.420	0.011
Attacks things or property	13/79	28/63	13.370	<0.001
Trouble with the law	9/79	24/63	14.010	<0.001
Alcohol abuse	13/78	23/63	7.216	0.007
Drug abuse	15/78	21/63	3.646	0.056

Haddad et al. 2009

Diagnostic Evaluation: Tics and ADHD

- **Structured diagnostic interviews, such as the Children's Schedule for Affective Disorders and Schizophrenia (K-SADS) can improve classification and assessment of comorbidity.**
- **Standardized rating scales have improved diagnostic reliability in research studies; helpful in clinical care.**
- **The Yale-Global Tic Severity Scale (YGTSS) (Leckman, Riddle, Hardin, Ort, Swartz, Stevenson, et al., 1989) is considered "gold standard." The YGTSS assesses domains of tic number, frequency, intensity, complexity and interference (0-50), and tic related impairment (0-50).**

TD/Tics + ADHD: Treatment Issues

Pharmacotherapy is cornerstone.

Tics: Most patients with mild tic symptoms need only monitoring, education, and guidance.
ADHD: Since ADHD symptoms are more likely to persist and cause significant functional impairment, treatment is usually necessary.

Behavioral treatment of tics (habit reversal training) is now established.

There are no published studies of comorbid ADHD and tic disorders of combination pharmacotherapy and behavioral treatment.

ADHD and Tics/TD: Can We Treat with Stimulants?

- *Old studies* suggested that stimulants increase tics, (Lowe et al. 1980) and pharmaceutical labeling states tics are a contraindication for stimulants (PDR, 2012)
- Long term methylphenidate treatment did not worsen tics in children with ADHD and multiple tic disorders (Castellanos et al, 1997)
- *More recent studies* demonstrated that some TD patients with significant ADHD may be candidates for methylphenidate (MPH) when no other treatments have been effective (Gadow, Nolan, Sverd. 1992; Gadow et al. 2007)

Meta-Analysis: Treatment of Attention Deficit Hyperactivity Disorder in Children with Comorbid Tic Disorders

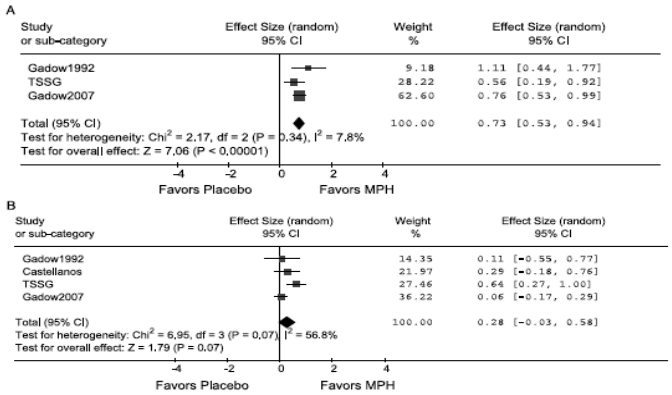
(Bloch, M. Panza, K. Landeros-Weisenberger, A. and Leckman, J. JAACAP. 2009; 48 (9);884-893)

- Aim: To determine relative efficacy of medications to treat ADHD and tic symptoms in children with both TD and ADHD.
- Design: PubMed search for all double blind, RCTs in children with ADHD and tics using random effects meta-analysis with standardized mean difference as primary outcome for effect size.
- Results: N=9 studies with 477 subjects. N=6 medications: dextroamphetamine, methylphenidate, alpha 2 agonists (clonidine and guanfacine), desipramine, atomoxetine, and deprenyl.

Meta-Analysis: Treatment of Attention Deficit Hyperactivity Disorder in Children with Comorbid Tic Disorders (Bloch, M. Panza ,K. Landeros-Weisenberger, A. and Leckman, J. JAACAP. 2009; 48 (9);884-893)

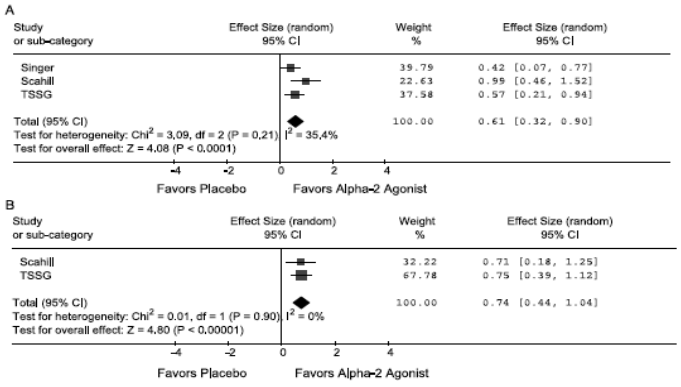
- Results: Methylphenidate, alpha 2 agonists, desipramine, and atomoxetine showed efficacy in improving ADHD symptoms in children with comorbid tics.
- Alpha agonists and atomoxetine significantly improved comorbid tics
- Supra-therapeutic doses of dextroamphetamine increase tics.
- There is no evidence that methylphenidate worsened tic severity in the short term.

Methylphenidate effect on ADHD (A) and tic severity (B)



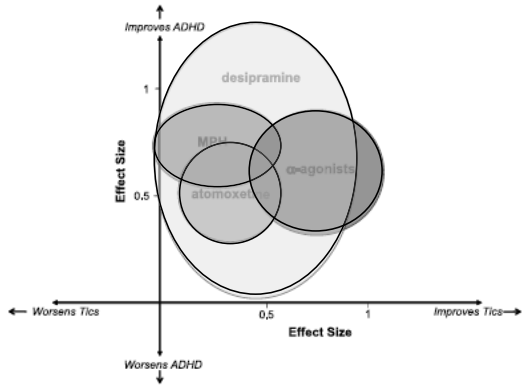
Bloch, JAACAP, 2009

Alpha-2 agonists effect on ADHD (A) and tic severity (B)



Bloch, JAACAP, 2009

Meta-Analysis: Effectiveness of medication in treating ADHD and tic disorders



Bloch, JAACAP, 2009

Meta-Analysis: Treatment of Attention Deficit Hyperactivity Disorder in Children with Comorbid Tic Disorders
(Bloch, M. Panza,K. Landeros-Weisenberger, A. and Leckman, J. JAACAP. 2009; 48 (9);884-893)

- Conclusion: Methylphenidate seems to offer the best and most immediate improvement of ADHD and does not seem to worsen tics.
- Alpha agonists offer the best combination of improvement in both tics and ADHD symptoms.
- Atomoxetine and desipramine provide additional evidence based treatment of ADHD in children with comorbid tics.
- Supra-therapeutic doses of dextroamphetamine should be avoided.

Novel Agents?

A Multicenter Randomized Placebo-controlled Clinical Trial of Pramipexole for Tourette Syndrome
(Kurlan, R. Crespi, G. Coffey, B. et al. Mov Disord. 2012 May;27(6): 775-8)

- Aim: Dopaminergic medications, including dopamine agonists, reduce tics, perhaps by selective stimulation of pre-synaptic autoreceptors at low doses or desensitization of postsynaptic dopamine receptors (result in reduction of dopaminergic neurotransmission).
- Design: 6 week multicenter randomized controlled study; N=63 children and adolescents
- Results: No difference between pramipexole and placebo in reduction of tics on YGTSS Total Tic score or CGI-improvement
- **In patients with ADHD, there was significantly more improvement in DuPaul ADHD score compared to placebo
- Conclusion: There was no evidence that pramipexole was efficacious in tic reduction. Pramipexole may improve ADHD symptoms in comorbid ADHD and tics.

Table 1. Summary of efficacy results after 6 weeks of treatment (FAS; LOCF)

End point	Placebo	Pramipexole	Level of significance
Number of patients	20	42	
YGTSS TTS, adjusted mean change[a] (SE)	−7.17 (2.0)	−7.16 (1.4)	0.9960
YGTSS Global Score, adjusted mean change[a] (SE)	−15.43 (4.4)	−15.58 (3.0)	0.9780
CGI-S, n (%)			0.7302
Improved	4 (20.0)	10 (23.8)	
Unchanged	16 (80.0)	32 (76.2)	
Worsened	0 (0.0)	0 (0.0)	
CGI-I response, n (%)			0.4944
Yes	7 (35.0)	11 (26.2)	
No	13 (65.0)	31 (73.8)	
PGI-I Response, n (%)			0.9389
Yes	6 (30.0)	12 (28.6)	
No	14 (70.0)	30 (71.4)	

[a]Mean change from baseline adjusted for pooled center, age group, and baseline.SE, standard error; FAS, full analysis set; LOCF, last observation carried forward.

Kurlan et al. 2012

Table 2. Summary of other secondary endpoint results after six weeks of treatment (FAS; LOCF)

End point	Placebo	Pramipexole
Number of patients	20	42
CY-BOCS		
n	18	42
Compulsive score		
Mean change[a] (SD)	−1.4 (2.5)	−0.6 (2.7)
Obsessive score		
Mean change[a] (SD)	−1.3 (3.1)	0.0 (1.4)
MASC total score		
N	19	42
Mean change[a] (SD)	1.8 (12.7)	−1.6 (10.2)
CDI-S total score		
N	19	42
Mean change[a] (SD)	0.3 (2.5)	−0.4 (0.9)
DuPaul ADHD total score		
Previously diagnosed[b]		
n	7	15
Mean change[a] (SD)	−4.0 (14.4)	−10.8 (12.0)
Not previously diagnosed[b]		
n	12	27
Mean change[a] (SD)	−3.1 (6.8)	−3.9 (7.3)

[a]Mean change from baseline.
[b]Diagnosis of ADHD at baseline per DICS-IV.SD, standard deviation; FAS, full analysis set; LOCF, last observation carried forward.

Kurlan et al. 2012

Comprehensive Behavioral Intervention for Tics Study (CBITS) or Habit Reversal Therapy (Piacentini, J. Woods, D. Scahill et al. JAMA; 2010;303 (19):1929-1937)

Two parallel studies compared behavior therapy to supportive therapy (ST)

Child study: 126 children (ages 9-17) with TD/CTD; JAMA; 2010

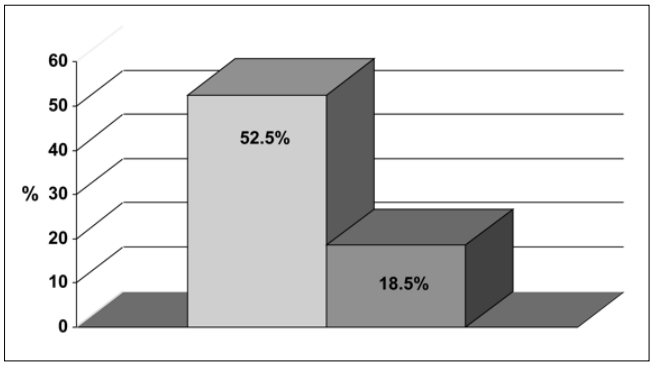
Adult study: 120 children and adults (ages 16+) with TD/CTD: Arch Gen Psych; 2012

Three phases:

1) Awareness training
2) Competing response training
3) Social support

***In CBIT child study, children with ADHD did not do as well as those without ADHD…….*

Responder Status at Week 10: Effect Size 0.68
(CGI-Improvement = 1 or 2) Courtesy of Piacentini, J. AACAP 2009



p < 0.0001

Testing Tic Suppression: Comparing the Effects of Dexmethylphenidate to No Medication in Children and Adolescents with ADHD and TD

(Lyon,G. Samar,S. Conelea, C. et al JCAP; 2010; (4) 283-289)

Aim: To test whether single dose, immediate release (IR) dexmethyl phenidate (d)-MPH can facilitate behavioral tic suppression in youth with ADHD and TD

Design: N=10 children in a random cross-over design were administered d-MPH on one visit and no medication on another.

Following baseline assessment, subjects were reinforced for suppressing tics using a behavioral reinforcement tic suppression paradigm (Woods et al; 2005)

Sociodemographic Data: Testing Tic Suppression

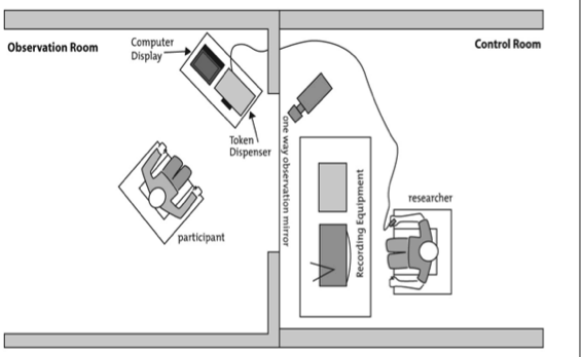
	Mean ± SD	*Range*
Age	12.7 ± 2.6	8–16
IQ	104 ± 13.3	85–118
dMPH dose (mg)	7.5 ± 3.1	2.5–12.5
	N	%
Male	9	90%
Hispanic	3	30%
White non-Hispanic	7	70%
Tourette's disorder diagnosis	10	100%
ADHD diagnosis	10	100%
Combined type	5	50%
Inattentive type	5	50%
ADHD-RS	25.3 ± 10.8	9–43
Concomitant medications	7	70%

Abbreviations: SD = standard deviation; IQ = intelligence quotient; dMPH = dexmethylphenidate; ADHD = attention-deficit/hyperactivity disorder; ADHD-RS = ADHD Rating Scale.

Lyon, JCAP, 2010

Figure 1.

General Setup



Testing Tic Suppression: Yale Global Tic Severity Scale Subscale Scores by Study Condition

	Baseline		*Nonmedication*		*Medication*	
	Mean ± SD	*Range*	*Mean ± SD*	*Range*	*Mean ± SD*	*Range*
Motor tic	13.2 ± 3.5	8–18	13.6 ± 2.9	9–19	12.1 ± 2.0	10–15
Vocal tic	10.6 ± 5.0	0–17	8.6 ± 4.8	0–15	4.9 ± 6.9	0–16
Total tic	23.8 ± 7.5	10–35	22.1 ± 7.6	9–34	17.0 ± 8.4	10–31
Impairment score	18.0 ± 8.9	10–40	22.8 ± 7.6	20–40	19.4 ± 9.4	10–40
Global severity	41.8 ± 13.4	20–64	45 ± 10.6	29–62	36.4 ± 15.2	20–63

Abbreviations: SD = standard deviation.

Lyon, JCAP, 2010

Testing Tic Suppression: Comparing the Effects of Dexmethylphenidate to No Medication in Children and Adolescents with ADHD and TD

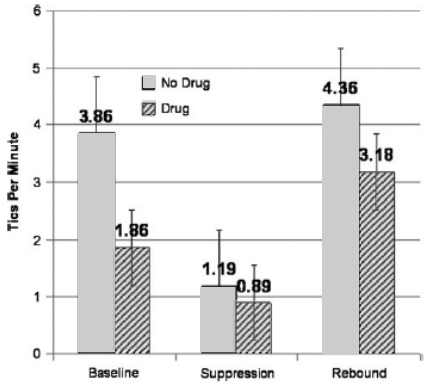
(Lyon,G. Samar,S. Conelea, C. et al JCAP; 2010; (4) 283-289)

Results: Relative to no medication, tics were reduced when subjects were given a single dose of d-MPH.

Behavioral reinforcement of tic suppression resulted in lower tic rates compared to baseline, but d-MPH did not enhance this suppression.

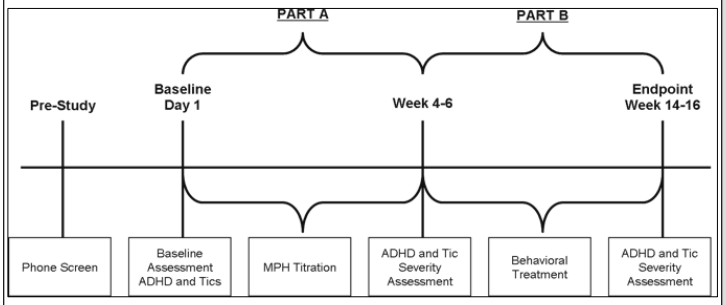
Conclusion: Results indicate replication of prior studies of behavioral tic suppression in youth with TD without ADHD, and tic reduction (vs. exacerbation) with acute d-MPH challenge.

Testing Tic Suppression: Mean number of tics per minute under the non-medication and one-time dose of MPH conditions during the TSP



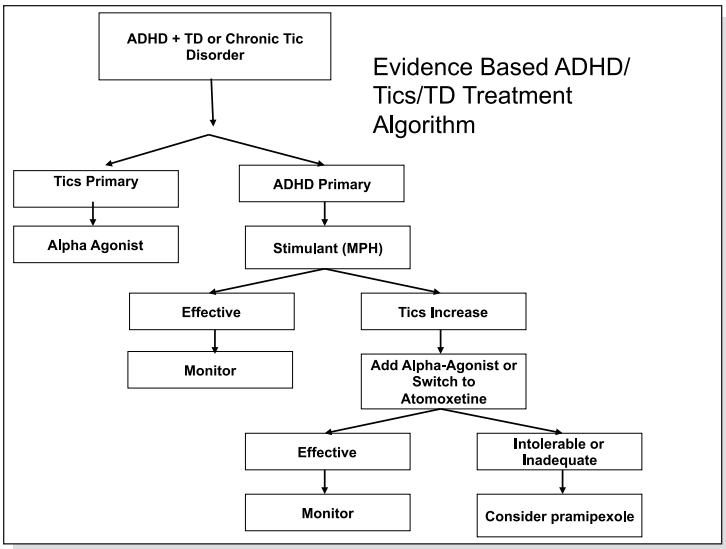
Lyon, JCAP, 2010

Current ADHD and Tics Study: Improving Tic-Related Response Inhibition: Comparing the Effects of MPH + HRT in Children and Adolescents with ADHD and CTDs – Study Flow Diagram



HRT2 Subjects: Preliminary Data

Subject	Phase A (Stimulant optimization)	Phase B (HRT)	Endpoint ADHD (CGI 1 or 2)	Endpoint Tics (CGI 1 or 2)
1	Guanfacine + Dex-MPH	No	Yes	Yes
2	Dex-MPH	Yes	Yes	Yes
3	Lis-dexamphetamine	No	Yes	Yes
4	Guanfacine + Oros MPH	Yes	Still in treatment	Still in treatment
5	Clonidine	Not yet	Preliminary Parent management	Preliminary Parent management
6	Guanfacine; could not tolerate stimulant or clonidine monotherapy	Not yet	Preliminary Parent management	Preliminary Parent management



Tics, Tourette's Disorder, and ADHD: Summary

****There is bi-directional overlap of ADHD and Tic Disorders**, including common neural substrates and phenomenology.

- Prevalence of ADHD in TD in clinically referred samples is 50-75%, and tics in ADHD patients 10-30%.
- GWAS results: **no markers achieved a genome wide threshold of significance**
- ADHD symptoms persist, but tic symptoms tend to remit over time.
- Much of the associated psychopathology (behavioral, neurocognitive) in Tourette's Disorder is secondary to ADHD
- Most clinically referred patients with ADHD and tic disorders will need treatment for ADHD, and tics may or may not need treatment.
- Alpha agonist is recommended as initial pharmacotherapy for ADHD + tics when tics are the primary issue
- Recent data reveals that methylphenidate is effective in treatment of ADHD in children with ADHD and tics, and does not increase tics in the short run
- Pramipexole may be promising for ADHD + tics
- Future directions: combination pharmacotherapy and behavioral treatment (HRT) underway, long acting stimulants in ADHD/ tic disorders, pre- and post treatment imaging studies.

- Icahn School of Medicine at Mount Sinai
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- Director, Pediatric Mood and Anxiety and Disorders Clinical Research Program
- Dorothy Grice, M.D.
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Driving and Working Impairments in ADHD

Ronna Fried, EdD

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Massachusetts General Hospital
Psychiatry Academy

The Impact of ADHD: Adults In the Workplace and On the Road

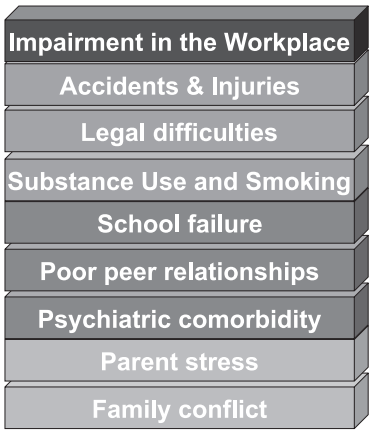
Ronna Fried, Ed.D.

Clinical and Research Programs in
Pediatric Psychiatry and Adult ADHD at
Massachusetts General Hospital

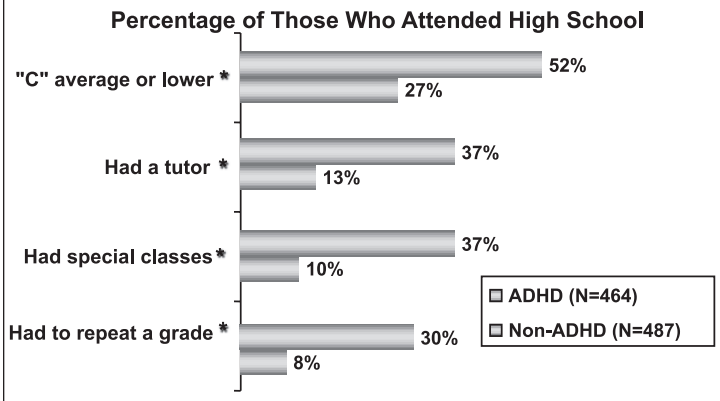
Disclosures of Potential Conflicts (2009-2013)

None

Impairment in ADHD



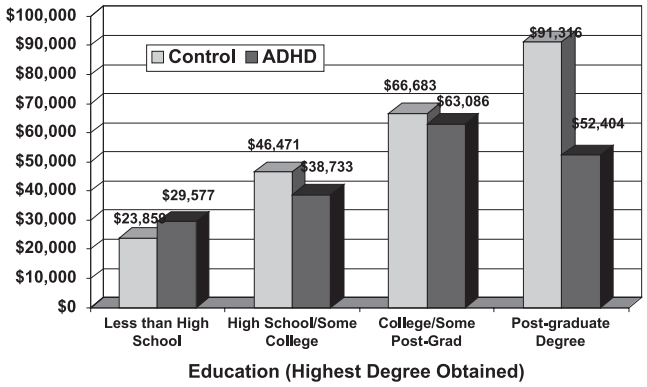
Educational Impairment in High School



* $p \leq .001$

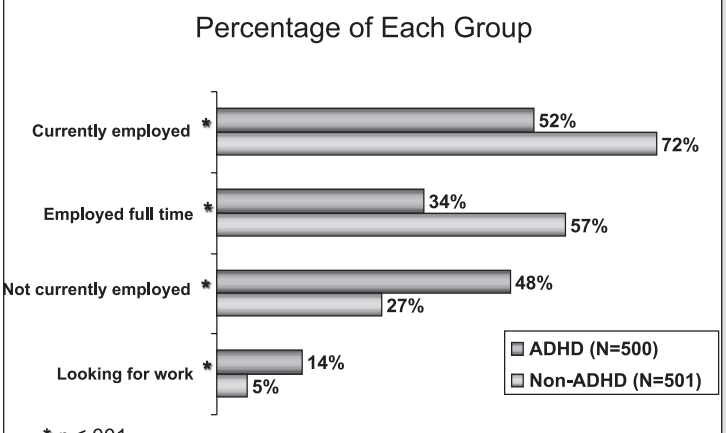
Biederman et al. *J Clin Psychiatry*. 2006 Apr; 67(4):524-40

Average Household Income by Education Level Attained



Biederman and Faraone. *Medscape General Medicine* 2006; 8:12.

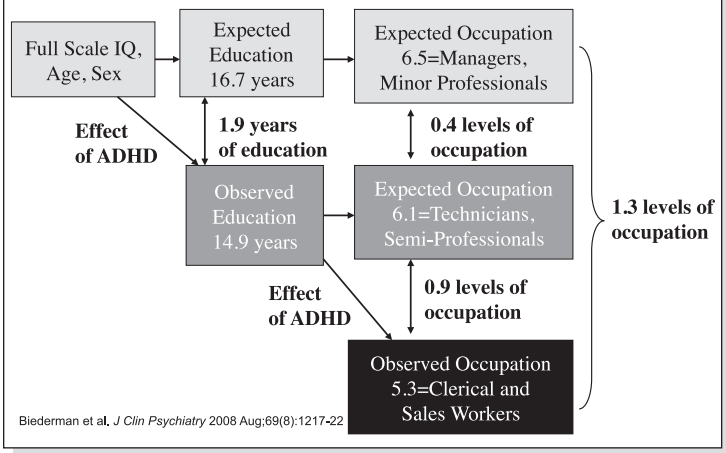
Current Employment Status



* $p \leq .001$

Biederman et al. *J Clin Psychiatry*. 2006 Apr; 67(4):524-40

Expected and Observed Years of Education and Occupational Status in Adults with ADHD



Biederman et al. *J Clin Psychiatry* 2008 Aug;69(8):1217-22

Adult Outcome of Attention-Deficit/Hyperactivity Disorder: A Controlled 16-Year Follow-Up Study

Joseph Biederman, MD; Carter R. Petty, MA; K. Yvonne Woodworth, BA; Alexandra Lomedico, BA; Laran L. Hyder, BA; and Stephen V. Faraone, PhD

ABSTRACT

Objective: To estimate the risks for psychopathology and functional impairments in adulthood among a longitudinal sample of youth with and without attention-deficit/hyperactivity disorder (ADHD) diagnosed in childhood.

Method: This was a case-controlled, 16-year (15–19 years) prospective follow-up study of ADHD: 140 boys with and 120 without *DSM-III-R* ADHD were recruited from pediatric and psychiatric settings. The main outcome measures were structured diagnostic interviews and measures of psychosocial, educational, and neuropsychological functioning. Data were collected from 1988 to 2006.

Results: At the 16-year follow-up, subjects with ADHD continued to significantly differ from controls in lifetime rates of antisocial, mood, anxiety, and addictive disorders, but with the exception of a higher interval prevalence of anxiety disorders (20% vs 8%; $z = 2.32$, $P = .02$) and smoking dependence (27% vs 11%; $z = 2.30$, $P = .02$), the incidence of individual disorders in the 6-year interval between the current and prior follow-up did not differ significantly from controls. At follow-up, the ADHD subjects compared with controls were significantly ($P < .05$) more impaired in psychosocial, educational, and

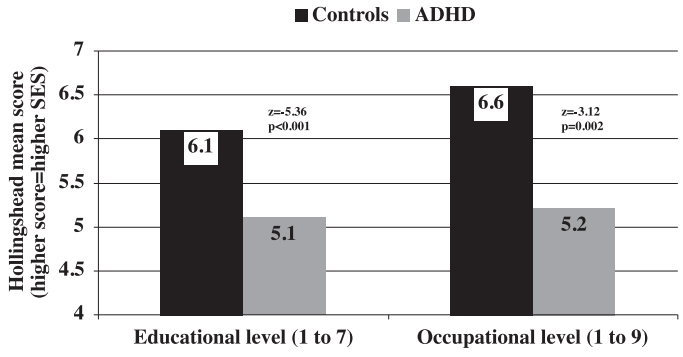
Among follow-up studies of children with attention-deficit/hyperactivity disorder (ADHD),[1–5] very few have assessed adult outcomes (Table 1). Moreover, the overwhelming majority of long-term follow-up studies of adults who had ADHD as children (eg, mean age >25 years) ascertained samples of children with "hyperactivity" and had a limited focus on antisocial and addictive disorders in adulthood (Table 1).[6–9] Ferguson et al[10] conducted the only adult outcome of adolescents diagnosed with *DSM-III* ADHD criteria (Table 1). However, because most prior long-term follow-up studies were not long enough, more work is needed to better connect the prospective pediatric literature with that of retrospective adult ADHD.

This issue is particularly relevant in the context of associated psychiatric disorders. Studies of adult ADHD clearly document that ADHD is associated with high levels of functional impairment.[11–13] However, because adult ADHD is also associated with high rates of other psychiatric disorders,[10–18] questions remain as to whether the morbidity and dysfunction associated with ADHD are due to ADHD itself or its associated psychiatric disorders.

The retrospective and cross-sectional findings in the literature on adult ADHD document a large discrepancy between the high lifetime and the low current rates of others psychiatric disorders,[19] along with high levels of current impairment in multiple domains. This pattern of findings suggests that the functional impairments of ADHD adults are not due to associated disorders but to ADHD itself. However, the discrepancy between lifetime and current disorders observable in prospective samples has not been adequately investigated. Prior longitudinal studies have also not disentangled the contributions of ADHD and other active psychopathology to functional impairments in adulthood. Clarifying these issues will lead to an improved

Biederman et al. *J Clin Psychiatry* 2012;73(3):941.

Educational and Occupational Level at the 16-Year Follow-Up



Biederman et al. 2012 JCP

Why Study Work Impairments in Adults with ADHD?

- Despite well documented evidence regarding workplace deficits in adults with ADHD , uncertainties remain as to what drives them
- Such knowledge is critical to develop strategies to help mitigate them

How Can We Study Workplace Performance?

- Obtaining direct information from the employer may be neither feasible nor ethical
- Simulation paradigms could offer an approach to study this problem in a safe and ethical manner

How Do We Develop a Valid Workplace Simulation Paradigm?

- Assess subjects with and without ADHD under double blind conditions
- Simulate a full work day
- Use tasks that require skills needed for productivity in the average work environment
- Use tasks that tax inattention, hyperactivity and impulsivity
- Measure subject's experiences through self reports
- Measure subject's objective performance through observer ratings

Do ADHD Symptoms Affect Work Performance?

- Moves Around Excessively (Hyperactivity)
- Interrupts and Disrupt Others
- Fails to Pay attention to Details
- Procrastinates

The Secretary's Commission on Achieving Necessary Skills (SCANS)

- Allocates Time
- Inhibition
- Shifting
- Initiation/Arousal/Activation
- Working Memory
- Planning/Organization
- Self-Monitoring
- Time Perception/Estimation

Does ADHD adversely affect these skills?

Main Aim

- To develop a workplace laboratory paradigm specifically developed to assess workplace deficits in adults with ADHD

Funding Source

- NIH/NIMH 1R21MH081085-01

Study Hypotheses

- Adults with ADHD will show more impairment in work performance than controls
- Individuals with ADHD will exhibit more behavioral disruption and impulsivity as rated by objective blind observers compared with control subjects
- Adults with ADHD will self-report more symptoms of ADHD than will control subjects

Methods: Subjects

- Inclusion Criteria:
  - Adults 18-55 years
  - Both sexes
  - DSM-IV diagnosis of ADHD based on clinical assessment by an expert clinician
- Exclusion criteria:
  - Major sensorimotor handicaps
  - Any significant other psychiatric condition
  - Use of any psychotropics or stimulant medication
  - Insufficient command of English
  - IQ < 80

Methods: Assessments

- Clinical Assessment
- SCID (supplemented with modules form KSAD-E to assess for ADHD, other childhood disorders)
- Neuropsychological battery: WASI; TOWRE;D-KEFS; WAIS-III Processing Speed & Digit Span; CANTAB
- Endicott Work Productivity Scale
- Self Evaluation Scale (ADHD symptoms)
- Observer Assessment (ADHD symptoms)

Work Simulation Schedule

Time	Tasks
08:00 AM - 08:30 AM	Orientation
08:30 AM - 10:00 AM	Period 1: Structured Tasks
10:00 AM - 11:30 AM	Period 1: Unstructured Tasks
11:30 AM - 12:15 PM	Lunch Break
12:15 PM - 01:45 PM	Period 2: Structured Tasks
01:45 PM - 03:15 PM	Period 2: Unstructured Tasks
03:15 PM - 03:30 PM	Break
03:30 PM - 05:00 PM	Period 3: Structured Tasks
05:00 PM - 06:00 PM	Period 3: Unstructured Tasks

Workplace Simulation Tasks

Each task below was administered 3 times during the work day:

Task	Time Allotment
Educational Video	30 min
Employment History Forms	10 min
Math	5 min
Lecture	15 min
Reading Comprehension	20 min
Editing	10 min
Unstructured Task Period	1 hour, 30 min
Total Time:	**9 Hours (each task 3xs)**

Observations: Hyperactivity

Criteria:

- 0=None=Out of room 1x for <10 min
- 1=Mild=Out of room 1x for >10 min
- 2=Moderate=Out of room 2x 10-15 min total
- 3=Severe=Out of room 3x or 2x >15 min total
- 4=Extreme=Out of room 4x or more >50% time-logic

Observations: Inattention

Criteria:

- 0=None= >90% of time spent on required tasks
- 1=Mild=81-90% of time spent on required tasks
- 2=Moderate=71-80% of time spent on required tasks
- 3=Severe=61-70% of time spent on required tasks
- 4=Extreme=≤60% of time spent on required tasks

Results

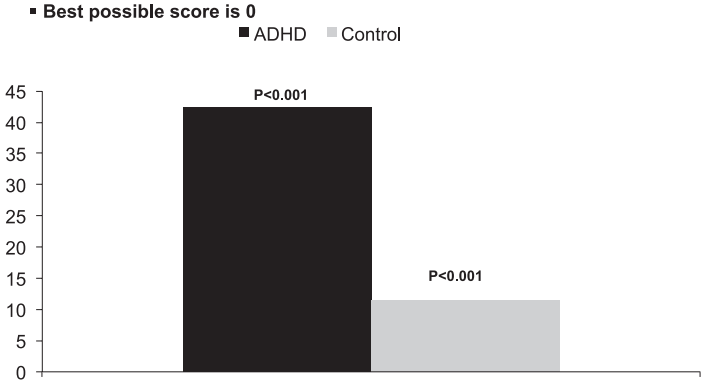
Demographics

	ADHD (N=56)	Controls (N=63)	Test statistic	p-value
	Mean ± SD or N (%)	Mean ± SD or N (%)		
Age	28.3 ± 8.5	30.8 ± 10.2	$t_{(113)}$=-1.40	0.16
Sex	29 (54)	25 (41)	$\chi^2_{(1)}$=1.86	0.17
Socioeconomic status	2.2 ± 1.2	2.2 ± 0.9	z=-0.48	0.63
Mean number of ADHD symptoms	8.2 ± 0.9	–	–	–
Global Assessment of Functioning	61.0 ± 4.8	70.5 ± 2.2	$t_{(113)}$=-13.76	<0.001
IQ	114.6 ± 10.8	118.4 ± 9.8	$t_{(111)}$=-1.92	0.06
Endicott Work Productivity Scale	42.4 ± 17.4	11.5 ± 10.4	$t_{(99)}$=11.10	<0.001
Number of jobs per year after completed education	0.82 ± 0.99	0.63 ± 0.69	z=0.82	0.41

Fried et al. *Psychiatry Res* 2012 May 16. [Epub ahead of print]

Endicott Work Productivity Scale

- 25 items
- Maximum score possible (i.e. the worst possible score) is 100
- Best possible score is 0



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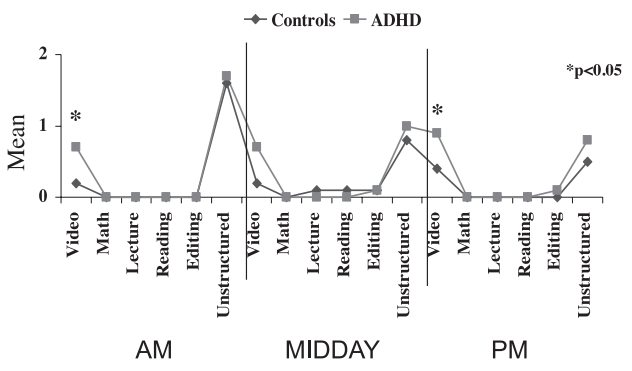
Work Simulation Results

- Skills
- Observer Ratings
- Self-Report

Observer Rating: Inattention



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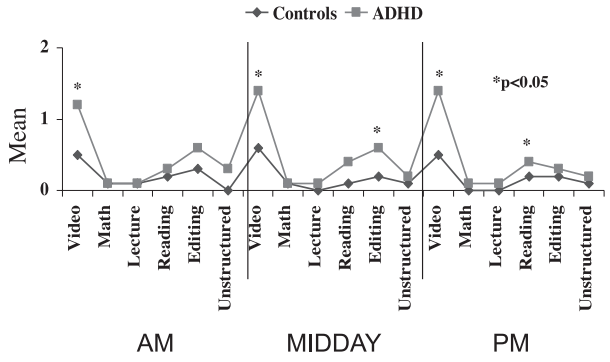
Observer Rating: Hyperactivity



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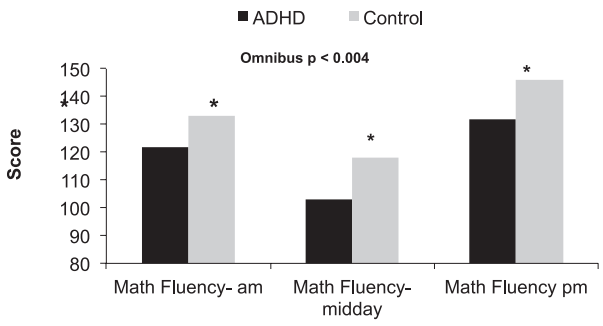
Math Fluency Scores



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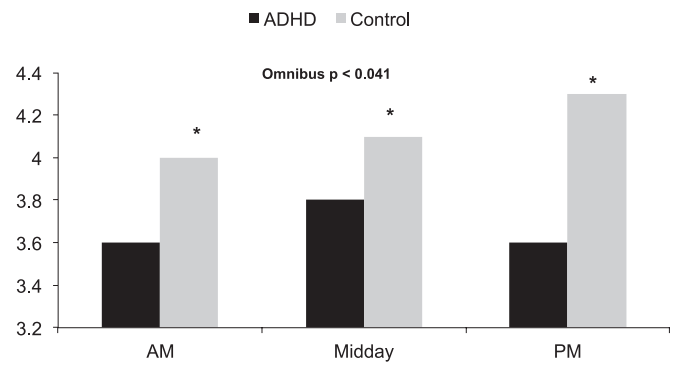
Reading Task



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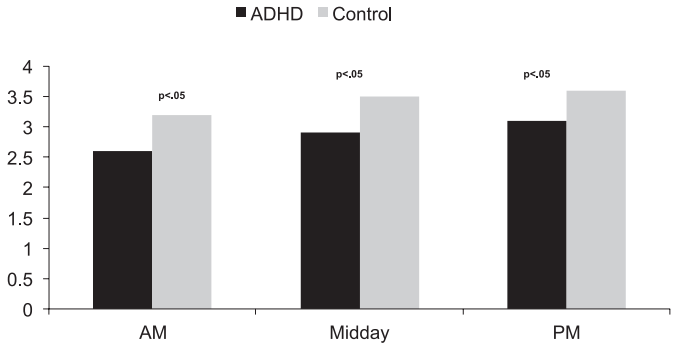
Editing (Punctuation)



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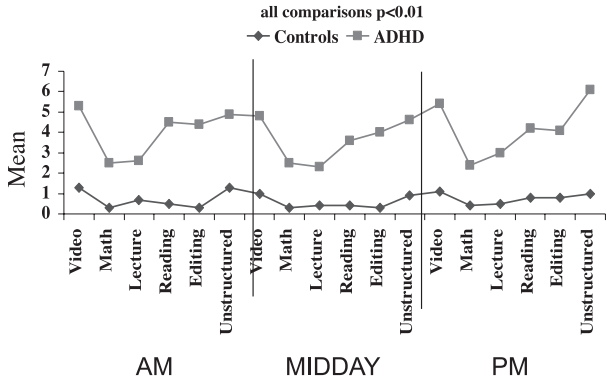
Self Rating: Hyperactivity



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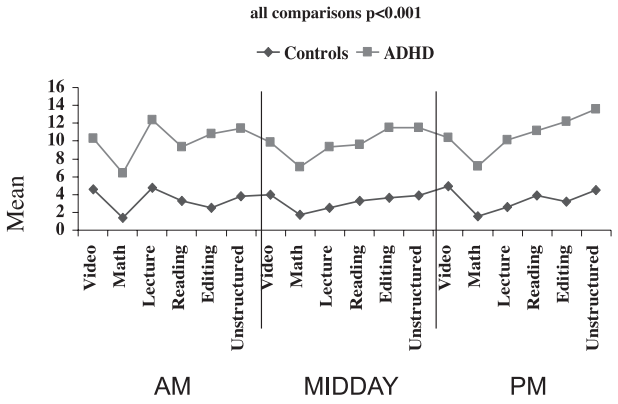
Self Rating: Inattention



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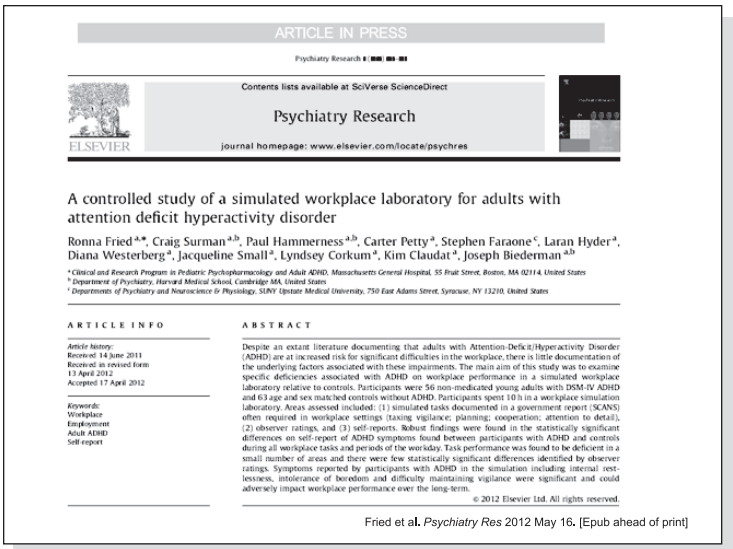
Main Findings

- ADHD subjects had more trouble than controls sitting still during boring tasks

- Internal struggle with symptoms of ADHD reported by ADHD subjects across the board, despite lack of observer rating of externalized symptoms
- Consistent with previous research: Adults with ADHD more likely to appear calm but suffer from internal restlessness than children with same diagnosis

Implications

- Adults with ADHD have specific workplace deficits
- Research is urgently needed to investigate whether treatments for ADHD will improve workplace performance



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A controlled study of a simulated workplace laboratory for adults with attention deficit hyperactivity disorder

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ARTICLE INFO

Article history:
Received 14 June 2011
Received in revised form
13 April 2012
Accepted 17 April 2012

Keywords:
Workplace
Employment
Adult ADHD
Self-report

ABSTRACT

Despite an extant literature documenting that adults with Attention-Deficit/Hyperactivity Disorder (ADHD) are at increased risk for significant difficulties in the workplace, there is little documentation of the underlying factors associated with these impairments. The main aim of this study was to examine specific deficiencies associated with ADHD on workplace performance in a simulated workplace laboratory relative to controls. Participants were 56 non-medicated young adults with DSM-IV ADHD and 63 age and sex matched controls without ADHD. Participants spent 10 h in a workplace simulation laboratory. Areas assessed included: (1) simulated tasks documented in a government report (SCANS) often required in workplace settings (taxing vigilance; planning; cooperation; attention to detail), (2) observer ratings, and (3) self-reports. Robust findings were found in the statistically significant differences on self-report of ADHD symptoms found between participants with ADHD and controls during all workplace tasks and periods of the workday. Task performance was found to be deficient in a small number of areas and there were few statistically significant differences identified by observer ratings. Symptoms reported by participants with ADHD in the simulation including internal restlessness, intolerance of boredom and difficulty maintaining vigilance were significant and could adversely impact workplace performance over the long-term.

Fried et al. *Psychiatry Res* 2012 May 16. [Epub ahead of print]

What About Driving?

Emerging Literature on Drivers with ADHD

- Drivers with ADHD are more likely than drivers without ADHD to commit traffic violations and have adverse driving outcomes
- Significantly more drivers with ADHD:
  - Drive without a license
  - Have a license revoked or suspended
  - Have multiple crashes (2+)
  - Have multiple traffic citations (3+), especially for speeding
- ADHD drivers are more likely to rate themselves as having poor driving habits

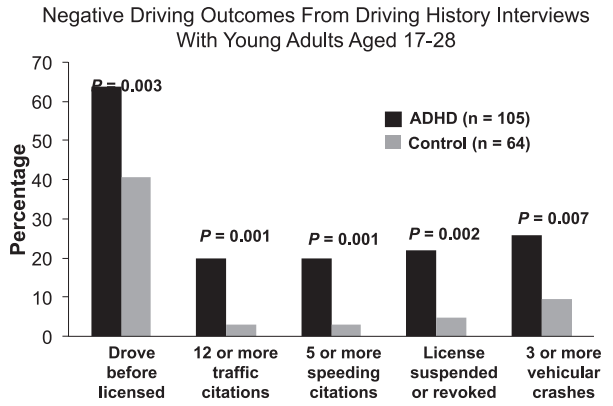
(Barkely et al., 1993; Nada-Raja et al., 1997; Woodward et al., 2000; Reimer et al., 2005)

What Makes ADHD Drivers High-Risk?

- "Inattention, impulsiveness and risk taking are likely to contribute to the observed high-risk behavior while driving."
- Individuals with ADHD have increased risk of traffic violations and accidents in situations that involve:
  - Speed
  - Inexperience
  - Inattention
  - Altered alertness / fatigue

(Barkley et al., 2003)

Traffic Accidents and Violations



Barkley et al. *J Int Neuropsychol Soc*. 2002;8:655-672.

Critical Needs in Research on ADHD Drivers

- To identify specific deficiencies in driving performance compared to controls
- To identify key susceptibility of drivers with ADHD to impairments such as distraction and inattention
- To identify different contexts under which ADHD drivers are at elevated risk of collision
- To evaluate the effects of treatments for ADHD on driving performance and behavior

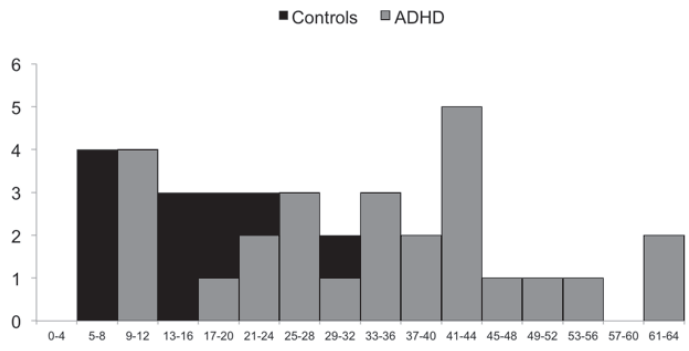
Approaches to Assess Driving in ADHD

- Rating scales (e.g.,Driving Behavior Questionnaire (DBQ))
- Laboratory driving simulator focused on deficits in attention, hyperactivity and impulsivity

Driving Behavior Questionnaire (DBQ)

- 24 questions divided into three self-reported risk behaviors:
  - Lapses – attention and memory
  - Errors – failure of planned actions to achieve their intended goal, “near misses”
  - Violations-deliberate deviations achieved to Be safe (accidents, speeding tickets)

Results: DBQ with ADHD vs. Controls



Characterizing Impaired Driving in Adults With Attention-Deficit/Hyperactivity Disorder: A Controlled Study

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Received April 7, 2005; accepted Sept. 15, 2005. From the Pediatric Psychopharmacology Department, Massachusetts General Hospital, Boston (Drs. Fried, Surman, Reimer, and Biederman and Mr. Petty and Mss. Aleardi and Martin); Department of Psychiatry, Harvard Medical School, Boston, Mass. (Drs. Fried, Surman, and Biederman); and AgeLab, Massachusetts Institute of Technology, Cambridge (Drs. Reimer and Coughlin).

This study was supported by the Johnson & Johnson Center at Massachusetts General Hospital.

Dr. Biederman receives research support from Shire, Eli Lilly, McNeil, and Cephalon and serves on the speaker/advisory boards of Shire, Eli Lilly, McNeil, Janssen, Novartis, and Cephalon. Drs. Fried, Surman, Reimer, and Coughlin and Mr. Petty and Mss. Aleardi and Martin report no additional financial or other relationships relevant to the subject of this article.

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Objective: We sought to confirm previously documented findings that individuals with attention-deficit/hyperactivity disorder (ADHD) demonstrate impaired driving behavior when compared with controls.

Method: Subjects were adults with (N = 26) and without (N = 23) DSM-IV ADHD ascertained through clinical referrals to an adult ADHD program and through advertisements in the local media. Driving behavior was assessed using the Manchester Driving Behavior Questionnaire (DBQ) and 10 questions from a driving history questionnaire. Neuropsychological testing and structured interviews were also administered to all subjects.

Results: Substantially more ADHD subjects had been in an accident on the highway (35% vs. 9%, p = .03) or had been rear-ended (50% vs. 17%, p = .02) compared with controls. Analysis of the DBQ findings showed that ADHD subjects had significantly higher mean ± SD scores than control subjects on the total DBQ (34.1 ± 15.2 vs. 18.0 ± 8.6, p < .001) and in all 3 subscales of the DBQ: errors (9.3 ± 5.4 vs. 4.6 ± 3.5, p < .001), lapses (12.4 ± 6.2 vs. 6.1 ± 3.5, p < .001), and violations (12.4 ± 5.2 vs. 7.4 ± 4.1, p < .001). Using the score that separated ADHD from control drivers on the DBQ as a cutoff, ADHD drivers at high risk for poor driving outcomes had more severe rates of comorbidity and exhibited more impaired scores on neuropsychological testing.

Conclusions: Our results confirm and extend previous work documenting impaired driving behavior in subjects with ADHD. Results also suggest that ADHD individuals at high risk for poor driving behavior might be distinguishable from other ADHD individuals on DBQ scores, neuropsychological deficits, and patterns of comorbidities.

(J Clin Psychiatry 2006;67:567–574)

MGH-MIT Driving Simulation Paradigm

- Our group developed and validated a novel driving simulation paradigm with varying driving demands in ways observed on actual roadways
  - Range of driving environments (rural, highway, urban)
  - Differing stimulus intensity (active, monotonous)
  - Periods of both single task driving as well as dual task driving, (e.g. driving while having a cellular phone conversation)

Overview of the MIT AgeLab Driving Simulator “Miss Daisy”

- State of the art full cab 90 degree field of view vehicle simulator provides an exceptional platform for human factors evaluations

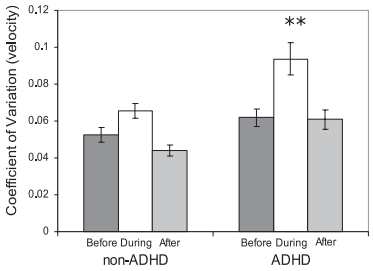
- Force feedback and sound system provide additional responsiveness to the driver
- Measures include: brake and throttle position; steering amplitude; acceleration; velocity; and lane position

MGH-MIT Driving Simulation Paradigm

- A series of recent studies demonstrated that our simulation differentiated ADHD drivers from controls

Highway Driving

- ADHD impacted speed control
- ADHD enhanced difficulties with speed control under dual task conditions (driving and cell phone use)

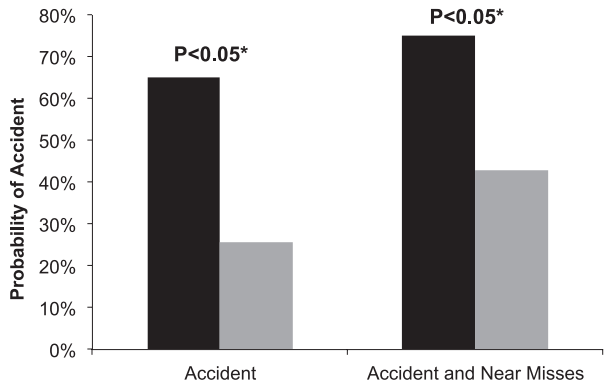


Reimer et al, DSC 2007 North America – Iowa City – September 2007

MGH-MIT Driving Simulation Paradigm

- ADHD subjects reported a higher frequency of speeding, passing and weaving in traffic, and number of real-life accidents, which corresponded with behaviors observed in the simulation, further supporting the validity of our driving simulation paradigm

Accidents and Near Misses

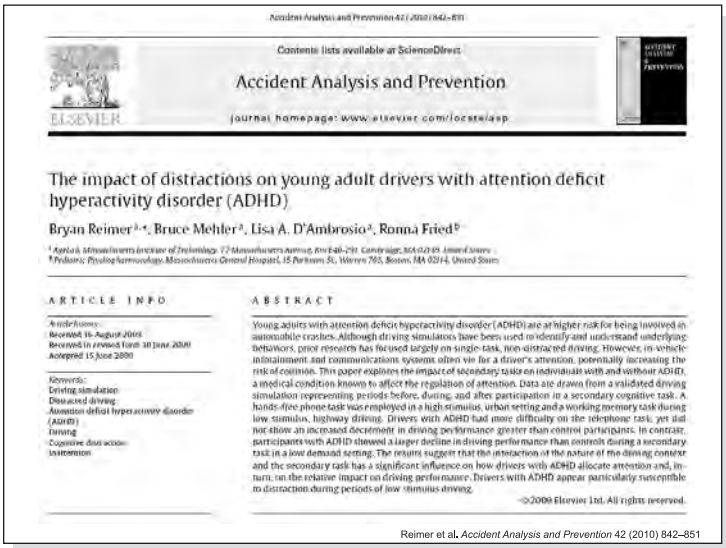


*Indicates P<0.05 after controlling for gender, age, time of day and the age*ADHD interaction

Reimer, B., et al. 2007. Traffic Inj Prev 8(3): 290-299.

Conclusion

- Context plays an important role in the performance of ADHD drivers
- Differences exist in how ADHD drivers regulate the attention based upon complexity of the driving environment and secondary task
- Potential for certain combinations of factors to be over represented in ADHD accidents



Contents lists available at ScienceDirect

Accident Analysis and Prevention

journal homepage: www.elsevier.com/locate/aap

The impact of distractions on young adult drivers with attention deficit hyperactivity disorder (ADHD)

Bryan Reimer[a,*], Bruce Mehler[a], Lisa A. D'Ambrosio[a], Ronna Fried[b]

ARTICLE INFO

ABSTRACT

Young adults with attention deficit hyperactivity disorder (ADHD) are at higher risk for being involved in automobile crashes. Although driving simulators have been used to identify and understand underlying behaviors, prior research has focused largely on single-task, non-distracted driving. However, in-vehicle infotainment and communications systems often vie for a driver's attention, potentially increasing the risk of collision. This paper explores the impact of secondary tasks on individuals with and without ADHD, a medical condition known to affect the regulation of attention. Data are drawn from a validated driving simulation representing periods before, during, and after participation in a secondary cognitive task. A hands-free phone task was employed in a high stimulus, urban setting and a working memory task during low stimulus, highway driving. Drivers with ADHD had more difficulty on the telephone task, yet did not show an increased decrement in driving performance greater than control participants. In contrast, participants with ADHD showed a larger decline in driving performance than controls during a secondary task in a low demand setting. The results suggest that the interaction of the nature of the driving context and the secondary task has a significant influence on how drivers with ADHD allocate attention and, in turn, on the relative impact on driving performance. Drivers with ADHD appear particularly susceptible to distraction during periods of low stimulus driving.

Reimer et al. *Accident Analysis and Prevention* 42 (2010) 842–851

Are Driving Impairments Treatable?

The Effects of LDX on Driving Performance in Young Adults with ADHD: A Randomized, Double-Blind, Placebo-Controlled Study

Study funded by Shire Pharmaceutical

Context

- While stimulant medications have proven efficacy in reducing ADHD symptomatology, the extent to which these clinical effects generalize to driving impairment associated with ADHD remains uncertain

Context

- Although several investigators have reported medication effects on driving simulation outcomes in subjects with ADHD, these studies are difficult to interpret, given limited information on the validity of the driving simulators and the informativeness of chosen outcome variables

Main Aim

- To assess the impact of lisdexamfetamine dimesylate (LDX) on driving performance in young adults with ADHD

Crashes per 100,000 Licensed Drivers (Traffic Safety Facts 2003)

Age	Fatal Crashes	Injury Crashes	Property Damage
16-20	62.02	4695	10801
21-24	45.98	2962	5965
25-34	31.17	2050	4283
35-44	26.79	1695	3495
45-54	23.45	1370	2953
55-64	10.51	1137	2426

Methods: Subjects

- Outpatients
- Both sexes
- 18-26 years of age
- Met full DSM-IV criteria for ADHD with onset of symptoms in childhood, a persistence of impairing symptoms into adulthood, and did not have pharmacological treatment for ADHD in the past month

Exclusion Criteria

- Any clinically significant psychiatric or medical condition including clinically significant laboratory or ECG values, hypertension, pre-existing structural cardiac abnormalities, or a known hypersensitivity to LDX or any amphetamine compounds
- Use of any medication with clinically significant CNS effects in the past month
- IQ< 80
- History of substance dependence or abuse within 6 months
- Pregnant or nursing females
- Individuals who never held a valid driver's license

Study Design

- This was a randomized, double-blind, parallel-design, placebo-controlled, 6-week study examining the effects of LDX and placebo on driving performance in young adults with ADHD using a driving simulation paradigm that had been shown to discriminate between ADHD and control drivers
- Eligible subjects underwent a baseline (pre-medication) driving simulation assessment and then were randomized, in double-blind fashion, to receive placebo or active medication

Study Design

- Medication was titrated from an initial dose of 30 mg at week 1 to 50 mg at week 2, and to a maximum of 70 mg by week 3
- Subjects experiencing adverse events were able to decrease in increments of 20 mg, if determined necessary by the treating clinician
- After 6 weeks of treatment with LDX or placebo, subjects underwent a second driving simulation assessment
- The two simulation assessments were identical except for the addition of five surprise events during the second visit

Assessments: Baseline

- Psychiatric evaluation (board certified psychiatrist with expertise in adult ADHD)
- DSM-IV-SCID plus modules from K-SADS-E (DSM-IV ADHD and disruptive behavior disorders)
- Medical Hx, vital signs, laboratory assessments (LFT's, CBC), weight, vital signs, & ECG

Assessment Measures

- CGI-S and CGI-I
- ADHD RS
- HAM-A
- HAM-D
- GAF
- Weight
- BP and HR
- ECG

Driving Simulation

- 43-mile virtual roadway
- Urban driving (stimulating) (±phone task)
- Straight unpopulated road (monotonous)
- Rural and highway driving (moderate demand) (±CPT)
- Straight unpopulated road (second monotonous period)

Driving Simulation

- The driving simulation was identical in the 1st and 2nd visits, but differed in the 2nd visit by the addition of 5 surprise events distributed throughout the simulation to minimize learning and expectation effects
- The surprise events included cyber dogs that appeared at the end of each of the two monotonous periods, and 3 vehicles that encroached on the lane of travel at various points in the scenario

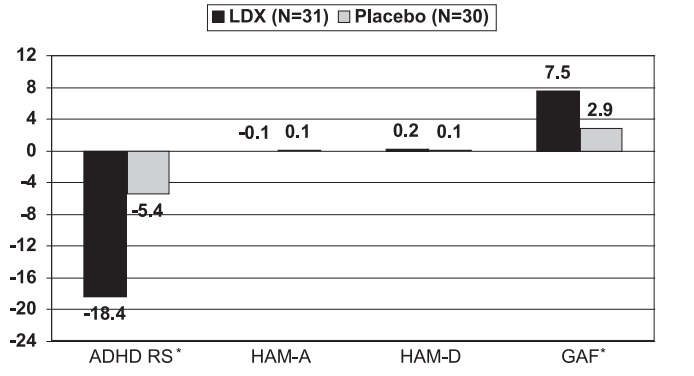
Statistical Approach

- Continuous dependant variables were assessed using either univariate or repeated measures GLM procedure as appropriate in SPSS (version 16)
- Pearson Chi-squared tests and logistic regression were used for binary data

Results

- 75 subjects enrolled in the study and 61 subjects completed the two driving simulations
- Sex: 62% % males
- Age: 21.6 ± 2.1 years
- No statistical differences in age or sex between drug and placebo
- No subject took a concomitant psychotropic medication

Mean Change from Baseline to Endpoint in Clinical Parameters



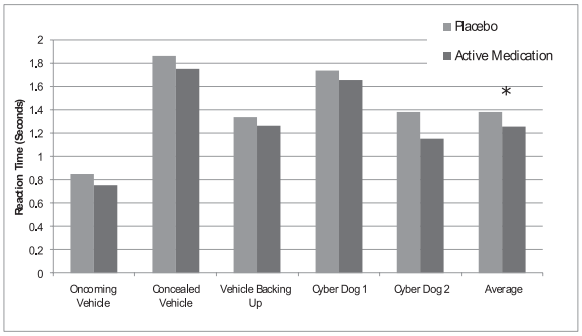
*p-value reflects drug by time interaction assessing the relative effects of LDX vs. placebo

Biederman et al. *J Psychiatr Res* 2012 Apr;46(4):484-91

Driving Outcomes

- There were no differences between drug and placebo in ratio of low to high mileage drivers (greater or less than 10,000 miles in the past year) or in the ratio of frequent to infrequent drivers (driving more or less than “a few” times per week)
- At baseline, 15% were involved in a crash in the past year (4/9 cases were in the active medication group) and 23% (N=10 in the active medication group) reported being stopped by the police for a traffic-related reason over the past year

Results: Reaction Times To Surprise Events

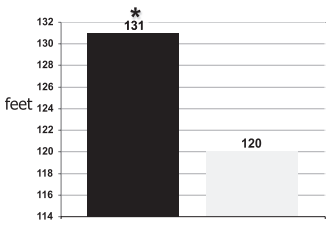


Biederman et al. *J Psychiatr Res* 2012 Apr;46(4):484-91

Summary: Surprise Events Reaction Time Results

- Significant effect of medication status on the average reaction time computed across all five events ($F(1,58)=5.231$, $p=.026$)
- Although not attaining statistical significance, examination of individual events showed that the active medication group consistently reacted faster than the placebo group
- Participants in the active medication group reacted 0.126 seconds or 9.1% faster, on average, than participants in placebo group

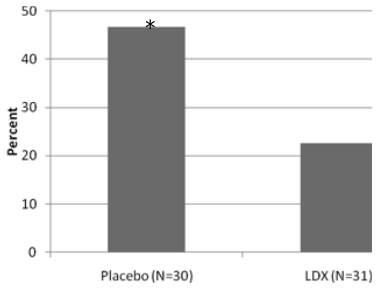
Implications for Surprise Events Reaction Time Results



- When considering a driver traveling at 65 mph the average reaction times translates to 131 and 120 feet, for placebo and LDX, respectively
- Therefore, non-medicated drivers traveled 11 feet further before reacting to an event which could results in hitting a pedestrian in a crosswalk

Biederman et al. *J Psychiatr Res* 2012 Apr;46(4):484-91

Percent of Subjects Involved in Collisions During Surprise Events



- During the five surprise events, drivers in the medication group were 67% less likely to have a collision than drivers in the placebo group

LDX = lisdexamfetamine dimesylate

Biederman et al. *J Psychiatr Res* 2012 Apr;46(4):484-91

Journal of Psychiatric Research

The effects of lisdexamfetamine dimesylate on the driving performance of young adults with ADHD: A randomized, double-blind, placebo-controlled study using a validated driving simulator paradigm

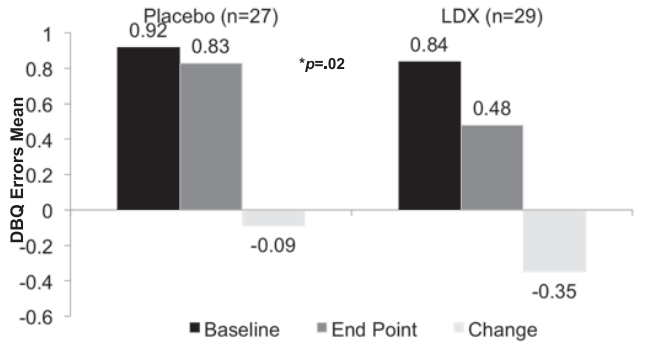
Joseph Biederman, Ronna Fried, Paul Hammerness, Craig Surman, Bruce Mehler, Carter R. Petty, Stephen V. Faraone, Carolyn Miller, Michelle Bourgeois, Benjamin Meller, Kathryn M. Godfrey, Bryan Reimer

ARTICLE INFO

ABSTRACT

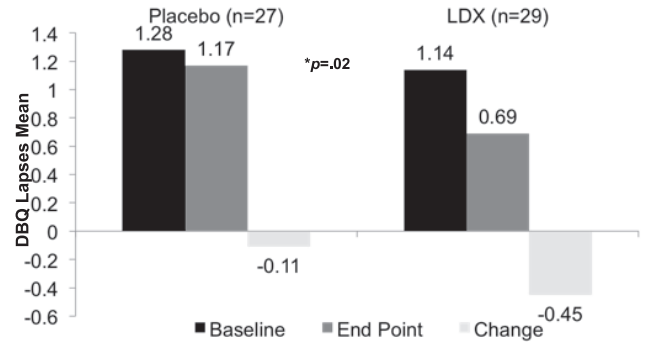
Effects of LDX on Driving Behavior as Assessed Through the DBQ

DBQ Errors Mean Scores



Biederman et al. *J Adolesc Health* 2012

DBQ Lapses Mean Scores



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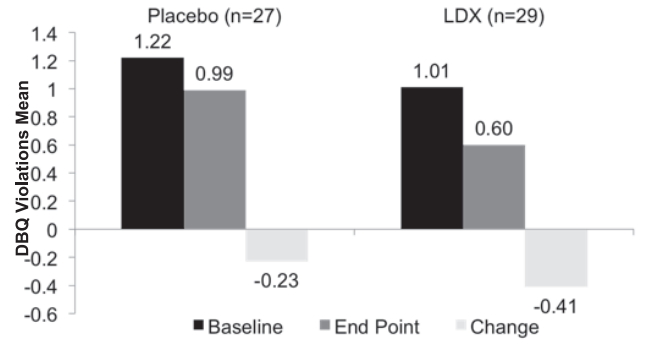
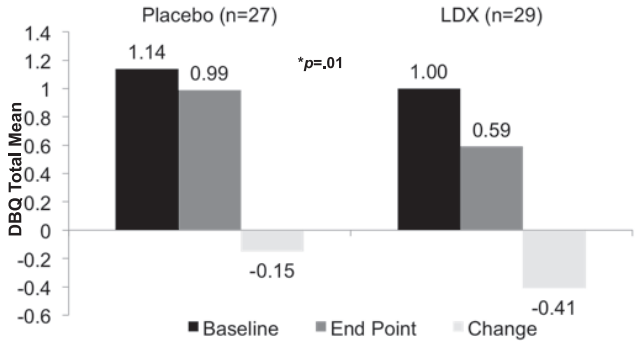
DBQ Violations Mean Scores



Biederman et al. *J Adolesc Health* 2012

DBQ Total Mean Scores



Biederman et al. *J Adolesc Health* 2012

Main Findings

- Treatment with LDX was associated with significant clinical improvement
- Treatment with LDX was also associated with faster reaction times and a lower likelihood of having a collision independently of the clinical effects

Main Findings

- There were no associations between clinical improvement in ADHD symptoms and driving outcomes

Comments

- Our finding that ADHD drivers taking LDX were 67% less likely to be involved in a collision than those on placebo has major public health relevance, considering the high prevalence of ADHD in the population and the high risk of accidents associated with this disorder
- In 2008, 4,378 pedestrians were killed and another 69,000 were injured in motor vehicle accidents in the US
- Two of the surprise events in the simulator consisted of dogs running across the road; the collisions could have been with pedestrians or bicyclists

Conclusions

- Results from this randomized, double-blind, parallel group, placebo-controlled study of LDX in young adult drivers with ADHD showed faster reaction times and a lower rate of simulated driving collisions in subjects taking LDX than in those taking placebo
- Marked Improvements in driving behaviors
- These results suggest that LDX may be useful in clinical practice to reduce driving risks of young adults with ADHD
- **Clinical Trials Registry:** Clinical Trials.gov NCT00801229

Management of ADHD in the Context of Autism Spectrum Disorders

Gagan Joshi, MD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

MANAGEMENT OF ADHD IN THE CONTEXT OF AUTISM SPECTRUM DISORDERS

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Disclosure

Neither I nor any member of my immediate family has a significant financial interest or affiliation with any manufacturer of commercial product(s) or provider(s) of commercial services discussed in my educational presentations for MGH Psychiatry Programs in 2013.

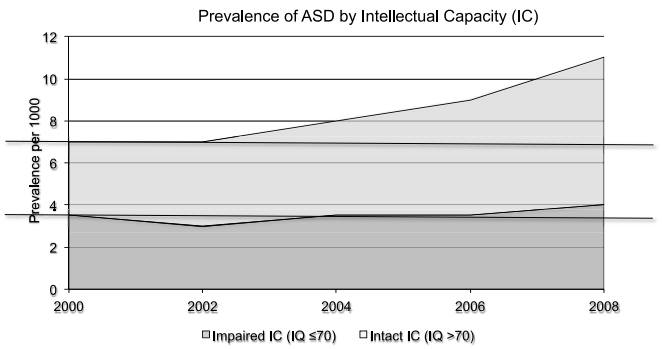
Autism Spectrum Disorders - Clinical Characteristics

CORE FEATURES

Impaired Social Interaction	Impaired Social Communication	Restricted/Repetitive Behaviors
• Non-verbal communication	• Language impairment	• Interests
• Social & emotional reciprocity	• Language oddities	• Routines / rituals
• Sharing activities & interests	• Sharing conversation	• Motor mannerisms
• Peer relationships	• Imaginative & imitative ability	• Persistent preoccupation with parts of objects

Low-Functioning Autism	Characteristics	High-Functioning Autism
Impaired IQ		Intact IQ
Non-verbal		Verbal
Asocial		Social
Stable	Prevalence	Increasing
Low	Genetic Transmission	High
Poor	Social Functioning	Poor
ASD	Initial Referral for Autism Diagnosis	Mental Health
Early		Late
Specialized	Social Milieu	Typical
Low	Social Stress	High
Low	Psychiatric Risk	High
Follow ASD Dx	Psychiatric Diagnosis (ADHD, Anxiety, Mood Disorder)	Precede ASD Dx

Prevalence of ASD in General Population



ADDM Network, 2007, 2009, 2012

Core Diagnostic Features of ADHD and ASD

Symptom Triad

ASD
- Impaired social interaction
- Impaired social communication
- Autistic Mannerisms

ADHD
- Inattention
- Hyperactivity
- Impulsivity

Although core diagnostic features do not explicitly overlap DSM-IV considers presence of ADHD symptoms as associated features of ASD

DSM-IV-TR ADHD Criterion E states:

"The symptoms of ADHD do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other psychotic disorder..."

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision. American Psychiatric Association; 2000:85-93

Rationale for Excluding Comorbid Diagnosis of ADHD with ASD

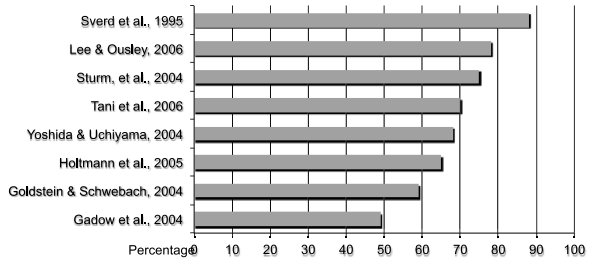
- Majority of ASD with impaired intellectual and language skills
- Presentation of ADHD cannot be elicited in this population
- ASD is not a neurotypical disorder thus presentation of ADHD will not be typical of ADHD
- Ability to hyper-focus on preferred activities rules out ADHD

Neurodevelopmental Disorders: ASD & ADHD Shared Characteristics

	ADHD	ASD
Prevalence in Children	6-8%	1.1%
Heritability Estimates	75%	> 90%
Male:Female Ratio	2.5:1	4:1
Manifest early in life	Yes	Yes
Lifelong Disorders	Yes	Yes

Bailey et al., 1995; Levy et al., 1997; Constantino & Todd, 2000, 2003; Ronald et al., 2005, 2006, 2008; Price et al., 2001; Fombonne, 2003; APA, 1994; MMWR, 2005; Kogan et al., 2009; ADDM Network, 2007, 2009; Bailey et al. 1996

Prevalence of Significant ADHD Symptoms in Populations with ASD

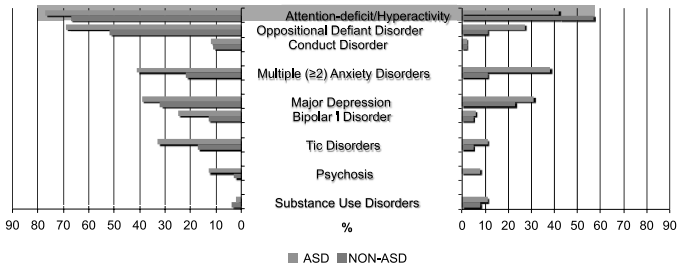


Clinical and Research Program in Pediatric Psychopharmacology, Massachusetts General Hospital

Psychiatric Conditions in Referred Populations with ASD

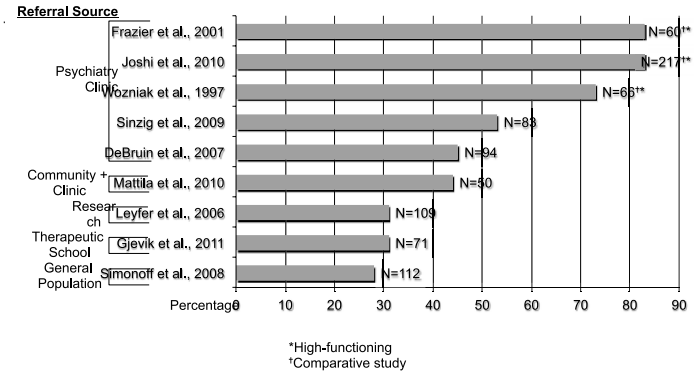
Current Psychiatric Conditions

Youth *Adults*



Clinical and Research Program in Pediatric Psychopharmacology, Massachusetts General Hospital

Prevalence of ADHD in Youth with ASD



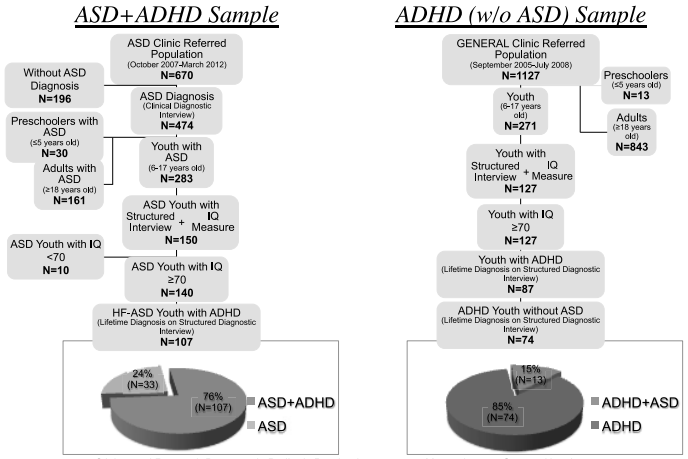
*High-functioning
†Comparative study

Implications of Lack of Recognition of ADHD Comorbidity with ASD

Lack of recognition of ADHD…..

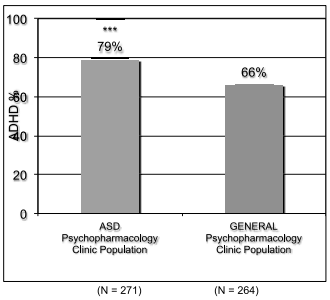
- Impairs intellectual/school performance
- Further worsens already compromised social performance
- Interferes with ASD specific behavioral interventions
- Treated with ASD specific interventions
- Fails to receive ADHD specific treatment
- Predisposes to increased risk for disruptive behaviors, mood dysregulation, and substance abuse

Study Sample Ascertainment Process

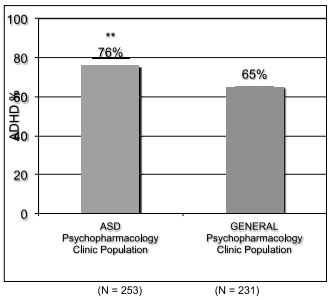


Prevalence of ADHD in Referred Populations

ADHD: Lifetime



ADHD: Current
(Last month)



Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

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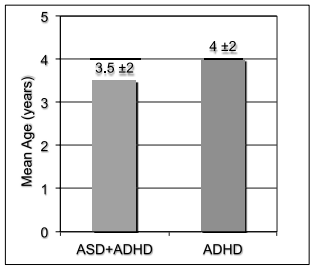
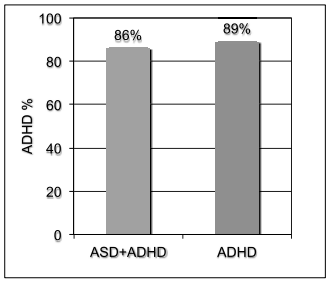
Clinical Correlates of ADHD in Youth with ASD

ADHD: Age at Onset



ADHD: Current



Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

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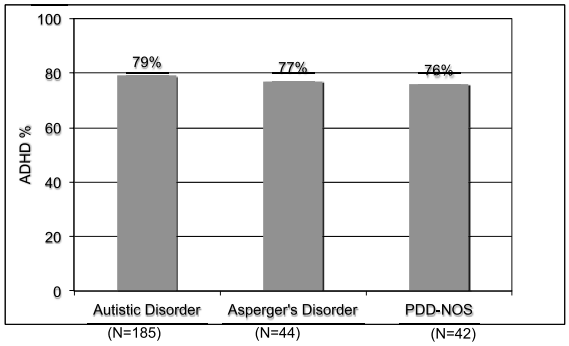
Clinical Correlates of ADHD in Youth with ASD

Lifetime ADHD: Distribution in Subtypes of ASD



Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

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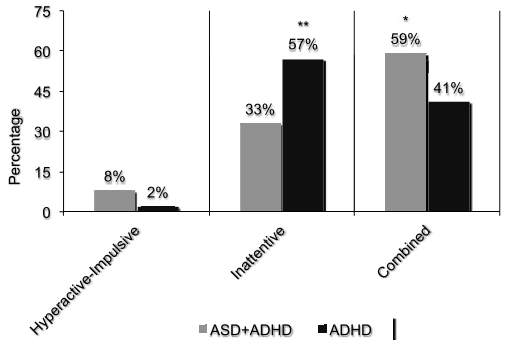
Clinical Correlates of ADHD in Youth with ASD

ADHD Subtypes: Distribution in ASD



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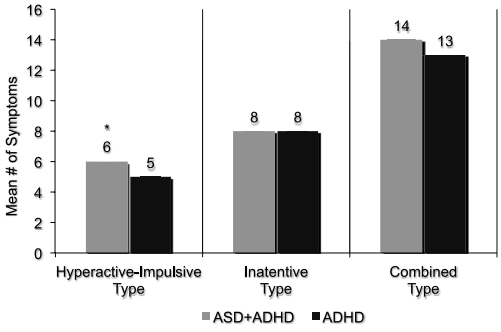
Clinical Correlates of ADHD in Youth with ASD

Loading of ADHD Symptoms



Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

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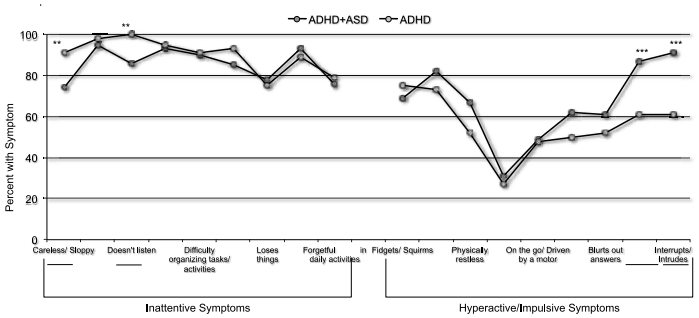
Clinical Correlates of ADHD in Youth with ASD

ADHD Symptom Profile



Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

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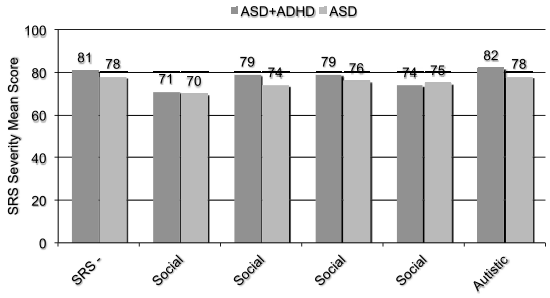
ADHD Comorbidity in Bressler Clinic Referred Youth with ASD

Severity of ASD Core Features Based on Comorbidity with ADHD



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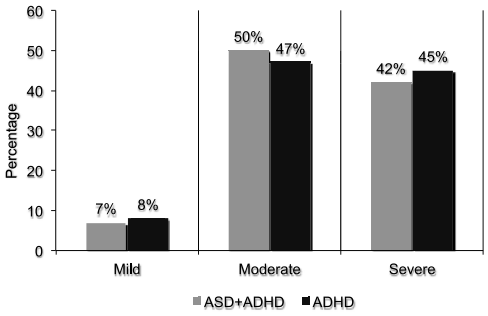
Clinical Correlates of ADHD in Youth with ASD

ADHD: Level of Severity



Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

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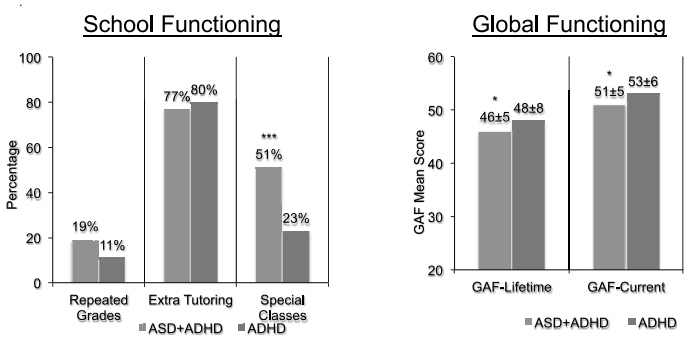
Clinical Correlates of ADHD in Youth with ASD

Level of Functioning

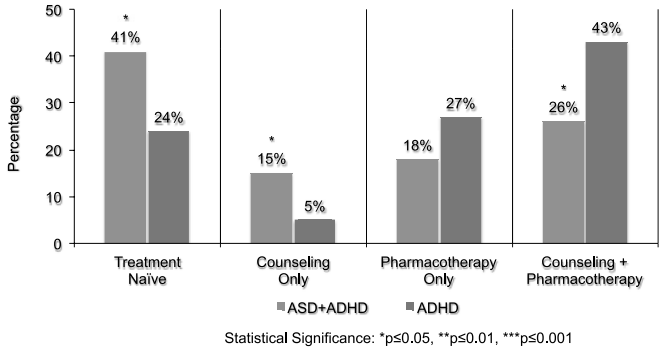


Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

Clinical and Research Program in Pediatric Psychopharmacology, Massachusetts General Hospital

Clinical Correlates of ADHD in Youth with ASD

ADHD: Treatment History



Statistical Significance: *p≤0.05, **p≤0.01, ***p≤0.001

Clinical and Research Programs in Pediatric Psychopharmacology, Massachusetts General Hospital

In Summary.....

- Greater than expected rates of ADHD in youth with ASDs
- A substantial majority of youth with ASDs suffer from ADHD
- The clinical presentation of ADHD in youth with ASD is typical of the disorder
- ASD youth with ADHD are significantly more impaired in their various indices of psychosocial functioning
- Significantly less ASD youth with ADHD received treatment for ADHD

Clinical and Research Programs in Pediatric Psychopharmacology, Massachusetts General Hospital

Pharmacotherapy for ADHD Symptoms in ASD

Stimulants

- Methylphenidate for Hyperactivity (3 RCT)

SNRI

- Atomoxetine for ADHD (2 RCT)

Alpha-2 Adrenergic Agonists

- Clonidine (2 RCT)
- Gunafacine (1 OLT)

Stimulants- Overview

- Stimulants are the most widely prescribed psychiatric medication in youth with ASD (12% of the ASD population)
- Methylphenidate is commonly prescribed stimulant in youth with ASD
- No trials conducted on Mixed Amphetamine Salts
- No trials on extended-release form of stimulants in this population

Methylphenidate

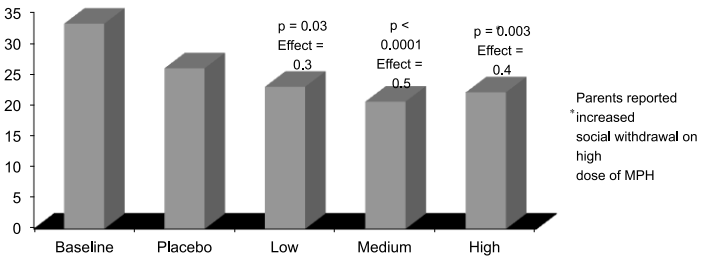
A Controlled Trial in ASD Children with Hyperactivity

- Diagnoses: ASD + Hyperactivity (moderate-severe)
- Ages: 5-14 years
- 3 Phases:
  - Tolerability Phase: 1-week test dose (n=72)
  - RCT phase: 4-week (n=66)
  - Open-label phase: 8-week (n=35)
- MPH Dose (TID): (mg/kg/day)
  - Low - 0.125
  - Medium - 0.25
  - High - 0.5

RUPP Autism Network, 2005

Methylphenidate – RUPP Trial

Crossover Phase: Parent Rated ABC-Hyperactivity Subscale

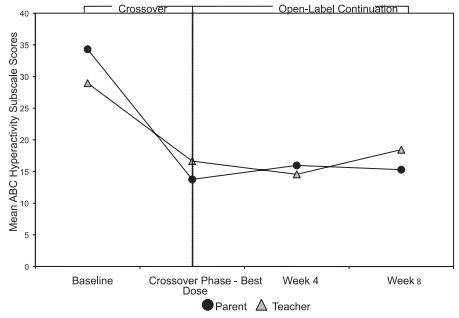


Dose-dependent ADHD response most apparent at higher (0.25 and 0.5 mg/kg) than lower (0.125 mg/kg) doses of MPH

RUPP Autism Network, 2005

Methylphenidate – RUPP Trial

Continuation Phase: Parent Rated ABC-Hyperactivity Subscale



RUPP Autism Network, 2005

Methylphenidate

RUPP Trial

Anti-ADHD symptoms response

- Rate of Response: 50% *(vs. 70% in MTA Trial)*
  (≤2 CGI-I & >25-30% ↓ in ABC-H)
- Magnitude of Response: ES 0.20 – 0.54 *(vs. 0.35 – 1.31 in MTA trial)*
- ADHD s/s response independent of
  - Level of IQ
  - Subtypes of ASD
- Lack of response on ABC subscales:
  - Irritability
  - Social withdrawal
  - Inappropriate speech
  - Stereotypy

MPH is less effective in children with ASD than in typically developing children with ADHD

RUPP Autism Network, 2005

Methylphenidate

RUPP Trial

Tolerability

- Common AEs:
  - Decreased appetite
  - Initial insomnia
  - Irritability
  - Emotional outbursts

  No exacerbation of stereotypes or other repetitive behaviors
- Total Dropout: 18% (13/72) *(vs. 1.4% in MTA Trial)*

  All dropout due to inability to tolerate medications
  - 50%$^{(6/13)}$ dropout due to irritability
  - 50%$^{(6/13)}$ dropout due to inability to tolerate test dose

MPH is associated with more frequent adverse effects in children with ASD than in typically developing children with ADHD

RUPP Autism Network, 2005

Methylphenidate

3-week Randomized-controlled Crossover Trial in Children with ASD

- 13 children (5-11yrs.)
- Diagnoses: Autistic Disorder or PDD-NOS
- MPH Dose: Higher (0.6 mg/kg/day) vs. Lower (0.3 mg/kg/day)
  - No difference in hyperactivity response
  - Significantly more AEs on higher dose
- High rates of AEs on placebo
- Irritability - most common AE and cause of D/C in 2/3 subjects

Handen et al., 2000

Methylphenidate

Single-dose & 12-week Open-label Trial in Children with ASD

- 5/13 subjects on test dose of 0.4 mg/kg MPH reported AEs of increased:
  - Hyperactivity
  - Repetitive behaviors (stereotypy, motor tics)
  - dysphoria
- 6/8 subjects improved on symptoms of hyperactivity/ impulsivity & none D/C due to AEs

Administering a single dose of MPH may be useful in identifying children with ASD who may benefit from prolonged therapy

DiMartino et al., 2004

Atomoxetine

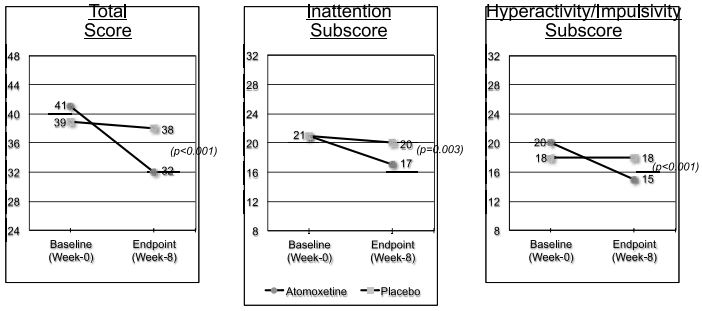
8-week Randomized-controlled Trial in Youth with ASD

- 97 subjects
- Ages 6-17 with IQ ≥60
- Diagnoses: ASD+ADHD
- Atomoxetine *once a day dosing* (mg/kg/day):
  - Week-1: 0.5
  - Week-2: 0.8
  - Week-3: 1.2

Harfterkamp et al., 2012

Atomoxetine

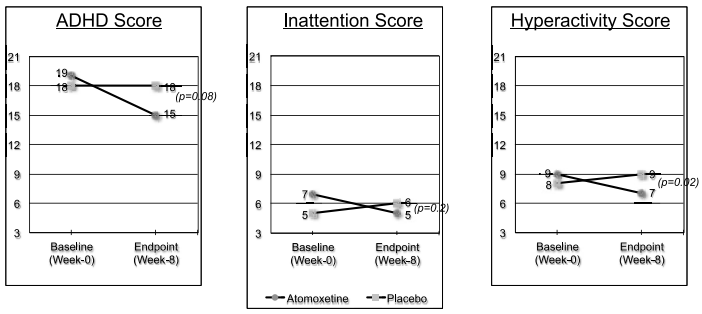
Clinician-rated: ADHD-RS



Harfterkamp et al., 2012

Atomoxetine

Teacher-rated: CTRS-R



Harfterkamp et al., 2012

Atomoxetine

Efficacy

- ADHD-CGI-I: 21%^{ATX} Vs. 9%^{Plbo} (p=0.14)
  (≤2 CGI-I)

ADHD-RS Mean Score Reduction

ASD *Versus* Typicals

-8.2 *Vs.* -13-19

Magnitude of ADHD response less than observed with typical ADHD

Tolerability

- Mild & transient AEs
  - Nausea (29%)(vs. Plbo=8%; p=0.009)
  - Aneorexia (27%)(vs. Plbo=6%; p=0.006)
  - Fatigue (23%) (vs. Plbo=8%; p=0.05)
  - Late insomnia (10%)(vs. Plbo=0%; p=0.03)
- Treatment-limiting AEs: 1 subject on ATX d/t fatigue
- Serious AEs: None

Tolerability profile similar to that observed with typical ADHD

Harfterkamp et al., 2012

Alpha-2 Adrenergic Agonist - Clonidine

Two Crossover RCTs in Males with Autistic Disorder

Oral Clonidine*
- 6-week trial with oral clonidine 4-10 micro gms/kg/day
- 8 males (mean age: 8 ±3 yrs.) with autistic disorder + hyperactivity (prior hx. of poor response)

Transdermal Clonidine**
- 4-week trial with transdermal clonidine 3.5 micro gms/kg/day
- 9 males (mean age: 13 yrs.) with autistic disorder + hyperarousal symptoms (including hyperactivity)

Efficacy

Oral Clonidine: Superior to placebo in reducing Hyperactivity(per teacher/parent & not clinician rating)

Transdermal Clonidine: No effect on ADHD symptoms(per parent rating)

Tolerability

Major adverse-effect - Drowsiness
- Fatigue

Jaselskis et al., 1992*; Fankhauser et al., 1992**

Alpha-2 Adrenergic Agonist - Guanfacine

8-week Open-label Trial in Children with ASD

- 25 children (mean age 9±3 yrs.)
- Diagnoses: ASD + Hyperactivity/Impulsivity (CGI-S ≥4) (with prior Hx. of poor response to MPH - ineffective or intolerable)
- Guanfacine Dose range: 1-3 mg/day (in divided doses)

Tolerability

- Common Adverse Effects - Irritability (28%)
  - Sedation (28%)
- Treatment-limiting AEs - 4/25 D/O d/t irritability/agitation
- Serious AEs - None

Scahill et al., (2006)

Guanfacine

8-week Open-label Trial in Youth

Efficacy

	Parent –Rated	Teacher-Rated
ABC Measure		
• Hyperactivity	+	+
• Irritability	+	-
• Repetitive behaviors	+	-
• Social interaction	+	-
SNAP Measure		
• Inattention & Hyperactivity	+	+

CGI-Global Improvement (≤2): 48% *(vs. 50% in Typicals)*

Scahill et al., (2006)

In Summary.....

- Less than expected and modest magnitude of response of ADHD symptoms to stimulant and non-stimulant treatment in ASD youth
- Guanfacine as a promising agent for treating ADHD symptoms in ASD children who failed Tx with MPH
- Less than expected tolerability to MPH & Guanfacine Tx. ATX is equally well tolerated by youth with ASD
- Clonidine is not well tolerated by ASD
- More trials with different anti-ADHD agents and in intellectually capable including adult populations with ASD are warranted

Clinical and Research Programs in Pediatric Psychopharmacology, Massachusetts General Hospital

Acknowledgements

The Alan and Lorraine Bressler Clinical and Research Program for Autism Spectrum Disorders

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Joseph Biederman, MD
Janet Wozniak, MD
Robert Doyle, MD
Rona Fried, EdD
Maribel Galdo, LCSW
Laura Tarko, MPH
Stephannie Furtak, BA

Neuroimaging of ADHD

Eve Valera, PhD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

Neuroimaging of ADHD

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Research Associate
Massachusetts General Hospital
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Harvard Medical School

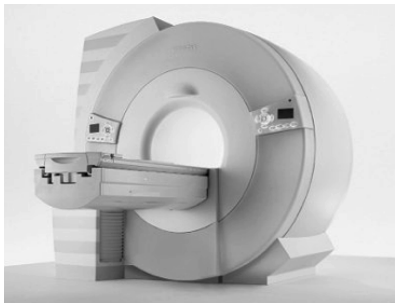
Disclosures

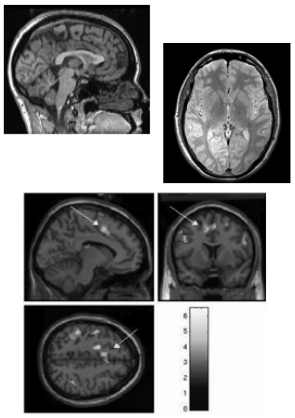
Neither I nor any of my immediate family has a significant financial interest or affiliation with any manufacturer of commercial product (s) or provider(s) of commercial services discussed in my educational presentations for MGH Psychiatry Programs in 2013.

Which Brain Regions Are Abnormal in ADHD?

Magnetic Resonance Imaging (MRI) Scanner and Images

Can examine structure and/or function





Structural and Functional Neuroimaging Data

- Studies show that there are widespread structural alterations in the ADHD brain:
  - Frontal, parietal, occipital, temporal, striatal regions; cerebellum, corpus callosum,
  - In volume, thickness, white matter microstructural integrity.
- Studies also show that there are widespread functional abnormalities in the ADHD brain:
  - In specific localized regions as well as connectivity between those regions;
  - For both task-based and resting-state neural activity.

Variables that Could Influence Results

- Particular brain region or task studied
- Methods used
- Sample size
- Subject demographics
  - Sex
  - Age
  - Comorbidities
  - History of stimulant medication

Varying Results Across Studies

- Conflicting results
  - Caudate:
    - No differences (Hill et al *Neuropsychology* 2003)
    - Larger (Mataro et al *Arch Neurol* 1997)
    - Smaller (Hynd et al *J Child Neurol* 1993)
  - Splenium of corpus callosum:
    - No differences (Giedd et al *Am J Psychiatry* 1994)
    - Smaller (Semrud-Clikeman et al *JAACAP* 1994)
- Unclear which regions are most affected

Meta-Analyses

- Analytical way to evaluate a literature to help resolve conflicting results and identify more replicable findings.
- For previous volumetric example:
  - Magnitudes of differences within each study are pooled across studies;
  - Variables such as sample size are used to weigh the degree to which a study contributes to an overall difference score;
  - Volumetric reductions for regions of interest can be compared since they are converted into the same metric.

Structural Imaging Data

Meta-Analyses of Structural Imaging Findings in ADHD

- 1 meta-analysis of studies using traditional area or volumetric analysis techniques (e.g., manual tracing of specific regions)
  - Valera et al *Biol Psychiatry* 2007
- 3 meta-analyses of studies using voxel based morphometry (VBM; a relatively quick, automated method of structural analysis of the entire brain, which allows for regionally specific findings)
  - Ellison-Wright et al *BMC Psychiatry* 2008
  - Frodl et al *Acts Psychiatry Scand 2011*
  - Nakao et al *Am J Psychiatry 2011*

Meta-Analysis of non-VBM Structural Imaging Studies

Valera et al *Biol Psychiatry* 2007

21 Studies with 22 samples

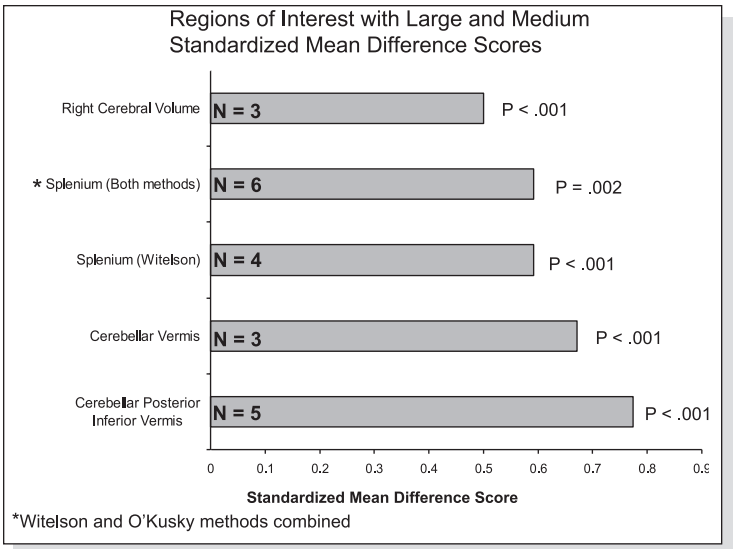
	Controls (N = 583)		ADHD (N = 565)	
	Mean	(SD)	Mean	(SD)
Mean Age	11.3	(1.6)	11.0	(1.5)
Range of Mean Age	9.3-14.8		9.1-14.6	
Sex	81.3% Male		81.2% Male	
Mean Sample Size	27.8		25.7	
Modal Sample Size	15		15	

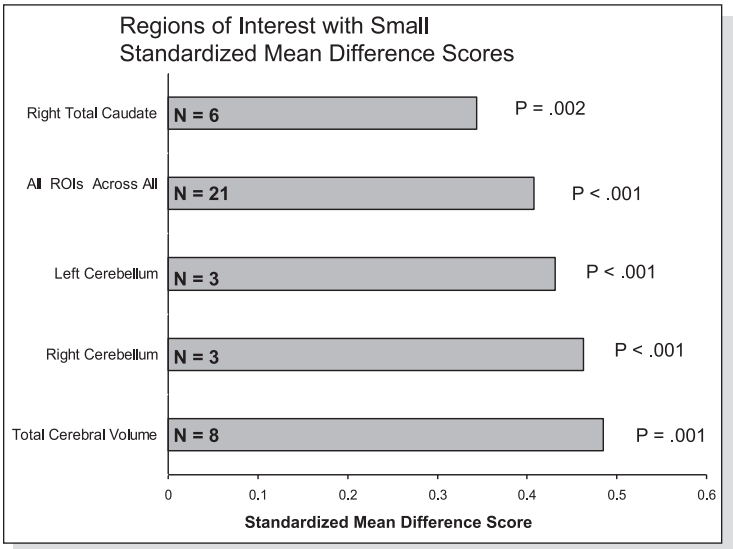
Effect Sizes

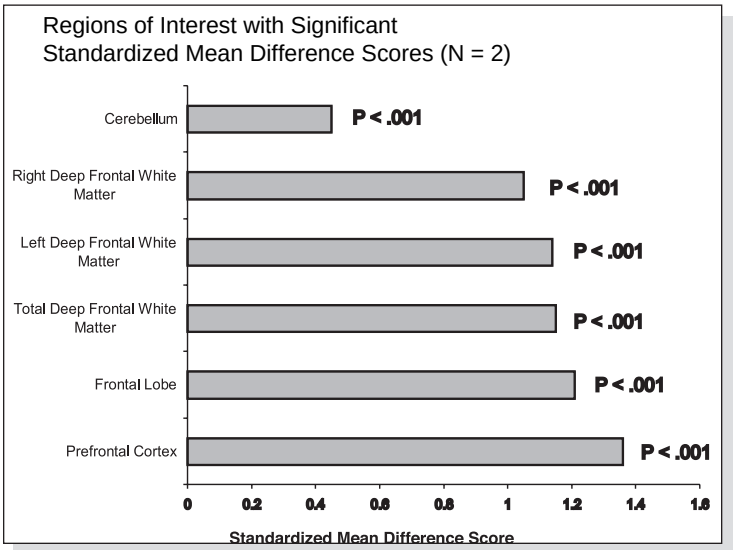
- Effect size = Standardized mean difference score

$$\frac{\text{Mean1} - \text{Mean2}}{\text{Pooled Standard Deviation}}$$

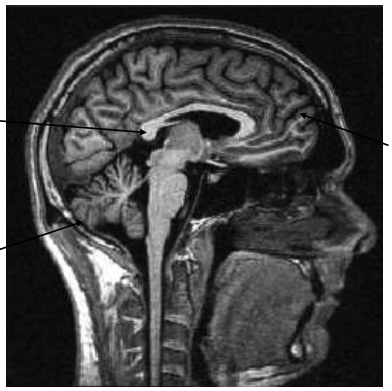
- Cohen's classification
  - Small = .20 to .49
  - Medium = .50 to .79
  - Large = .80 and larger


Regions of Interest with Large and Medium
Standardized Mean Difference Scores
Right Cerebral Volume
N = 3
P < .001
* Splenium (Both methods)
N = 6
P = .002
Splenium (Witelson)
N = 4
P < .001
Cerebellar Vermis
N = 3
P < .001
Cerebellar Posterior
Inferior Vermis
N = 5
P < .001
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
Standardized Mean Difference Score
*Witelson and O'Kusky methods combined

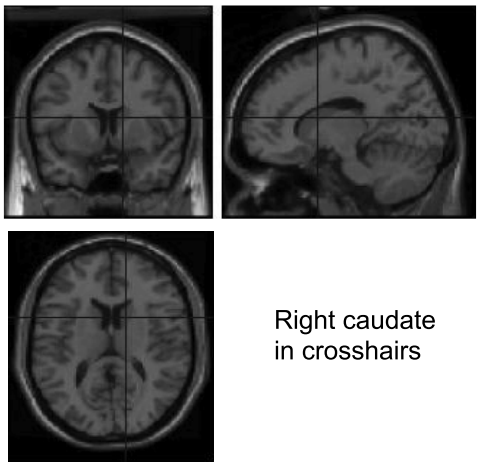

Regions of Interest with Small
Standardized Mean Difference Scores
Right Total Caudate
N = 6
P = .002
All ROIs Across All
N = 21
P < .001
Left Cerebellum
N = 3
P < .001
Right Cerebellum
N = 3
P < .001
Total Cerebral Volume
N = 8
P = .001
0
0.1
0.2
0.3
0.4
0.5
0.6
Standardized Mean Difference Score


Regions of Interest with Significant
Standardized Mean Difference Scores (N = 2)
Cerebellum
P < .001
Right Deep Frontal White
Matter
P < .001
Left Deep Frontal White
Matter
P < .001
Total Deep Frontal White
Matter
P < .001
Frontal Lobe
P < .001
Prefrontal Cortex
P < .001
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
Standardized Mean Difference Score

Meta-Analytic Results



Meta-Analytic Results



Right caudate in crosshairs

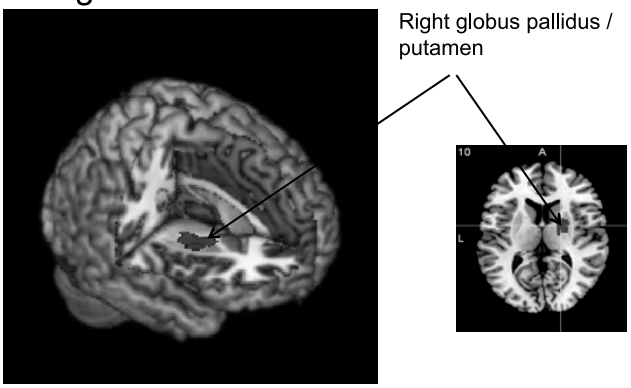
Regions of Interest Assessed in N ≥ 3 Studies with No Significant Standardized Mean Difference Scores

- Left cerebral volume
- Bilateral prefrontal white
- Bilateral prefrontal gray
- Bilateral caudate head
- Caudate (head and tail)
- Left caudate (head and tail)
- Bilateral globus pallidus
- All other regions of the corpus callosum, regardless of segmentation method
- Cerebellar anterior vermis
- Cerebellar posterior superior vermis

Meta-analyses of VBM Studies

- Ellison-Wright et al *BMC Psychiatry* 2008
  - 6 studies with 7 samples (114 ADHD children and 143 controls)
  - Published from 2001-2007 (mostly 2007)
  - Found gray matter reductions in the right putamen / globus pallidus region.
  - Small number of studies, so limited power to detect differences in other regions (individual studies showed reductions in other regions); need more studies to increase power.

Gray Matter Reductions in ADHD Using VBM



Ellison-Wright et al *BMC Psychiatry* 2008;
Copyright permission granted.

Meta-analyses of (mostly*) VBM Studies

- Frodl et al *Acta Psychiatry Scand* 2011
  - 11 studies (7 children; 4 adults) - 320 ADHD and 288 controls
  - ADHD Children: show reductions in right globus pallidus and putamen, as well as bilateral caudate for manual tracing studies; Basal ganglia changes seem to diminish over time from childhood to adulthood.
  - ADHD Adults: show reductions in anterior cingulate cortex (ACC).
  - Stimulants seem to attenuate effect on amygdala and ACC in ADHD children.
  - Generally, a higher percentage of treated ADHD subjects was associated with smaller differences.
  - *Included VBM studies plus caudate manual tracing studies.

Meta-analyses of VBM Studies

- Nakao et al *Am J Psychiatry* 2011
  - 14 data sets (9 children; 5 adult) - 378 ADHD and 344 controls
  - Global *reductions* in gray matter localized in right lentiform nucleus (putamen and globus pallidus) extending to the caudate.
  - Both increasing age and percentage of patients taking stimulant medications were associated with more normal values.
  - No differences with only adults included, suggesting that effects attenuate over time.
  - ADHD subjects had slightly *greater* gray matter volumes in the left posterior cingulate cortex extending to the precuneus.

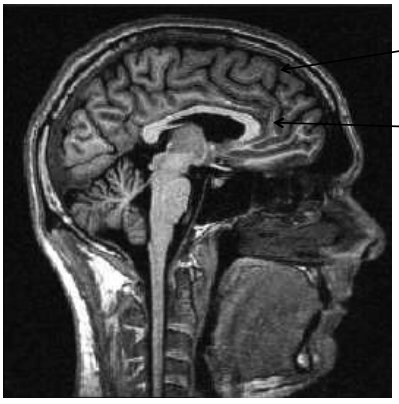
Manual tracing vs. VBM Structural Imaging Results

- Although manual tracing and VBM meta-analyses both show right caudate reductions for the ADHD samples, they otherwise appear to yield somewhat varying results (e.g., many more structures seem to be abnormal in the tracing studies consistent with other data).
- Possible reasons why?
- Manual tracing studies such as studies in the Valera et al 2007 meta-analysis are typically more specified ROI based analyses which afford more power to detect between group differences.

In contrast

- VBM analyses often include the entire brain and have less sensitivity (less power) to detect differences. Also, variability in exact location of differences in individual studies could lead to non-significant findings.
- Sex? Age?

Volumetric Reductions in ADHD Adults



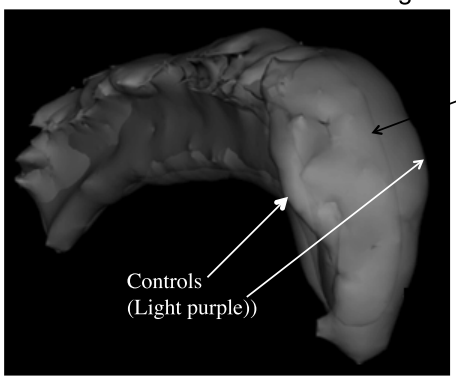
Sample size (50% Male)
18 Controls
24 ADHD

Mean IQ
117.5 ADHD
117.9 Controls

Seidman et al *Biol Psychiatry* 2006

3D Isosurface of the Anterior Cingulate: ADHD vs. Controls

14% reduction in ADHD Anterior Cingulate



Seidman et al *Biol Psychiatry* 2006

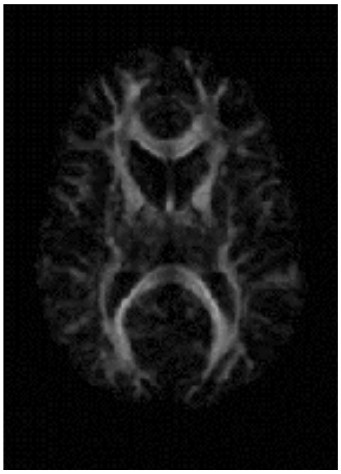
Structural MRI in Adult ADHD

- Hesslinger et al *Neurosci Lett* 2002 (non-VBM)
  - Showed volumetric reductions in left orbitofrontal volumes for ADHD adults.
- Biederman et al *Psychol Medicine* 2008 (non-VBM)
  - Showed volumetric reductions for ADHD subjects in superior frontal gyrus, anterior cingulate and cerebellar cortex.
- Seidman et al *Biol Psychiatry* 2011 (VBM study)
  - Relative to control subjects, only the caudate remained significantly smaller at the family-wise error rate for the ADHD adults.

White Matter Abnormalities in ADHD

- Diffusion Tensor Imaging (DTI)
  - Measure of diffusion of the water molecules allowing one to infer white matter (WM) microstructural organization and integrity.
  - Often used to assess fractional anisotropy (FA) of the WM tracts in the brain, but other measures can also be obtained such as mean diffusion (MD) and axial and radial diffusivity.
    - MD and FA – provide measures of organization and orientation of WM tracts and myelination.
    - Axial diffusivity – if decreased, may suggest axonal damage or degeneration.
    - Radial diffusivity – if increased (with low changes in axial diffusivity), likely represents decreased myelination.

DTI Color Map



Meta-Analysis of DTI Abnormalities in ADHD

- Van Ewijk et al *Neurosci Biobehav Reviews* 2012
- 9 studies (179 ADHD and 169 controls)
- Showed widespread alterations in WM with 5 clusters reliably being altered across all studies including the right anterior corona radiata, right forceps minor, bilateral internal capsule and left cerebellum.
- These regions are located in WM tracts subserving fronto-striatal-cerebellar neurocircuitry.
- Supports ideas that deficits in networks may at least partially originate from disturbed microstructural connectivity.

Meta-Analysis of DTI Abnormalities in ADHD

- Van Ewijk et al *Neurosci Biobehav Reviews* 2012
- Also reviewed 7 ROI studies of which some of the same (anterior corona radiata, internal capsule, cerebellum) and numerous additional regions were found to show differences including: inferior and superior longitudinal fasciculus, corticospinal tract, cingulum, corpus callosum, and caudate nucleus.
- Increases vs. decreases in fractional anisotropy: Only voxel based whole brain analyses, rather than ROI based analyses, showed relative increases for ADHD subjects. This could be the result of including more regions with large amounts of fiber crossing in these studies.

Meta-Analysis of DTI Abnormalities in ADHD

- Van Ewijk et al *Neurosci Biobehav Reviews* 2012
- Clinical correlations between:
  - FA with ADHD symptoms (moreso with inattentive symptoms);
  - FA and/or MD with attentional focus, impulsivity and interference inhibition.
- Limitations:
  - Heterogeneity, statistical corrections, head motion.
- Future of DTI studies – use other measures which can give more insight into exact underlying neurobiological mechanisms (e.g., mode of anisotropy).

Other Structural Abnormalities in ADHD

- Cortical thinning
  - Shaw et al *Arch Gen Psychiatry* 2006
  - Makris et al *Cerebral Cortex* 2007
- Decreased surface area
  - Plessen et al *Arch Gen Psychiatry* 2006
  - Wolosin et al *Human Brain Mapping* 2009
- Decreased cortical folding
  - Wolosin et al *Human Brain Mapping* 2009
- Different shape
  - Qiu et al *Am J Psychiatry* 2009

Use of Multiple Techniques Simultaneously

- The use of multiple techniques could lead to an increasing understanding of the underlying neural abnormalities and/or be used towards classifying ADHD vs. other subjects.
  - For example, use of structural MRI with fMRI and resting state could allow us to see whether functional and structural abnormalities exist in the same place, and using DTI and structural MRI could allow one to see whether both macro-and microstructural abnormalities exist in the same locations.
- Kobel et al *Psychiatry Res* 2010 – Used VBM, DTI, magnetization transfer imaging (MTI), fMRI and independent component analysis.
- Qiu et al *Brain Topogr* 2010 – Used structural MRI, DTI, resting state analysis.

Future Directions for ADHD Structural Imaging Studies

- Females – very underrepresented
- Continue to use newer techniques such as:
  - Voxel-based morphometry
  - Diffusion tensor imaging – other measures
  - Cortical thickness and folding analysis
  - Surface area analysis
- Use of multiple techniques in same study
- Effects of genes
- Longitudinal studies – delay in maturation? (Shaw et al *Proc Natl Acad Sci* 2007)

Functional Imaging in ADHD

Single Photon Emission Computed Tomography Imaging (SPECT) in ADHD

- Earliest studies in the mid 1980s used SPECT to study children and adolescents with ADHD.
- Few well-designed studies because use of radioactive materials made it difficult to justify using healthy controls.
- Has relatively poor spatial and temporal resolution.

Positron Emission Tomography Imaging (PET) in ADHD

- First large, well-designed ADHD study in 1990 (Zametkin et al *N Engl J Med* 1990).
- Most studies have been conducted with adults and adolescents because the use of radioactive materials makes it less ideal for children.
- Continuous performance task is used to match subjects' cognitive state in most studies, with some exceptions (decision making, gambling task).
- Often used to examine pharmacological or neurochemical changes/alterations.

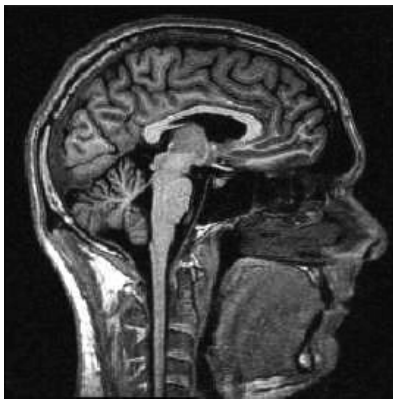
Functional Magnetic Resonance Imaging (fMRI) in ADHD

- Most studies have been conducted with children and adolescents.
- Growing number of adult studies.
- Typically use a "cognitive activation" paradigm to determine areas of abnormality for specific cognitive functions.
- More recently use "resting state" procedures
- Majority of subjects are male.

fMRI - Recent Advances

- Functional connectivity studies focus on networks:
  - Provide information on inter-regional correlations of brain activity;
  - Can provide information regarding strength and direction of relationships between regions (effective connectivity);
  - Both model free and seed based analysis approaches;
  - Can examine connectivity during "rest" or cognitive task performance.

Abnormalities in Relationships Among Regions vs. Isolated Regions



fMRI - Networks

- During the resting state: Task Negative Network/ Default Mode Network (DMN) includes precuneus/ posterior cingulate cortex, medial prefrontal cortex, medial, lateral, and inferior parietal cortices.
- During cognitive tasks: Task Positive Network includes dorsolateral prefrontal cortex, intraparietal sulcus and supplementary motor area (associated with increased alertness, response preparation and selective attention).
- Task negative and positive networks are typically anti-correlated.

Cognitive Processes of Focus

- Response inhibition
- Executive functioning
- Attention/vigilance
- Working memory
- Motor control
- Reward anticipation/motivation
- Timing

Neural Regions Often Targeted and Findings

- Strong focus on frontal and striatal regions:
  - Dorsolateral prefrontal cortex
  - Ventrolateral prefrontal cortex
  - Dorsal anterior cingulate cortex
  - Striatum (caudate and putamen)
  - Parietal regions
- Repeated hypoactivity in:
  - Anterior cingulate cortex
  - Striatum (caudate and putamen)
  - Frontal cortex
  - Parietal regions

Meta-Analysis of fMRI Studies in ADHD

- Dickstein et al *J Child Psychol Psychiatry* 2006
  - 16 studies (11 child/adolescent and 5 adult)
  - Significant patterns of *hypoacti*vity in ADHD subjects in:
    - Frontal areas
      - Anterior cingulate
      - Dorsolateral and inferior prefrontal cortices
    - Parietal cortices, basal ganglia, right thalamus and claustrum and left occipital gyrus
  - Most consistent areas of hypoactivation were fronto-striatal and fronto-parietal circuits.
  - Showed *hyperactivity* in ADHD subjects for left insula, middle frontal gyrus and thalamus, as well as right paracentral lobule.

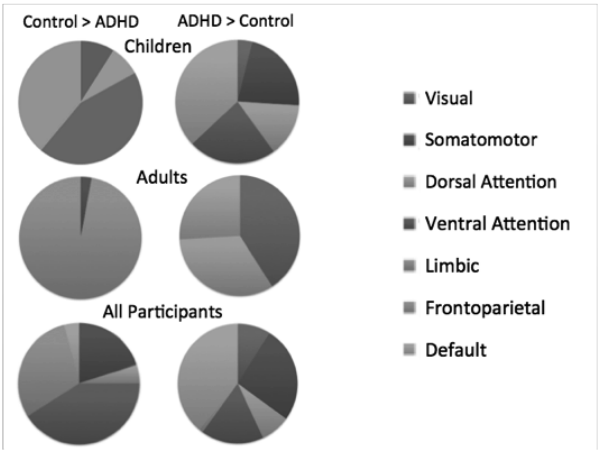
Meta-Analysis of fMRI Studies in ADHD

- Cortese et al *Am J Psychiatry* 2012
  - 55 studies (39 child/adolescent and 16 adult samples with 741 ADHD and 801 controls)
  - Mapped findings onto 7 networks (in contrast to isolated regions) established by Yeo et al 2011:
    - Visual
    - Somatomotor
    - Dorsal attention
    - Ventral attention
    - Limbic
    - Frontoparietal
    - Default

Meta-Analysis of fMRI Studies in ADHD

- Cortese et al *Am J Psychiatry* 2012
  - Significant patterns of *hypoactivity* in ADHD subjects primarily in frontoparietal executive control and ventral attention networks:
    - Children - frontoparietal and ventral attentional network regions
    - Adults - frontoparietal network regions
- Significant patterns of *hyperactivity* in ADHD subjects primarily in default and visual networks:
  - Children - default, ventral attention and somatomotor networks
  - Adults - visual, dorsal attention and default networks

Proportions of ADHD-Related Hypo- or Hyperactivation In Meta-Analysis (Cortese et al 2012)



Meta-Analysis of Inhibition and Attention fMRI Studies in ADHD

- Hart et al *Arch Gen Psychiatry* 2012
- 21 datasets for inhibition (287 ADHD and 320 Controls)
- 13 datasets for attention (171 ADHD and 178 Control)
- Inhibition – ADHD subjects showed *reduced* activation primarily in right inferior frontal cortex, supplementary motor area, anterior cingulate cortex, and striato-thalamic areas.
- Attention – ADHD subjects showed *reduced* activation primarily in right dorsolateral prefrontal cortex, thalamus, insula, inferior parietal lobe, precuneus and superior temporal regions as well as bilateral basal ganglia; showed *increased* activation in right cerebellum and left cuneus.

Meta-Analysis of Inhibition and Attention fMRI Studies in ADHD

- Hart et al *Arch Gen Psychiatry* 2012
- Attention – Meta-regression showed that long term stimulant medication use was associated with more similar right caudate activation relative to controls and at a trend level for interference inhibition (possible power issue).
- Inhibition – Possible age effects; supplementary motor area and basal ganglia were underactivated solely in ADHD children relative to controls while the right inferior frontal cortex and thalamus were underactivated solely in ADHD adults relative to controls.

Meta-Analysis of Timing fMRI Studies in ADHD

- Hart et al *Neurosci Biobehav Reviews* 2012
- 8 studies with 11 datasets (150 ADHD and 145 Controls)
- Most consistent areas of *reduced* activation were in typical areas of timing such as left inferior prefrontal cortex (IFC), insula, inferior parietal lobe, superior temporal gyrus and right cerebellum.
- Meta-regression showed right dorsolateral prefrontal cortex activation was reduced in medication naive patients but normal in long term stimulant medication patients relative to controls, suggesting normalization of function for this particular region.

Meta-Analysis of Timing fMRI Studies in ADHD

- Hart et al *Neurosci Biobehav Reviews* 2012:
- ADHD subjects showed *greater* activation in the precuneus, cuneus and posterior cingulate gyrus possibly reflecting problems with deactivating the DMN.
- Findings of left fronto-parietal-cerebellar deficits contrast with the right fronto-striatal deficits found in meta-analysis of attention and inhibitory deficits.
- Suggests cognitive domain-specific neurofunctional deficits in ADHD.

Review of fMRI Studies in ADHD

- Paloyelis et al *Expert Rev Neurotherapeutics* 2007:
  - Inhibitory control: differences in various regions but inconsistencies in direction of group differences.
  - Inhibition errors and motor functioning: ADHD group almost always showed reduced activation in frontal areas.
  - Attention: ADHD group almost always showed reduced activation in temporal and parietal regions.
  - Most consistent finding in terms of direction of activation was the striatum - lower activation in the ADHD group.
  - Clearly fronto-striatal reductions but also temporal and parietal.

fMRI Network Abnormalities in ADHD

- Connectivity during the "resting state":
  - Evidence for both hyper- and hypoconnectivity:
    - Decreased connectivity within the DMN (Castellanos et al *Biol Psychiatry* 2008; Fair et al *Biol Psychiatry* 2010);
    - Increased connectivity between dorsal anterior cingulate and other brain regions (Tian et al *Neurosci Lett* 2006);
    - Increases and decreases in connectivity (Yu-Feng et al *Brain Dev* 2007; Cao et al *Bain Rsch* 2009).
  - Evidence for altered connectivity relating to cognitive and reward processes (Costa et al *Eur Neuro* 2012; Mills et al *Front Psychiatry* 2012)
  - Evidence for detecting distinct neural signatures for ADHD subtypes (Fair et al *Front Syst Neurosci* 2012).
  - Evidence for normalization with MPH (Li et al *Neuropsychopharmacology* 2012).

fMRI Network Abnormalities in ADHD

- Increased and decreased connectivity during cognitive task performance:
  - Vloet et al *JAACAP* 2010 – Reduced fronto-parietal connectivity during stimulus response compatibility task and reduced fronto-cerebellar connectivity during time discrimination task.
  - Wolf et al *Hum Brain Mapp* 2009 – Reduced connectivity in ventrolateral prefrontal cortex, anterior cingulate, superior parietal lobe and cerebellum but increased connectivity in inferior and superior frontal gyrus, dorsal cingulate, and cuneus during working memory task.
  - Massat et al *PLoS One* 2012 - Increased connectivity between cerebellar and brainstem activity during working memory task.

Functional Neuroanatomy of Working Memory in Adults with ADHD

Valera et al *Biol Psychiatry* 2005

- Purpose:
  - To examine neural activation in ADHD adults using the 2-back working memory task as a probe of frontal functioning.
  - To investigate whether other regions, such as the cerebellum, would show functional differences.

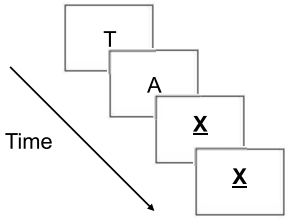
Demographics

	Controls (N = 20)		ADHD (N = 20)	
	Mean	(SD)	Mean	(SD)
Age	33.0	(10.6)	34	(11.8)
Age Range	18-54		18-54	
Sex (M/F)	12/8	60% Male	12/8	60% Male
Education (years)	16.5	(2.2)	15.2	(2.8)
Estimated IQ	118.8	(12.7)	118.3	(14.7)
WRAT-Reading	108.1	(8.3)	108.8	(7.4)
WRAT-Arithmetic	108.5	(14.7)	102.7	(11.4)

No significant differences for any demographic variables.

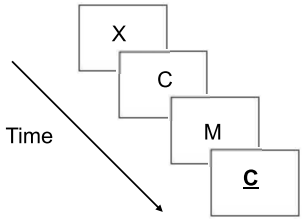
X-Task and 2-Back

"Respond 'Yes' to the letter X. Respond 'No' to all other letters."



X-Task

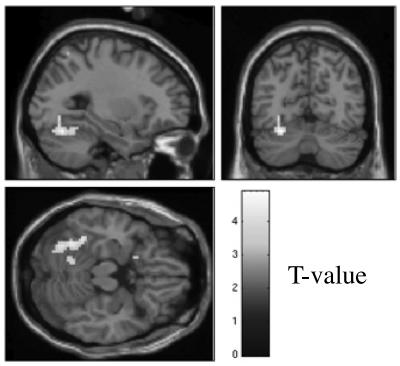
"Respond 'Yes' to any letter that is the same as the letter you saw 2 letters back. Respond 'No' to all other letters."



2-Back

Results

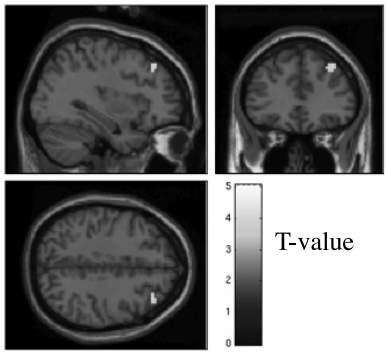
Left Cerebellar and Occipital Activation
Controls minus ADHD



Valera et al *Biol Psychiatry* 2005

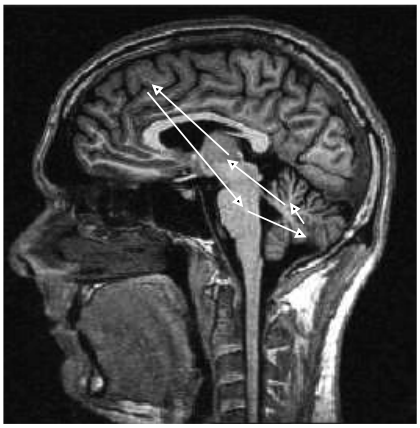
Results

Right Prefrontal Activation
Controls minus ADHD for *a priori* region of interest
Trend level significance, *P* = .07



Valera et al *Biol Psychiatry* 2005

Cerebro-Cerebellar Connectivity



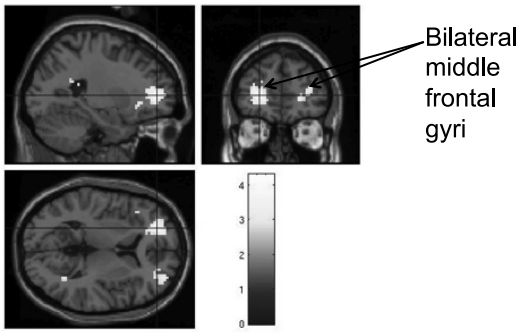
From Cerebral Cortex →
Pontine Nuclei →
Cerebellar Cortex →
Deep Cerebellar Nuclei →
Thalamus →
Back to Cerebral Cortex

Demographics of Expanded Study

	Controls (N = 49) Mean	(SD)	ADHD (N = 44) Mean	(SD)
Age (Range: 18-54)	32.5	(10.1)	36.8	(11.0)
Estimated IQ	114.0	(12.6)	118.1	(14.2)
Sex (M/F)	23/26		23/21	
WRAT-Reading	107.2	(7.8)	107.6	(8.1)
WRAT-Arithmetic	105.6	(13.6)	102.3	(12.5)

Control Activation > ADHD Activation

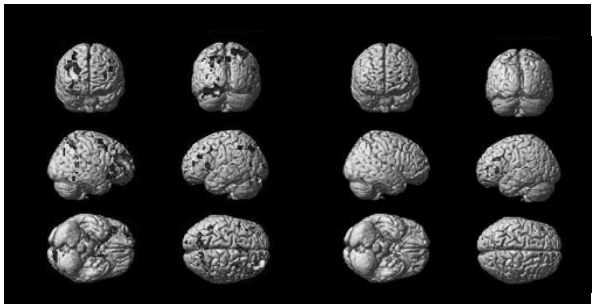
N = 44 ADHD, 49 Controls



Valera et al *Am J Psychiatry* 2010

Control Activation > ADHD Activation

Males	Females
N = 23 ADHD, 23 Controls	N = 21 ADHD, 26 Controls

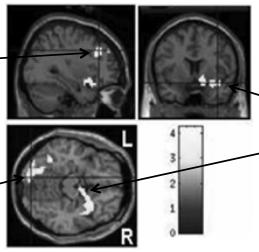


Several significant clusters of reduced activation.	No significant clusters of reduced activation.

Valera et al *Am J Psychiatry* 2010

ADHD-vs.-Control Differences for Males Are Greater than ADHD-vs.-Control Differences for Females

Group by Sex Interaction



Valera et al *Am J Psychiatry* 2010

ADHD Symptom Counts by Sex

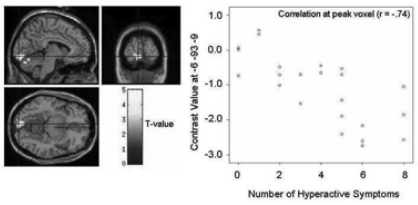
	Male	Female
Hyperactive	3.9	4.5
Inattentive	6.1	5.6

Symptom Correlations Differ by Sex

Males

# of hyperactive symptoms correlated with cluster in occipital/cerebellar region.

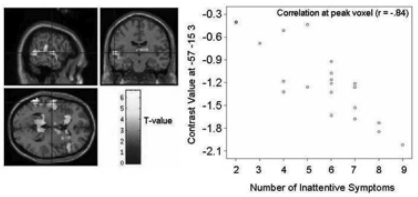
No correlation with inattentive symptoms.



Females

# of inattentive symptoms correlated with large posterior cluster.

No correlation with hyperactive symptoms.



Valera et al *Am J Psychiatry* 2010

Cerebellum, Timing and ADHD

- Traditional view of the cerebellum as being responsible for balance and motor control is incomplete.
- Cerebellum is involved in the timing of motor and cognitive processes (Hallett & Grafman *Intl Rev Neurobiol* 1997; Ivry *Intl Rev Neurobiol* 1997).
- "Faulty" cerebellum could contribute to deficits in cognitive and motor processes requiring timing.
- It has been argued that timing abnormalities are fundamental to impulsiveness, a core symptom of ADHD.

Motor Timing and ADHD

- Up to 50% ADHD children have been found to have motor abnormalities in both fine and gross motor tasks (Pitcher et al *Dev Med Child Neurol* 2003):
  - Goal directed arm movements (Eliasson et al *Dev Med Child Neurol* 2004);
  - Motor leg movement (Nigg et al *J Abnorm Psychol* 1998);
  - Motor speed on Purdue Pegboard Test (Pitcher et al *Dev Med Child Neurol* 2003);
  - Dynamic balance (Kroes et al *Dev Med Child Neurol* 2002);
  - Manual dexterity skills (Piek et al *Dev Med Child Neurol* 1999).

Cognitive Timing and ADHD

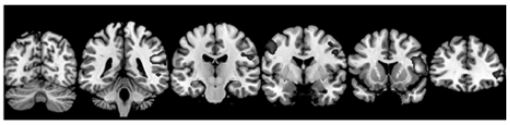
- ADHD children are shown to be impaired on various timing tasks (Toplak et al *J Neurosci Methods* 2006; Rubia et al *Phil Trans R Soc B* 2009; Sonuga Barke et al *JAACAP* 2010):
  - Motor timing (paced finger tapping);
  - Duration discrimination;
  - Duration reproduction;
  - Verbal time estimation;
  - Anticipation tasks.
- Performance is either slower or more variable.

Eyeblink Conditioning and ADHD

- Timing components of eyeblink conditioning are significantly impaired in children with ADHD (Coffin et al *Cortex* 2005; Frings et al *Exp Brain Res* 2009).
- Cerebellum is critical for learning temporal relationships in eyeblink conditioning (animal lesion studies).

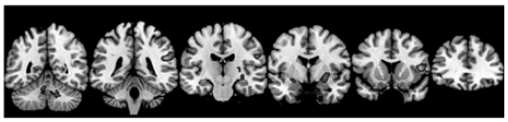
Control Activation > ADHD Activation in Timing Network: Finger Tapping

Paced Finger Tapping



Frontal, cerebellar, parietal lobule, temporal, and insula regions

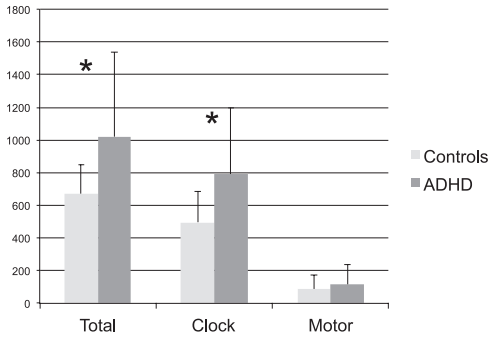
Unpaced Finger Tapping



Frontal, cerebellar, and basal ganglia regions

Valera et al *Biol Psychiatry* 2010

Unpaced Tapping Intrasubject Variability



Valera et al *Biol Psychiatry* 2010

Motor Abnormalities in ADHD

- Modified International Cooperative Ataxia Rating Scale (MICARS)
  - provides an assessment of the clinical signs of the cerebellar motor syndrome
  - 100-point semi-quantitative validated scale
  - 19 items in 4 subscales:
    - posture and gait disturbances
    - limb kinetic functions
    - speech disorders
    - oculomotor disorders

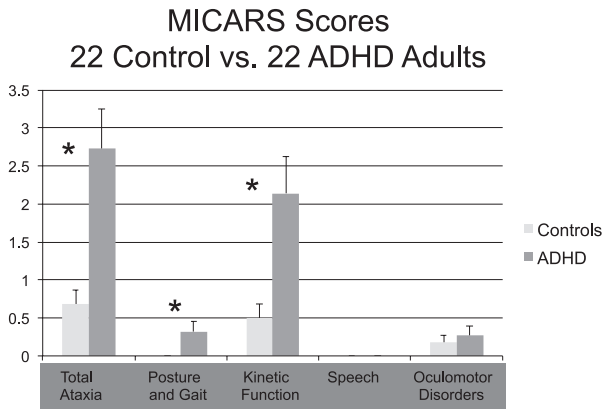
Valera et al *In preparation*

Motor Abnormalities in ADHD

- Collected structural scans.
- The VBM8 (cerebral hemispheres) and SUIT (cerebellum/ brainstem) toolboxes were used for structural image preprocessing and SPM8 was used for statistical modeling.
- Regression analyses: Associations of regional gray matter volume of cerebral hemispheres and cerebellum with ataxia scores were investigated using ANCOVA.

Valera et al *In preparation*

Motor Abnormalities in ADHD



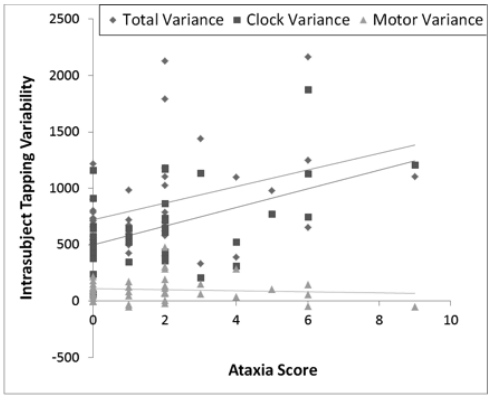
Valera et al *In preparation*

Motor Abnormalities in ADHD Clinical Correlates

- Total ataxia scores were positively correlated with:
  - Intrasubject variability from the unpaced tapping task;
  - Inattentive symptoms but only when examined across both ADHD and controls.

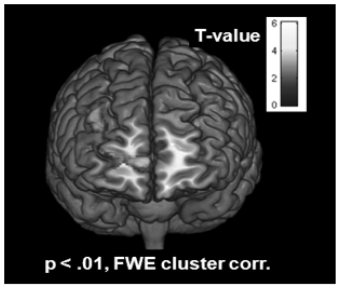
Valera et al *In preparation*

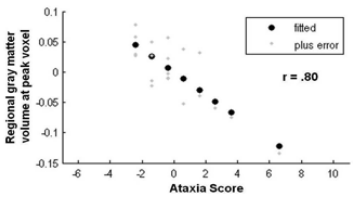
Correlation Between Ataxia Scores and Intrasubject Variability



Valera et al *In preparation*

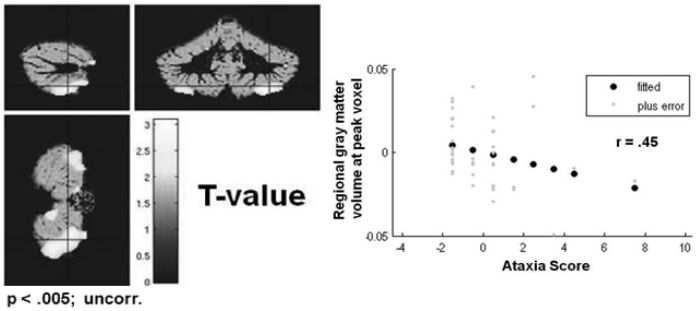
Relationship Between Ataxia Scores and Middle and Superior Frontal Gyri





Valera et al *In preparation*

Relationship Between Ataxia Scores and Lobule VIII of the Cerebellum



Valera et al *In preparation*

Treatment Effects on Brain Structure and Function

- Treatments:
  - Stimulants;
  - Neurofeedback;
  - Cognitive training.
- Overall conclusion: The meta-analyses, as well as individual studies, provide evidence that despite varied methodologies, if anything, treatments tend to normalize structure and function.

Stimulant Effects on Brain Structure

- Evidence for normalization with treatment:
  - Sobel et al *Am J Psychiatry* 2010 - morphological features of the basal ganglia;
  - Schnoebelen et al *J Atten Disord* 2010 - splenium size;
  - Bledsoe et al *Biol Psychiatry* 2009 - areas of the cerebellar vermis;
  - Pliszka et al *Neurology* 2006 – right anterior cingulate volume;
  - Castellanos et al *JAMA* 2002 - white matter volumes.
- Evidence for no effect of treatment:
  - Makris et al *J Atten Disord* 2010 – anterior cingulate volume (adults).

Stimulant Effects on Brain Function

- Evidence for normalization in specific regions and connectivity:
  - Stoy et al *Psychopharmacology* 2011 – Evidence for greater abnormal activation in insula in drug naïve subjects for outcome of loss avoidance; no differences for basal ganglia during reward processing.
  - Peterson et al *Am J Psychiatry* 2009 – Evidence that psychostimulants in ADHD youth improved suppression of DMN activity in ventral anterior and posterior cingulate cortices, and also improved functional interactions with the prefrontal cortex.
  - Rubia et al *Neuropharmacology* 2009 – Data suggest that methylphenidate (MPH) normalized attention networks by up-regulating dysfunctional fronto-striato-thalamo-cerebellar and parieto-temporal regions and down-regulating reward processing orbitofrontal activation.

Other Types of Treatment Effects on Brain Function

- Hoekzema et al *Hum Brain Map* 2010 – Showed increased activity in various frontal regions, temporal regions and cerebellum after a 10-day cognitive training program.
- Beauregard et al *Appl Psychophysiol Biofeedback* 2006 – Limitations to study, but preliminarily suggests the possibility that neurofeedback can help normalize functioning in relevant brain regions.

Ongoing Questions of fMRI in ADHD

- Testing for functional and structural connectivity abnormalities in the ADHD brain.
- Medication effects on structure/function: Harmful? Helpful?
- Are there compensatory effects in the ADHD brain?
- Sex differences?
- How genotype by brain structure/function may contribute to ADHD.
- Can imaging methods be used to classify/diagnose ADHD?

Current Value of Neuroimaging

- Establish pathophysiology of ADHD.
- Decrease stigma by delineating the neurobiological nature of the disorder.
- Increase treatment compliance.
- Aid in treatment by targeting specific regions based on neuroimaging findings.
- Examine effects of medication or other treatment on the brain.

Challenges to Using Neuroimaging to Diagnose ADHD

- Validity – identifying a gold standard.
  - What is *THE* test/measure?
  - What indicates that you have ADHD? Yes/No; Continuum?
- Sensitivity – how well does it detect all cases?
- Specificity – how well does it discriminate from other disorders (e.g., anxiety, depression, sleep apnea)?
- Cost effectiveness?
- Feasibility?
- Test–retest reliability?
- Diagnosis is not possible at this time.

Thank You for Your Attention

Diagnostic Assessment Approaches to Adult ADHD

Craig Surman, MD

www.MGHCME.org

Massachusetts General Hospital
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Approaches to Diagnosis of ADHD in Adults

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Lifetime Disclosures

- Speaking / Education
  - McNeil, Janssen, Janssen-Ortho, Novartis, Shire and Reed/ MGH Academy (funded by multiple companies)
- Consulting
  - McNeil, Nutricia, Takeda, Shire, Somaxon
- Research Support, MGH Adult ADHD Program
  - National Institutes of Health, Abbot, Cephalon, Hilda and Preston Davis Foundation, Eli Lilly, Magceutics, J & J / McNeil, Merck, Nordic Naturals, Nutricia, Pamlab, Pfizer, Organon, Shire, and Takeda

Dr Surman also receives royalties from:

Springer (Humana) for:
ADHD in Adults:
A Practical Guide to Evaluation and Management

&

Penguin (Berkeley) for:
FAST MINDS:
How To Thrive If You Have ADHD
(or think you might)

Typical Concern in Simple ADHD

"I have trouble getting around to, sticking with, and finishing things"

"Simple" ADHD is marked by limited control over how a person engages in the moment*

Thus poor control over:

- **sensory processing, thought and intention**
  = inattention
- **physical, verbal, emotional expression**
  = impulsivity
- **drive and physical activity**
  = hyperactivity

(*This is one way of looking at ADHD - not the only!)

Inattentive ADHD: disengagement from low salience tasks

Difficulty:

– **Focusing on low novelty tasks**
– **Ignoring "shiny" (interesting) distractions**
– **Working towards long-term rewards**
– **Keeping on track without "multitasking"**

Stress & pressure increase salience

– **Creates reactive rather than proactive pattern**
– **Extra hours and late nights**

Impulsive / Hyperactive ADHD: low control over choice & pace

Impulse control (choice):

- **Making good choices - shopping, emails, talking …**
- **Waiting**
- **Holding thoughts / plans in mind to act on later**

Activity control (pace):

- **Speed of physical activity / communication**
- **Feeling grounded, at ease**
- **Tolerating low activity tasks**

Adult ASRS

- 18 items reflecting adult manifestation of DSM-IV ADHD traits
- Screener: 6 of the ASRS items
- Validated in National Comorbidity Survey sample in patients with and without ADHD
- Also validated versus ADHD-RS in NYU and MGH ADHD program patients

Adult ASRS Screener (cont'd)

- Threshold for Likely to Have ADHD: ≥4 significant items
- Sensitivity = 68.7%
- Specificity = 99.5%
- Positive predictive value (PPV) using 3% estimate of prevalence = 80%

Screening Adults for ADHD

- The first 6 questions from the Adult ADHD Self-Report Scale (ASRS) correlate highly with diagnosis of ADHD.
- Individuals who note 4 or more of these symptoms at the shaded frequency levels should undergo a comprehensive assessment for ADHD

Adult ADHD Self-Report Scale (ASRS-v1.1) Symptom Checklist

Patient Name		Today's Date				
Please answer the questions below, rating yourself on each of the criteria shown using the scale on the right side of the page. As you answer each question, place an X in the box that best describes how you have felt and conducted yourself over the past 6 months. Please give this completed checklist to your healthcare professional to discuss during today's appointment.		Never	Rarely	Sometimes	Often	Very Often
1. How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?						
2. How often do you have difficulty getting things in order when you have to do a task that requires organization?						
3. How often do you have problems remembering appointments or obligations?						
4. When you have a task that requires a lot of thought, how often do you avoid or delay getting started?						
5. How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?						
6. How often do you feel overly active and compelled to do things, like you were driven by a motor?						

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The complete ASRS can be used to identify other ADHD symptoms during diagnosis and treatment. It can be found at www.med.nyu.edu/psych/psychiatrist/adhd.html.

The 4 Tasks of Diagnosis

Are sufficient "presentation" SYMPTOMS met?

What is their longitudinal COURSE?

Are TWO OR MORE ROLES impaired?

Is impairment due to ANOTHER CONDITION?

4 Challenges of Adult ADHD Diagnosis

Other conditions overlap with ADHD

Pattern of challenges vary between people

Developmental history hard to confirm

There is no "test" for ADHD

Sufficient Current Symptoms

Self-report and third-party inventories can be efficient

- Supplement with interview to confirm how you would rate!

"Think of a recent, typical week. For the symptoms we will discuss, I want to know:

- How often they occur
- How much effort it takes to avoid or manage them
- How they matter in your daily life."

Try to "walk in their shoes" and imagine how symptoms may manifest

Doing a Rating Scale

Identify recent challenges

- Orient patient to discuss a recent or typical week

Symptom frequency

- "How often? Several times a day? Once a week?"

Establish a method of rating symptom severity

- Mild: Sometimes / not a problem
- Moderate: Often / a problem
- Severe: Very often / impairing

Identify specific examples of challenges

- Success at roles? (work, home, school)
- Missed opportunities for recognition?
- Opportunity cost of compensatory effort?

Capture examples of struggles - to track them

Kinds of Adult ADHD Rating Scales

- Diagnostic instruments
- Symptom instruments
  - Clinician-administered
  - Self-administered
  - Frequency versus severity-based
  - Normed

Adult ADHD Instruments: Symptom Assessment

Scale	Scale available from:
Brown ADD Scales	*The Psychological Corporation*
Conners' Adult ADHD Rating Scale	*Multi Health Systems, Inc.*
Wender-Reimherr Adult Attention Deficit Disorder Scale	*Fred W. Reimherr, MD, Salt Lake City*
ADHD Rating Scale (ADHD-RS)	*Guilford Press*
Barkley Adult ADHD Rating Scale-IV (BAARS-IV)	russellbarkley.org
ASRS v1.1 (18-item)	www.hcp.med.harvard.edu/ncs/asrs.php
Adult Investigator/Clinician Symptom Report Scale (AI/CSRS)	*Lenard Adler, MD, New York University School of Medicine, New York City*
Self, Informant, & Clinician Adult Symptom and Role Impairment Inventories	*Humana Press: Surman, Editor:* **ADHD in Adults: A Practical Guide to Evaluation and Management**

Adult ADHD Instruments: Diagnostic

Scale	Scale available from:
Conners Adult ADHD Diagnostic Interview	*Multi Health Systems, Inc.*
Barkley Adult ADHD Rating Scale-IV + Supplemental scales	russellbarkley.org
Brown ADD Scale Diagnostic Form	*The Psychological Corporation*
Kiddie-SADS Diagnostic Interview ADHD Module	*www.wpic.pitt.edu/ksads*
Adult ADHD Clinical Diagnostic Scale (ACDS) v1.2	*Lenard Adler, MD, New York University School of Medicine, New York City*
Adult ADHD Diagnosis Checklist and supporting scales	*Humana Press: Surman, Editor:* **ADHD in Adults: A Practical Guide to Evaluation and Management**

Compensatory / Avoidant Efforts May Hide Symptom Impact

Patients opt out or defer challenging activities

- What roles or opportunities have they avoided?
- "If you were in school … had to manage bills … do paperwork"

Compensation may be a burden

- Efforts to maintain attention, control behavior
- Reliance on organizational, reminder systems
- Reliance on others for structure, deferred tasks
- Long hours to compensate for inefficiency
- "How much effort does it take you to … "

Challenges To Identifying Impairment

Is impairment attributable to
- another challenge or condition?
- incompatible environment or demands?
- a time-limited situation?

Is impairment misperceived by the consumer?
- extreme beliefs, values, work/school cultures

Are symptoms in the way of thriving?

Accommodation vs. Enhancement
- - Consistent healthy function vs new capabilities

Prompts for Symptom + Role Impairment

Difficulty being accurate with details		
Prompt: How much effort does it take to be accurate or catch mistakes in your work? How often do you make errors that matter?		
Self/Home: Filling out forms incorrectly.	School/Work: "Careless mistakes," missed instructions.	Relationships: Missing important details in emails.

Excessive internal drive		
Prompt: Is it hard to linger at activities? How often does the urge to stay busy cause problems?		
Self/Home: Rarely taking time to relax.	School/Work: Taking on too many new activities or responsibilities.	Relationships: Others find the person to be rarely "present" because of urge to move on.

Surman, Ed. A Practical Guide …

Explore Longitudinal Course

- **What did your teachers or parents say about you as a child?**
- **What age did you first have these challenges?**
- **Did you ever have more of these symptoms?**
- **Are there times when you are free of these challenges? Situations now, or times in your life?**
- **Where do you expect to have problems thriving in the future?**

Are Two or More Settings Impaired?

- Strengths influence patterns
- Ask about third party impression: Job, spouse feedback
- Consider using Weiss Functional Impairment Rating Scale (www.caddra.com)
- Adults avoid roles that would show impairment
- Often difficult to separate out whether circumstances or other traits are to blame
- Is VERY useful to get to know the patient longer!!

Rule out other conditions

- For comorbid mood or anxiety:
  - Was ADHD present when comorbidity absent?
  - Is mental distress the cause?
    - "What kinds of thoughts distract you?"
- Differential diagnosis explored by:
  - Interview
  - Neuropsychological testing
  - Laboratory studies

Rule out other conditions

Mental health conditions (affective, anxious, substance, psychosis, eating, posttraumatic disorders, etc.)
Learning or processing disorders
Tourette's or tic disorder
Chronic systemic medical conditions
Developmental disorder/autism
Asperger's/Social skill deficits
Medication, substance, poison effects (e.g., lead)
Nutritional deficiency (e.g., iron, B12)
Brain trauma (e.g., post-concussive syndrome)

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Rule Out Other Conditions

Delirium
Degenerative neurologic condition (e.g., dementia)
Endocrine disorder (e.g., thyroid disorder)
Seizure disorder
Sleep disorder (e.g., insomnia, phase delay, apnea)
Dietary allergy or sensitivity
Major life stress (loss, trauma)
Familial/genetic disorders Other Encephalopathies (e.g., fetal alcohol)

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Identify Contraindicating Conditions

Arrhythmia, structural or other cardiac defect.
Agents with sympathomimetic properties
Monoamine Oxidase Inhibitors (antidepressants, linezolide) Medications or substances with drug-drug interactions
Past or current psychosis (eg. hallucinations, paranoia); past or current states of agitation (eg. hypomania / mania) Elevated intraocular pressure (eg. narrow angle glaucoma)
Substance misuse or abuse
Tic disorder
Untreated hyperthyroidism
Untreated hypertension Hypersensitivity or allergy to the treatement

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ADHD Diagnosis

Note I have not mentioned a "test" for ADHD …

- Many cases meeting DSM criteria lack impairment on neuropsychological testing
- Where deficits present, patterns are variable
- Neuropsychological testing may rule out other cognitive disorders

Understand limits of marketed "tests"

- Are findings "generalizeable" - do subjects match your patients?
- Are controlled, blinded methods used?
- How are cases confirmed? Is comorbidity accounted for?

By DSM criteria "Real life" is the test that demonstrates ADHD

Organizational Challenges Beyond the Core Symptoms of ADHD:

Control of Engagement across roles and over time

Typical Complaint:

"I don't do the right things at the right time!"

(Occurs in other disorders)

Explore Executive Abilities

Questions to characterize organizational capacities:

- Do you use a planner? "To do" list? Reminder system?
- Do you have a dedicated time to plan? For self-care?
- Do you have a goodd sense of what needs to get done and how you will do it?
- Do you prioritize daily tasks?
- Do you estimate time tasks will take well?
- Are you often late?
- Are you able to outsource things you are not good at?
- Can you start and stick with new habits / routines?

Measuring Executive Function (organization capacities)

Neuropsychologically Defined:

- EFD in 31% of ADHD vs. 16% of non-ADHD
- ADHD+EFD: lower education, occupation, and socioeconomic status than non-ADHD
- Control+EFD more likely to have repeated a grade

Behaviorally defined

- eg. BRIEF-A, Barkley scales - more ecological

Biederman et al, Am J Psychiatry 2006

Emotional Dysregulation Questions

- **Do you over-react emotionally?**
- **Do you often get angry or frustrated?**
- **Do you regret your emotional decisions or actions?**
- **Do other people think your emotions cause problems?**
- **Do you wish you had more control over how you express emotion?**

Evaluate Treatment Appropriateness

Medication benefits "simple ADHD":

- often improves behavior control, engagement in tasks
- may not change ability to do the right thing at the right time

What can improve adherence to treatment / skill practice?

- can they manage medication schedule and self-monitoring?
- what will help them practice new habits?

ADA accommodations possible where:

- ability matches core role (job description; curriculum content)
- "reasonable" change in format

Treatable Factors

↑ Self-regulation skills
self-care; executive; emotional
Environmental Accommodation

↓ ADHD symptoms
Other limits to adaptive adjustment
comorbidity; negative self-talk

Treatment Targets

Core ADHD Symptoms
List important role daily challenges that are a direct result of ADHD traits.

Self/Home:

Work/School:

Relationships:

Other Organizational Problems
List other important daily patterns of disorganization in major life roles.
(e.g., poor sleep pattern, overwhelmed by work, last-minute social planning)

Self/Home:

Work/School:

Relationships:

Developed by Craig B.H. Surman, MD

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Treatment Planning

For Core ADHD Symptoms: list medication options that could improve core ADHD symptoms (new agent, dose change, cover longer duration)

For Improved Organization: List critical situations where better habits (decisions or actions) can be practiced (e.g., taking time to prioritize/plan; more reliance on others or electronic devices; using reminders; isolating from lower priority distractions).

For Adherence: List what will ensure practice of the treatment plan. Consider factors in past success (e.g., deadlines, reminders, tracking, involving others, other accountability).

For Environmental Accommodation: List accommodations, e.g.: for weaknesses (e.g., extra time to check work, recording meetings/class); to make tasks more engagable (e.g., clearer steps/goals, better match to interests); for accountability (e.g., involving others, deadlines); for work space (lower distraction).

Surman, Ed.
A Practical Guide…

Cardiovascular Risk in the Management of ADHD

Paul Hammerness, MD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

CARDIOVASCULAR RISK IN THE MANAGEMENT OF ADHD

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Disclosures

- In the past 12 months, Dr. Hammerness has participated in CME activities/writing supported by Shire Pharma. Dr. Hammerness has participated, as an investigator/principal investigator, in research studies funded by the following companies: Cephalon, Forest, GlaxoSmithKline, Johnson & Johnson, McNeil, Novartis, Ortho-McNeil Janssen, Shire, Takeda Pharmaceuticals and Elminda Ltd.
- Books: Royalties from Greenwood, Harlequin Press

Goals

- To review the evidence base regarding the cardiovascular impact of stimulant class medications for ADHD
- To review current recommendations for assessment of cardiovascular risk and safety monitoring during medication treatment of ADHD

Known Cardiac Effects of Stimulants

- Occur in the context of therapeutic, oral stimulant dosing for ADHD

- *Healthy, medically screened individuals*
- *FDA approved dose range*
- *Largely short term exposure*
- *Divergent methodology*
  - *e.g., timing of reading*

Early Clinical Studies (pediatric)

- Early controlled studies in 1970s-1980s:
  - response at 1-2 hrs post immediate release (IR) stimulant, largely methylphenidate (MPH)
  - heart rate viewed as sensitive to MPH
    - significant increases compared to placebo
    - greater elevations in med-naïve vs previously treated (e.g., 11 bpm vs. 4 bpm)
    - dose dependent (e.g., greater following 1.0mg/kg vs. 0.3mg/kg dose)

Safer, J Child Adol Psychopharm 1992;2(4):279290; Rapport & Moffitt. Clin Psychol Rev. 2002;22(8):1107-31; Solanto & Conners. Psychophysiology. 1982;19(6):658-67; Kelly et al. Int Clin Psychopharmacol. 1988;3(2):167-81; Tannock et al. Pediatrics. 1989;84(4):648-57

Contemporary Controlled Trials

- MAS XR (Adderall XR)
  - adolescents (N=327; 10-60mg/day)
  - statistically significant effect for pulse
    - 5-9 bpm vs. <1 bpm with placebo
- LDX (Vyvanse)
  - children (N=297; 30-70mg/day)
  - statistically significant effect for pulse
    - 1-4 bpm vs. <1 bpm with placebo
- Adult trials - increases in blood pressure (1-5 mm Hg) and heart rate (4-10 bpm) during short term IR and SR stimulant treatment
  - Not all are significantly different than placebo

Wilens CNS Spectr. 2005;10(Suppl15):22-30; Findling J Pediatr. 2005;147:348-354; Weisler AACAP annual meeting,Oct 2009 ; Biederman 2007; Medori 2008; Spencer 2007; Adler 2009a,2009b; Rosler 2009; Bejerot 2010

Longer Term Studies

- open extension trials following RCT
- statistically significant elevations from baseline
  - 1-5 bpm increase in heart rate
  - 1-5 mmHg increase in blood pressure
- suggest a lack of tolerance
  - elevations in BP appear to persist (i.e., remain statistically elevated up to 24mos endpoint).
- longer term studies do not indicate dose-dependent effects upon HR or BP

Wilens.CNS Spectr. 2005;10:22-30; Findling.J Pediatr. 2005;147:348-54; Weisler/Lopez. AACAP mtg, Oct 2009; Wilens.JAACAP. 2005;44:1015-23; McGough.JAACAP.2005 Jun;44:530-8; Findling.CNS Spectr. 2008 Jul; 13:614-20; Findling.Clin Ther. 2009;31:1844-55.

Longer Term: Alternate methods (pediatric ambulatory monitoring)

- N=17 on chronic stimulant (vs. 3 days off med)
  - awake SBP and DBP (2-5mmHg) *
  - awake, asleep and 24-hour HR (2-8bpm) *
- N=11 on chronic stimulant (vs. 3 days off med)
  - awake and 24-hour DBP (~3-4mmHg) *
  - 24-hour HR (~6bpm) *
  - *24-hour BP "load" (% of readings >95th%tile) was not statistically significant increase on-medication*

Stowe et al.Ann Pharmacother. 2000;36(7-8):1142-49; Samuels et al.Pediatr Nephrol. 2006;21:92-5
** Statistically significant on medication vs off medication*

Heart Rate and Blood Pressure: Outliers

- Exceed a threshold
  - (e.g., ≥120/80mmHg; ≥140/90mmHg)
- Change from baseline
  - (e.g., increase in SBP≥20mmHg, DBP≥10mmHg, HR>25bpm) at least once on medication
- Consistently reported, in up to 15% of pediatric and adult samples, across formulations, in short/longer term treatment

Wilens CNS Spectr. 2005;10(Suppl15):22-30; Findling J Pediatr. 2005;147:348-354; Childress J Child Adolesc Psychopharmacol. 2009;19(4):351-361; Findling J Child Adolesc Psychopharmacol. 2010;20(5):365-375; Hammerness J Pediatr. 2009;155(1):84-89; Adler 2009, 2009; Weisler 2005

Heart Rate and Blood Pressure Outliers

- When reported, elevated readings appear sporadic and resolve during treatment
  - 7 wk dose optimization pediatric (LDX; N=318)
    - 6%,15% of children with one DBP,SBP>95th%tile;
    - <1%,3% elevated DBP,SBP at 2 consecutive visits
- Elevations may be similar to placebo group
  - 5 week fixed dose adult (OROS MPH; N=401)
    - 27% BP >140 mmHg or >90mmHg at endpoint; similar BP elevations in up to 20% of placebo
    - HR >90 bpm at endpoint in 10-14% of MPH subjects vs 6% of placebo

Findling et al.J Pediatr. 2005;147:348-54; Donner et al.Biol Psychiatry. 2007;61(5):706-12; Medori 2008

Electrocardiogram (ECG)

- Since early reviews, no statistically significant, clinically meaningful changes in ECG intervals in adults/children
- A wide range of subjects (1-19%) will have an "abnormal" ECG report (e.g., ST–T wave changes; ectopic atrial beats; bundle branch block)
  - not typically associated with CV adverse events
  - not deemed clinically significant nor related to medication
- Findings appear consistent with normal ECG variants found in similar rates in healthy individuals

Safer 1992;2(4):279-90; Vetter 2008;117:2407-23; Elia Paediatr Drugs.2010 ;12(3):165-75; Wilens CNS Spectr. 2005;10 (22-30) Donner *Biol Psychiatry*. 2007;61(5):706-12; Childress *J Child Adolesc Psychopharmacol*. 2009;19(4):351-61; Findling *J Child Adolesc Psychopharmacol*. 2010;20(5):365-75; Vetter *Am Heart J*. 2011;161(5):1000-06; Mahle *Am J Cardiol*. 2009 Nov 1;104(9):1296-9

Objective Effects: Limitations

- CV safety profile is derived from routine, office-based assessments taken at rest
  - Very limited investigations with in-depth, or provocative methodology
- Uncertainty with increasing exposure
  - extended duration agents
  - chronic prescription
- Unknown moderators/mediators
  - Age
  - Medical comorbidity
  - Weight/Diet (e.g., salt intake)

Subjective Complaints:
Epidemiological and Clinical Trials

- ~3,000-4,000 patients present to ER nationally for AE of a CV nature associated with stimulants
  - Despite concerning symptoms, e.g., palpitations, dyspnea, chest pain, serious events associated with complaints are rare, consistent with national rates
- Clinical trial literature documents AE of a CV nature associated with stimulants in children and adults
  - palpitations, tachycardia, and dyspnea most common, up to ~20% of stimulant treated subjects, and can occur more frequently than on placebo

Cohen N Engl J Med. 2006;354(21):2294-2295.; Winterstein Pediatrics. 2007;120:e1494-e1501; Winterstein Pediatrics. 2009;124(1):e75-80; Findling J Pediatr. 2005;147:348-54; Donner Biol Psychiatry. 2007;61(5):706-12; Findling J Child Adolesc Psychopharmacol. 2010;20(5):365-375; Findling Clin Ther. 2009;31(8):1844-1855

Serious Cardiovascular Events

- In the early 2000's, a series of serious/fatal CV events reported in association with stimulants
- FDA convened a Drug Safety and Risk Management Advisory Committee on the topic
  - Nissen voiced concerns about CV toxicity and overuse
- FDA Div. Psychiatry Products concluded - rate of sudden death with stimulant below national rates
- March 2006; FDA Pediatric Advisory Committee voted - black box warning unnecessary
  - Instead, FDA issued warnings about stimulants in patients with underlying CV disease; directed industry to develop Medication Guides

Nissen N Engl J Med. 2006 Apr 6;354(14):1445-8; Villalba Food and Drug Administration. Feb 28, 2006; Liberthson NEJM. 1996;34(16):1039-1044

Stimulants and Cardiovascular Events Large scale Cohort Studies (pediatric)

- No sudden cardiac death in 42,612 person-yrs of stimulant use (N=55,383; age 3-20)
  - 20% increase in ED visits for cardiac causes or cardiac symptoms
  - Similar among current and past MPH and AMP use

Winterstein, Pediatrics. 2007;120:e1494-e1501 and Pediatrics 2009;124(1):e75-80;

Stimulants and Cardiovascular Events Large scale Cohort Studies (pediatric)

- No increased sudden death/ventricular arrhythmia (N=1,207,085; age 3-17)
  - 0.06/10,000 p-yrs of stimulant/ATX use
  - vs. 0.04/10,000 p-yrs of non-use
- No increased serious CV events (death/MI/stroke) (N=1,200,438; age 2-24)
  - 1.06/100,000 p-yrs of stimulant/ATX use (sudden death)
  - vs. 1.60/100,000 p-yrs of non-use (sudden death)

Schelleman, Pediatrics. 2011 May 16. [Epub]; Cooper, November 1, 2011, at NEJM.org

Stimulants and Cardiovascular Events Large scale Cohort Studies (pediatric)

- No increased cardiac events or symptoms (N= 171,126; age 6-21)
  - Events: angina, dysrhythmia, transient cerebral ischemia
    - 0.92 event/million days (current use)
    - 1.55 event/million days (no use)
  - Symptoms: tachycardia, palpitations, syncope
    - 3.08 event/million days (current use)
    - 2.90 event/million days (no use)

Olfson J Am Acad Child Adolesc Psychiatry. 2012 Feb;51(2):147-56

Stimulants and Cardiovascular Events Large scale Cohort Studies (adult)

- 107,322 person-years of current use

Among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events

Habel et al, *JAMA. 2011;306(24):doi:10.1001/jama.2011.1830*

FDA Summary Statements

[11/01/2011] "a large, recently-completed study in children and young adults treated with medication for ADHD has not shown an association between use of certain ADHD medications and adverse cardiovascular events"

[12/12/2011] "a large, recently-completed study, that included one study that evaluated heart attacks and sudden deaths in a sample of adults, and a second study that assessed strokes in these adults, has not shown an increased risk of serious adverse cardiovascular events in adults treated with ADHD medication"

http://www.fda.gov/safety/medwatch

FDA Recommendations

- "Stimulant products (and atomoxetine) should generally not be used in patients with serious heart problems, or for whom an increase in blood pressure or heart rate would be problematic"
- "Patients treated with ADHD medications should be periodically monitored for changes in heart rate or blood pressure"
- Use Patient Medication Guides to alert patients to possible cardiovascular risks

FDA press release, June 15th,2009;http://www.fda.gov/cder/drug/infopage/ADHD/default.htm

Initiation and Safety Monitoring: History

- Personal cardiac symptoms and medical history
  - Fainting or dizziness (particularly with exercise)
  - Chest pain or shortness of breath with exercise
  - Palpitations, increased heart rate, extra/skipped beats
  - Seizures
- Family member's relevant history
  - Sudden or unexplained death in young (<35 yrs)
  - Sudden death during exercise
  - Cardiac arrhythmias; Cardiomyopathy; Marfan

Perrin-American Academy of Pediatrics AACAP Policy Statement 2008; Vetter. Circulation. 2008;117:2407-2423; Gutgesell Congenit Heart Dis. 2011;6;88-97

Initiation and Safety Monitoring:
Blood Pressure/Heart Rate Assessment/Referral

- Be familiar with guidelines
- Multiple visits with elevated readings:
  - i.e., pre-HTN (pediatric) $\geq 90^{th}$ percentile or >120/80
  - i.e., pre-HTN (adult):120–139 Or 80–89 mmHg
  - i.e., HR >60bpm, greatest risk if >90bpm (adult)
- Assessment technique is critical
  - Patient position, cuff size
  - Automated BP may yield values ~5-10 mmHg higher than auscultatory method

BP Ed Program Work Group. Pediatrics 2004;11(2):555-576; Park 2005 Pediatr Cardiol 26(5):601-7; Chobanian, 2003; Cooney 2010; Jouven 2009; Fox 2007

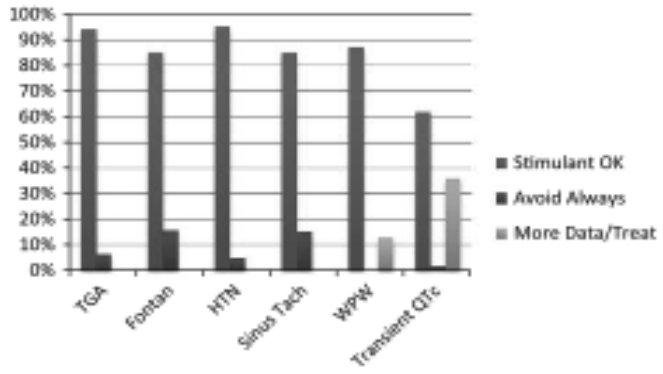
Initiation and Safety Monitoring:
Electrocardiogram

- Although an area of controversy and ongoing consideration, screening electrocardiogram (ECG) is not recommended at present for persons with ADHD

- Common Cause SUD identified by ECG
  - Hypertrophic Cardiomyopathy; Wolff-Parkinson-White; Long QT syndrome (pediatric)
  - Ischemic heart disease (adult)

Perrin-American Academy of Pediatrics, ACAP Policy Statement 2008; Hammerness, JAACAP 2011; Leslie et al, Circulation 2012; 125:2621-2629

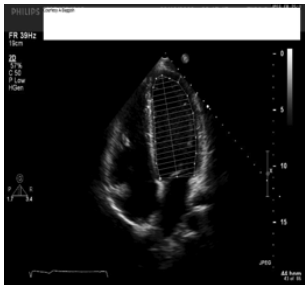
Specialty (e.g., Cardiology) Referral



Batra et al, Pediatr Cardiol 2012;33:394-01

Future Directions
In depth and provocative studies

- Echocardiogram



Apical 4 chamber view; LV

- Cardiopulmonary Testing

MGH Protocol - Electronically braked ergometer, 12-lead ECG Metabolic cart (MedGraphics)

Hammerness…Wilens, May 2012 WJBPsych

Summary

- Objective cardiovascular effects of stimulants
  - Mean elevations in blood pressure (≤5mmHg) and heart rate (≤10bpm) in healthy individuals
  - Greater BP increases in 5-15%
    - *multiple* elevated BP readings in <5%
- Subjective complaints in 5% of subjects
- Serious CV events at the population level
  - Multiple cohort studies have not shown an increased risk of serious cardiovascular events
- Reassuring, yet clinical monitoring is indicated

Attention Deficit Hyperactivity Disorder Across the Life Span

SATURDAY MARCH 16, 2013

EVENING SEMINARS

Saturday, March 16, 2013

6:30PM – 7:30PM

Evening Seminars

1. Perspectives on Proposed Changes for ADHD in DSM-V
Craig Surman, MD

2. Educational Assessment and School Accommodations for Children and Adolescents with ADHD, Ronna Fried, EdD

Perspectives on Proposed Changes for ADHD in DSM-V

Craig Surman, MD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

DSM V ADHD

Craig B.H. Surman, MD

MGH Clinical & Research Program In Pediatric Psychopharmacology and Adult ADHD

Lifetime Disclosures

- Speaking / Education
  - McNeil, Janssen, Janssen-Ortho, Novartis, Shire and Reed/ MGH Academy (funded by multiple companies)
- Consulting
  - McNeil, Nutricia, Takeda, Shire, Somaxon
- Research Support, MGH Adult ADHD Program
  - National Institutes of Health, Abbot, Cephalon, Hilda and Preston Davis Foundation, Eli Lilly, Magceutics, J & J / McNeil, Merck, Nordic Naturals, Nutricia, Pamlab, Pfizer, Organon, Shire, and Takeda

Dr Surman also receives royalties from:

Springer (Humana) for:
ADHD in Adults:
A Practical Guide to Evaluation and Management

&

Penguin (Berkeley) for:
FAST MINDS:
How To Thrive If You Have ADHD
(or think you might)

Current Symptoms

- Subtypes?
- Symptom threshold?
-Adult Language?
- New Items?

"Presentations"

Is ADD a separate disorder from ADHD

- Suggested on release of DSM-IV Diamond 2005; Milich et al 2001
- Authors have proposed a latent-class of Inattentive severity +/- presence of I/H symptoms might be better (Schmitz et al, 2010)
- "Restrictive Inattentive Subtype"
- Neuropsychologically impaired subtype (Nigg et al, 2005)
- Executive function deficit adult subtype (Biederman, 2006)
- Subtype with comorbity
  (eg. Jensen et al 1997, Pliska et al 2006)

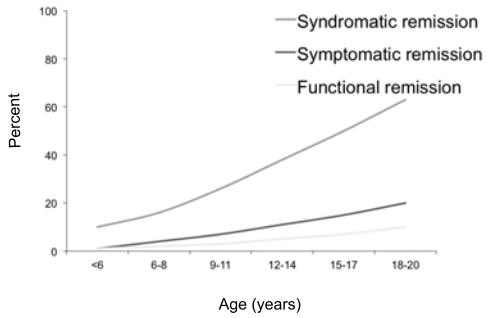
"Presentations"

Evidence

- Parents and their children may have different subtypes (Faraone et al 2000; Stawicki et al 2006)
- Classification may differ between one and two informants (Valo & tannock 2010)
- Similar response to medication (Buitelaar et al 2004)
- Shift in subtype from ADHD-I or -H to -C common in 118 4-6 year olds over 8 years (Lahey et al 2005)
- No difference in clinical correlates based on presence or absence of H/I symptoms in ADD-I non-referred children; both different than controls (n=200) (Schmitz et al, 2010)

Age-dependent Decline of ADHD Symptoms

Age-specific prevalence of remission from ADHD among 138 boys, according to definition of remission and symptom type



n=138

Biederman J *et al.* Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry. 2000 May;157(5):816-8.

Symptom Threshold

Murphy & Barkley 1996

- 4 or more symptoms is at 93rd %ile

Solanto et al 2011

- Age-related decline greater for hyperactive-impulsive cases

Symptom Descriptions

DSM symptoms originally developed from children

Symptoms and pattern may change with age and context

Age-related decline in number of symptoms

Proposed Additional Symptoms

Kessler et al, 2010 - Argue for better impulsivity coverage:

- Act without thinking
- Impatient
- Uncomfortable doing things slowly and systematically
- Difficult to resist temptationsor opportunities

Ghanizadeh, 2013

- 26 to 63% of non-ADHD children had these traits

Longitudinal Course

- Current duration
- Age of onset

Age of onset

Applegate (2007)

- DSM-IV field trial analysis
  Symptoms preceded impairment in many
  Current inattentive impairment group had onset between 9 to 14 yo

Kessler (2007)

- Current Adult ADHD: Recalled onset by 7 in 50%, by 12 iin 95%

Faraone et al (2006)

- Familial transmission similar for full and late onset
- Impairment: full = late onset > subthreshold > > no ADHD
- Most late onset cases younger than 12
- Also little neuropsychological or personality difference

Karam et al (2009)

- Late onset have less severe symptoms - more generalized anxiety
- Childhood onset ADHD - more externalizing symptoms

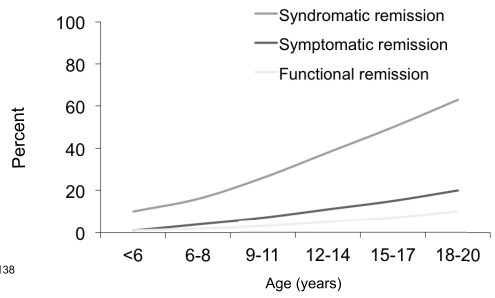
Polanczyk et al 2010

- 12 does not increase prevalance

Impairment in Two or More Settings

Age-dependent Decline of ADHD Symptoms

Age-specific prevalence of remission from ADHD among 138 boys, according to definition of remission and symptom type



n=138

Biederman J *et al.* Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. Am J Psychiatry. 2000 May;157(5):816-8.

Impairment

Gordon et al 2006

- Correlation between symptom burden & impairment explained < 10% of variance

Severity modifiers

- Ramsey & Rostain (2006)
-

Not explained by another condition

- Exclusionary conditions?

Autism

Exclusionary for ADHD in DSM (and ICD-10)

Unknown if “ADHD” neuropathology is different in autism

Identification of ADHD more challenging in autism

Third party informant

Informants

Single informant report inadequate

de Nijs et al., 2004; Mitsis, McKay, Schulz, Newcorn, & Halperin, 2000; Sayal & Goodman, 2009; Sayal & Taylor, 2005; Valo & Tannock, 2010).

Currently 2 or more informants is TEXT recommendation

DSM-V ADHD

"Neurodevelopmental" - not "disruptive"

Inattentive / Hyperactive-impulsive / Combined "Presentations"

Appendix: Restricted inattentive subtype worth further study

≥ 6 inattentive and / or ≥ 6 impulsive / hyperactive symptoms over last six months

5+ current symptoms for adults

Elaboration of symptoms for adults

DSM-V ADHD

Symptoms caused impairment by 12

Impairment in 2 or more settings (school, work, home)

Not explained by another disorder

Autism / PDD non-exclusionary

Two or more informants

DSM V Adult Symptom Language

Inatt b: Often has difficulty sustaining attention in tasks or play activities (e.g., difficulty remaining focused during lectures, meetings, conversations, or reading lengthy material)

Inatt e: Often has difficulty organizing tasks and activities (e.g., difficulty managing sequential tasks, keeping materials or belongings in order, producing work that is messy or disorganized, showing poor time management, or tending to fail to meet deadlines)

Inatt i: Is often forgetful in daily activities (e.g., for older adolescents and adults, forgetting to return calls, pay bills, keep appointments)

Imp h: Often has difficulty awaiting turn (e.g., waiting in line)

Tannock, J Learn Disabil 2013

Educational Assessment and School Accommodations for Children and Adolescents with ADHD

Ronna Fried, EdD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

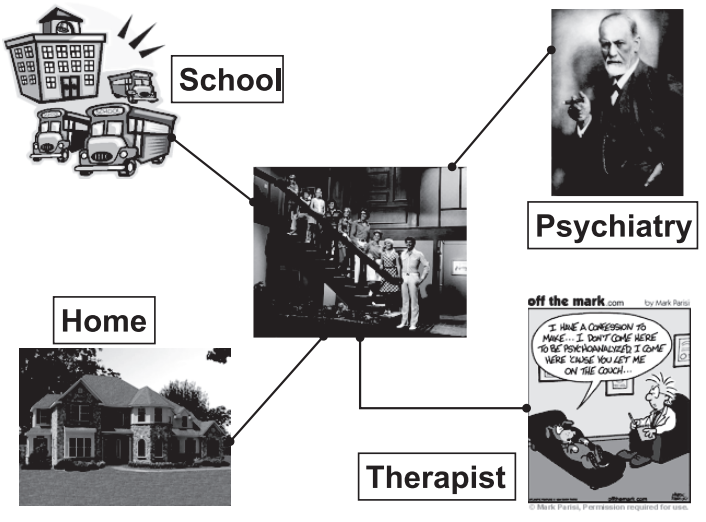
Ronna Fried EdD

Clinical & Research Programs in Pediatric Psychiatry and Adult ADHD at Massachusetts General Hospital

WORKING WITH SCHOOLS AND TEACHERS IN CHILD AND ADOLESCENT PSYCHIATRY

Disclosure

Dr. Fried has indicated that neither she nor her spouse has a relevant financial relationship to disclose



Why Is School Important?

- Approximately 1,000 hrs/year in school
  - Max 50 hrs/year with clinicians
- Mixed objective & subjective feedback
  - Generally positive subjective feedback from clinicians
- Social environment

Some Numbers

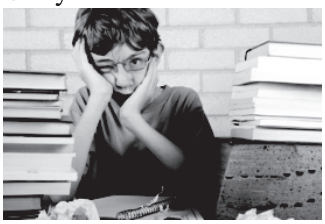
- 20% of children have some form of learning problem
- Almost 1 million children receive special education for some kind of learning disability
- Many not diagnosed before second grade

Red Flags - Preschoolers

- Late talking
- Difficulty learning and recognizing rhyme
- Pronunciation problems
- Difficulty finding the right word in speech
- Difficulty Learning Color Names

Red Flags – Elementary Years

- Difficulty pronouncing words; reverses or substitute parts of words
- Doesn't hear fine differences in words; e.g., "pin" for pen"; confuses order of letters
- Spells a word several different ways; doesn't recognize the correct version
- Doesn't recognize words previously learned
- Problems stating thoughts in an organized way
- Difficulty carrying out a sequence of directions
- Poor reading comprehension



Red Flags – Later School Years

- Difficulty remembering what was just read
- Difficulty concentrating when reading or writing
- Unable to tell important information from unimportant details

- Spells poorly; misspelling is not phonetic
- Problems taking notes accurately
- Difficulty organizing and completing written projects

Social/Emotional Red Flags Indicating School Problem

- Withdrawn affect
- Angry when asked about school
- Resistant to working on homework
- Missing assignments
- Reduction in grades

RTI: Response to Intervention

the practice of providing high-quality instruction/intervention matched to student needs

and

using learning rate over time and level of performance

to

inform educational decisions

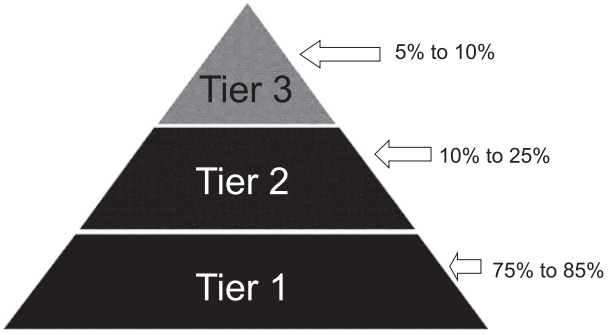
What do we mean by RTI?

1. RTI has two goals: prevent academic problems and determine students with LD.
2. 2 or more tiers of increasingly intense interventions.
3. Use a problem solving model or standardized treatment protocol for intervention tiers.
4. Implementation of a differentiated curriculum with different instructional methods.
5. Varied duration, frequency, and time of interventions.

and

6. Explicit decision rules for judging learners' progress.

Percents of Students*



*Includes students with disabilities

Legal Background

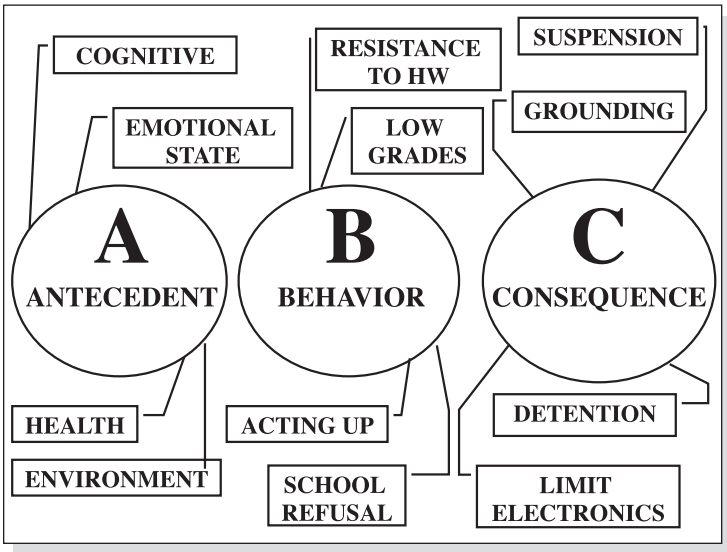
Why RTI is now being adopted by schools

Congress passed the revised Individuals with Disabilities Education Improvement Act (IDEIA) in 2004

- This Federal legislation provides guidelines that schools must follow when identifying children for SPED
- Based on the changes in IDEIA 2004, the US Department of Education updated its regulations to state education departments which include:
  - ~ Explicitly ALLOW states to use RTI to identify LD
  - ~ FORBID states from forcing schools to use a 'discrepancy model' to identify LD

Joey: Problem Solving: Problem Statement in Behavior

- Joey is off task
- Joey initiates disruptive behavior that violates classroom rules Joey does not complete classroom work
- Non-compliant behavior—does not follow directions and direct requests, i.e., when asked, Joey ignores requests



Functional Analysis of Behaviors

- Descriptive Analysis
  - Systematic classroom observation (or other situation)
  - Develop hypotheses about function of behavior
  - Identify variables that seem to occasion and maintain behaviors: Identify antecedent, situational, and consequences of behavior
  - Hypothesis: Student appears to be off task when task demands are more challenging

Joey: Problem Solving Problem Analysis

- Interpretation: Joey exhibits
  - Skills deficits (poor reading fluency, poor decoding) and
  - Performance problems (inattentive, disruptive classroom behavior, non-compliance at school and home).
  - Emotional regulation is adequate

Evaluate! Evaluate! Evaluate!

- Need to document disability to get services
- Need to look at cause in order to choose appropriate interventions
  - Psychotherapy, behavioral interventions and medication won't help learning disabilities
  - Resource room won't help OCD

Testing through School

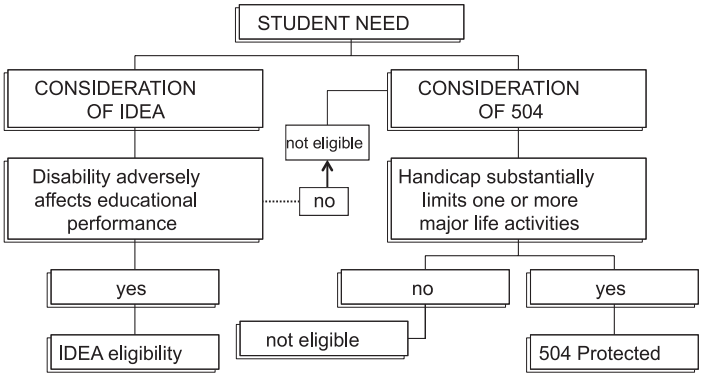
•Parent submits written request

•Letter addressed to building administrator or Committee on Special Education chairperson:

"I am writing to refer my child ____ for an individual evaluation to determine whether he / she has a disability and would be eligible for special education services. I am concerned because ___."

	IDEA	SECTION 504
PURPOSE	To insure that all children with disabilities have available to them a free education	To prohibit discrimination on the basis of disability in any program receiving federal funds
WHO IS PROTECTED	13 categories of specific disabilities	Much broader, all school-age students with a physical or mental impairment that substantially limits a major life activity
DUTY TO PROVIDE A FREE APPROPRIATE EDUCATION	Requires the district to provide IEPs. "Appropriate education" means a program designed to provide "educational benefits."	"Appropriate" means education comparable to the education provided to non-handicapped students

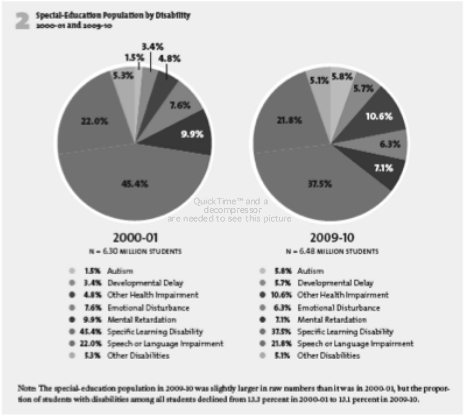
IDEA/504 CHART



13 Categories from IDEA

- **autism**
- deaf-blindness
- deafness
- developmental delay
- emotional disturbance
- hearing impairment
- intellectual disability
- multiple disabilities
- orthopedic impairment
- **other health impairment (ADHD)**
- specific learning disability
- speech or language impairment
- traumatic brain injury
- visual impairment (including blindness)

Increase in "Other Health Impaired"



Skull and Winkler, 2011

Services

- If meets for disability but making "effective progress" --> Section 504 (ADA)
- If meets for disability and NOT making effective progress --> IDEA
- This does not consider "at what cost?"
  - Emotional distress
  - Excessive Homework (5-6 hrs/night)
  - Family Conflict to get work completed

Getting 504 Services

- A referral can be made by a parent, care-giver, or professional working with the child to the school principal or 504 coordinator
- A 504 team consisting of parents, school staff, and the student if appropriate, gathers information to determine nature of disability and impact on student's education
- Team develops 504 accommodation plan to ensure student participates in all aspects of school.
- Parents who disagree with the school's plan and cannot resolve the complaint through the school can contact the Program Quality Assurance Services (PQA) at the Massachusetts department of education
- Student eligibility must be reevaluated every 3 years

ADHD: ELEMENTARY SCHOOL YEARS

Observations:

- Difficulty sitting still
- Easily overwhelmed by settings
- Easily Bored
- Talks Out in Class

Interventions:

- Preferential Seating
- Silent Signal for Disruptive
- Physical Breaks (send to Office with note)

ADHD:MIDDLE SCHOOL YEARS

Observations:

- Teachers Complain about Inattention
- Grades Fall
- Described as Overly Social

Interventions:

- Coach at School (daily check-in)
- Teachers Adapt Output Expectations
- Accommodations for Time Management

ADHD:HIGH SCHOOL YEARS

Observations:

- May Cut Classes or School
- Peer Group May Change due to Behavior
- Missing Assignments/Procrastination
- Poor Test Grades
- Substance Use

Interventions:

- Adapt Classes to Meet Abilities
- Provide Coaching on Daily Basis
- Have Notes Provided
- Technology Use for Assignments/Test Reminders

Getting Services after High School

- Typically no IEP in college
  - MA is required to pay for needed services until child turns 22, or until graduates from high school
- Can still get a 504
  - Must establish presence of diagnosis and impact student's ability to learn
  - Many schools have a Student Disabilities Service office to facilitate the process

Assessment of Disability

- Past academic/work history
- Objective medical data, test scores, clinical observations and assessment
- Individuals actions and statements regarding condition
- Legitimacy of the findings and conclusions of the individual's experts
- Any evidence of achievement without accommodation

ADA Amendments Act: of 2008 (adaaa)

- Inclusions of episodic conditions if impairing when active
- An impairment need not be severely restricting to be substantially limiting
- Mitigating measures should not be considered (except glasses)
  - Meds for ADHD cannot eliminate determination

ADHD Documentation

- Establish childhood onset of symptoms (report cards, support services, medication…)
- Use DSM criteria to describe current and childhood symptoms
- Demonstrate the substantial impairment in daily life activities
- Connect Accommodation recommendations to functional limitations

Accommodations

- Accommodation is the modification , adjustment , or elimination of a barrier to a program or service that enables a student with a disability to participate on an equitable basis

Sample Academic Accommodations

- Extended time for test taking
- Reduced distraction testing environment
- permission to record lectures (smart pen use)
- Use of computers during lectures
- Use of computers for exams
- Use of text readers for exams
- Note takers

Accommodations (cont.)

- Housing
  - Single room
  - Roommate of choice
  - Alternate formats of print materials
  - Auxiliary aids and adaptive equipment
    - FM listening device
    - Tape recorders
    - Text reading software

"Unreasonable" Requests in Higher Ed. (per colleges)

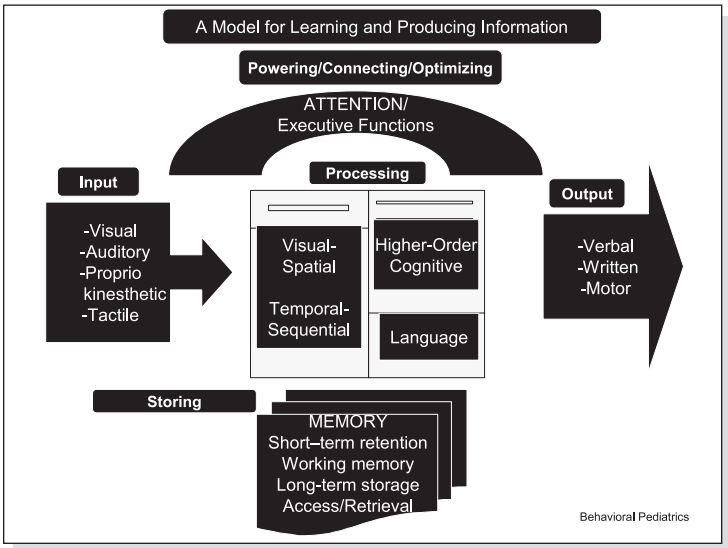
- Reducing the amount of work required in a course
- Extended time for all assignments
- Reduced caseload every term
- Modifying assessments to student preference
- Priority in registration when not connected to a specific disability ,related issue

Types of Learning Disabilities

- Dyslexia
- Dysgraphia
- Dyscalculia
- NLD
- **Executive Functioning Disorder**
  - **At least 33% of ADHD have EFD**

Executive Function Definition

- Executive function is the ability to do all that it takes to keep your mind on what you are doing in order to execute
- These abilities include:
  - Maintaining attention
  - Controlling impulses
  - Keeping free of distractions
  - Engaging in mental planning and problem solving
  - Maintaining Flexibility
  - Time management
  - Setting priorities
  - Organizing
  - Executing a task



Executive function includes the following components:

•Ability to initiate behavior toward achieving goals and inhibit behavior incompatible with achieving those goals

• Ability to monitor and evaluate performance in relation to the goals

• Ability to flexibly revise plans and strategically solve problems in the event of difficulty or failure

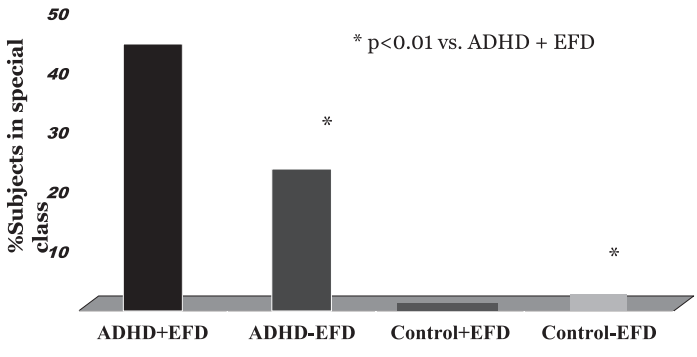
Ylvisaker, M. & DeBonis, D. (2000)

Executive Dysfunction in Children

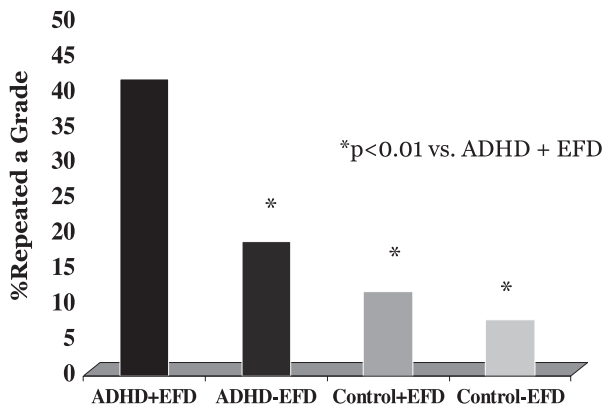
- There is no singular disorder of Executive Dysfunction
- Executive Dysfunction is reflected by a number of symptoms
- Executive Dysfunction is often reflected in other primary difficulties such as LD, Tourette's Syndrome, ADHD, TBI, or cranial radiation treatment for leukemia

Mele-McCarthy, 2005

Special Classes



Repeated Grades



Executive Functions in School

- In the classroom, the task most frequently impacted by executive function-driven producing difficulties is written expression.

Executive Functions in School

- What Tommy told me:

"My favorite game is rolling marbles. I think it is fun. I just learned it yesterday. It can be pretty hard at times. It can be fun and it's interesting if you make it challenging. I like making the boxes to roll the marbles into. You probably need to be pretty skilled with eye hand coordination to do it. To get up the ramp you need to roll it really fast."

Executive Functions in School

- **What Tommy wrote for me:**

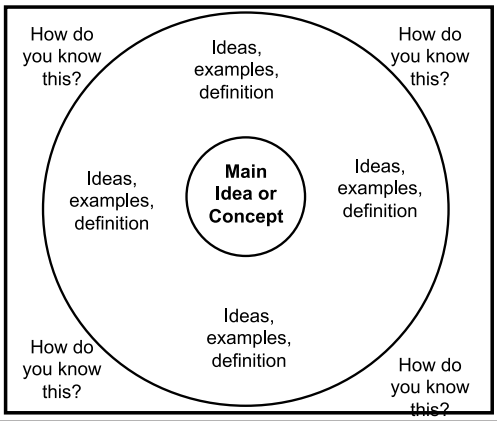
My favorite game is … "mabul roling it is fun. I like making the box to role in to. Iam prety gode as well. It is rell inters ing. It is so fun

Interventions for EFD

- Scaffolding for organization
- Time management w/ teacher for planning
- Tasks Broken Down for working memory
- After school Checking Time for inhibition
- Sheet with Lecture Bullets for attention

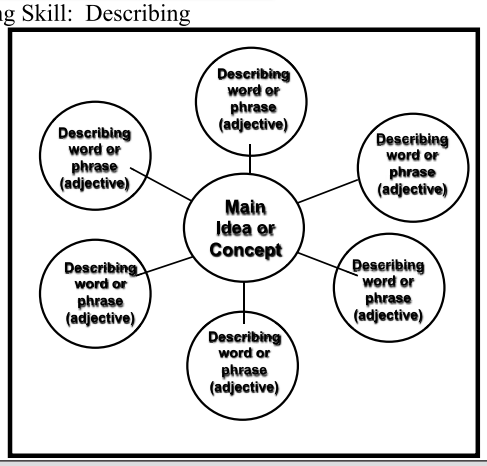
CIRCLE MAP

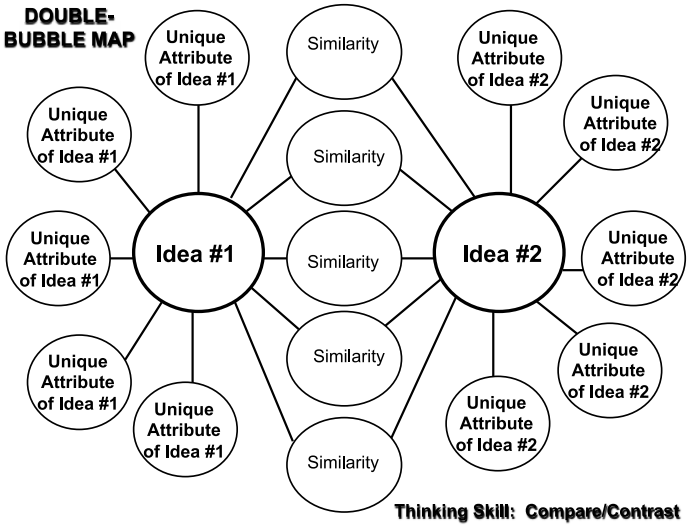
Thinking Skill: Defining in Context & Brainstorming



BUBBLE MAP

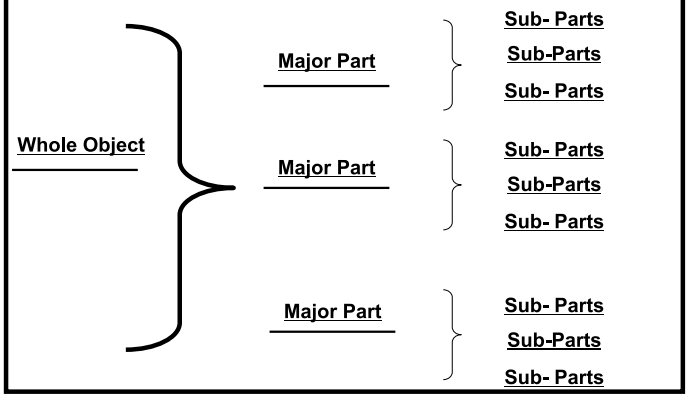
Thinking Skill: Describing





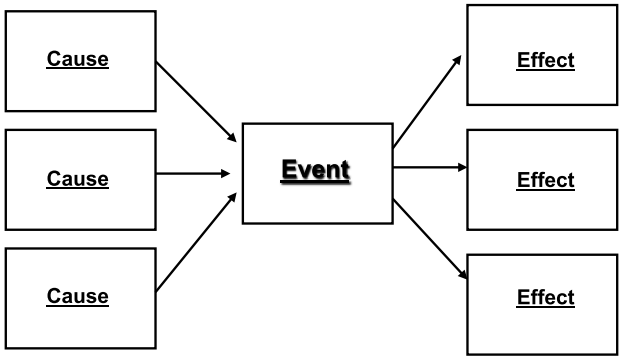
BRACE MAP

Thinking Skill: Whole to Part Reasoning



MULTI-FLOW MAP

Thinking Skill: Comparing/Contrasting



Recommendations

- Mapthemind.com
- inspiration.com
- Draftbuilders
- Dragon Naturally Speaking v. 11.

Examples of Accommodations

- Reduce rate (untimed tests), volume, complexity
- Use a staged approach
- Present information in different format
- Allow student to produce work in medium that works best for him/her
- Modify grading system
- Modify curriculum
- Use of calculator, word processor etc

Attention Deficit Hyperactivity Disorder Across the Life Span

SUNDAY
MARCH 17, 2013

Sunday, March 17, 2013

7:30AM – 8:00AM	**Continental Breakfast**
8:00AM – 9:00AM	**Neuropsychology of ADHD** Ronna Fried, PhD
9:00AM – 10:00AM	**Adult ADHD** Thomas J. Spencer, MD
10:00AM – 10:15AM	**Coffee Break**
10:15AM – 11:15AM	**Pharmacology of Adults with ADHD** Thomas J. Spencer, MD
11:15AM – 12:15PM	**Neurobiology of Dyslexia** Bennett A. Shaywitz, MD and Sally E. Shaywitz, MD
12:15PM – 1:30PM	**Lunch Break (On Your Own)**
1:30PM – 2:30PM	**Legal Issues in Treating Individuals with ADHD Disorders*** Ronald Schouten, MD, JD
2:30PM	**Adjourn**

* Sessions are eligible for risk management credit

Neuropsychology of ADHD

Ronna Fried, EdD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

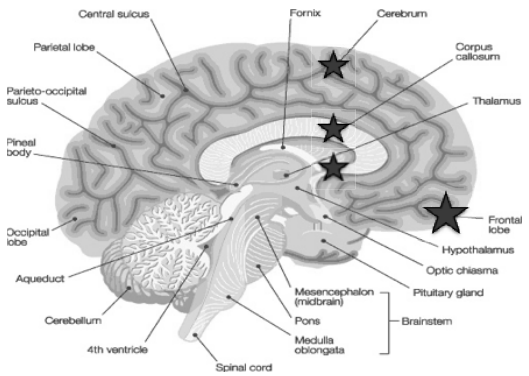
Neuropsychology of Attention Deficit Hyperactivity Disorder (ADHD)

Ronna Fried, Ed.D.
Director of Neuropsychology
Clinical & Research Programs in Pediatric Psychopharmacology and Adult ADHD
Massachusetts General Hospital,
Instructor in Psychology
Harvard Medical School

Disclosures

Dr. Fried has indicated that neither she nor her spouse/partner have a relevant financial relationship to disclose.

Brain Areas Implicated in ADHD



Retrieved January 25, 2013 from Google: http://www. farm1.staticflickr.com/150/429949624_3e198c96e9.jpg

Brain Areas Implicated in ADHD

- Areas of the brain implicated in ADHD include:

  basal ganglia, cerebellum, and corpus callosum which are closely interconnected with the **prefrontal regions**

- Prefrontal regions are involved in, **executive functioning**: emotion regulation temporal organization, social judgment, and motor control

Nigg, J.T. (2006). *What causes ADHD?: Understanding what goes wrong and why.* New York, NY: The Guilford Press.

Executive Functions

- Mental operations involved in goal directed behavior and self-regulation, including
  - Inhibiting, set shifting, self-monitoring, initiating, planning/organizing, task organizing, organizing materials, emotional control, and working memory
- Originally derived from the frontal lobe syndrome in which patients with brain lesions showed disturbances in the area of self-regulation

Fried, R. (2010). *Impact of Executive Functions in Youth with Bipolar I Disorder: A Controlled Study* [PowerPoint Slides]. Retrieved from Dr. Ronna Fried, Ed.D.

Executive Functioning as a Deficit (EFD)

- Neuropsychological testing
  - At least two EF measures have scores $\leq$ 1 standard deviations below the norm
- Rating scales
  - BRIEF-A (at least 2 area in clinical range $\geq$65)
    - The BRIEF-A checklist is a quick, easy, and reliable way to screen patients for EFDs
  - CBS-Barkley- 1 SD below Controls

Biederman, J., Petty, C.R., Fried, R., et al. (2006). Impact of psychometrically defined deficits of executive functioning in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry,* 163, 1730-1738.

Executive Functioning Deficits in ADHD

- EFDs are common in ADHD but not ubiquitous
  - **30-50% of individuals with ADHD have EFDs**
- Individuals with both ADHD and EFD have more negative outcomes across areas of functioning

Barkley, B.A. & Fischer, M. (2011). Predicting impairment in major life activities and occupational functioning in hyperactive children as adults: Self-reported executive function (ef) deficits versus ef tests. *Developmental Neuropsychology, 36(2),* 137-161.

Neuropsychological Testing

- A large meta-analysis domains of **executive functioning** deficits in ADHD

Domains of Executive Functioning	Meta-analytic Effect Size (*d*)
Set shifting	0.50
Working memory (verbal)	0.45
Working memory (spatial)	1.00
Planning	0.55
Inhibition	0.60

Nigg, J.T. (2006). *What causes ADHD?: Understanding what goes wrong and why.* New York, NY: The Guilford Press.

Neuropsychological Tests

Neuropsychological Test	Executive Function
Color Word (D-KEFS)	Inhibition
Trails Making (D-KEFS), IED (CANTAB), Letter-Number Test (WAIS)	Set Shifting
Stockings of Cambridge (CANTAB)	Planning/Organizing
Symbol Search (WAIS/WISC)	Task Monitoring, Initiating
Digit Span, Arithmetic, Letter-Number Test (WAIS/WISC)	Working Memory
Coding (WAIS)	Initiating
Matrix (WAIS)	Inhibition, Spatial Working Memory

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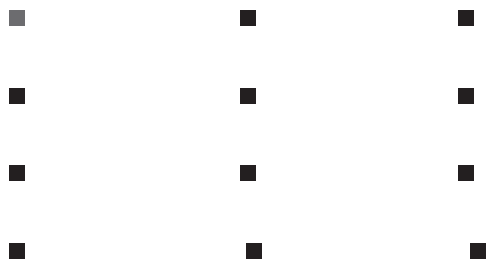
Inhibition

- Ability to control impulses and stop one's own behavior at the appropriate time
- Test
  - Color Word (D-KEFS)
- BRIEF examples
  - Interrupts or disrupts group activities
  - Has trouble putting on the brakes
  - Says/does things impulsively without thinking
  - Makes decisions that get them into trouble

Roth, R.M., Isquith, P.K., & Gioia, G.A. (2005). Behav*ior rating inventory of executive function-adult version: Professional manual.* Lutz, FL: PAR Psychological Assessment Resources, Inc.

Color Word



Delis, D.C., Kaplan, E., & Kramer, J.H. (2001). Delis-kaplan executive function system (d-kefs). San Antonio, TX: Pearson Education.

Color Word

red	blue	red
green	red	blue
red	blue	green
blue	green	red

Delis, D.C., Kaplan, E., & Kramer, J.H. (2001). Delis-kaplan executive function system (d-kefs). San Antonio, TX: Pearson Education.

Color Word

red	blue	red
green	red	blue
red	blue	green
blue	green	red

Delis, D.C., Kaplan, E., & Kramer, J.H. (2001). Delis-kaplan executive function system (d-kefs). San Antonio, TX: Pearson Education.

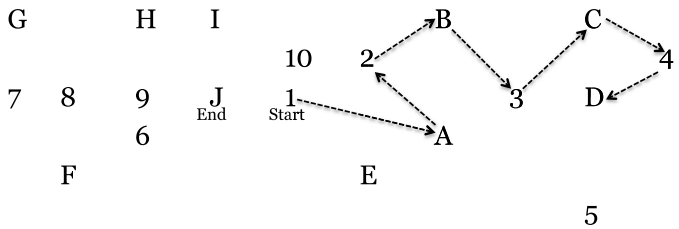
Set Shifting

- Ability to move from one situation, activity, or part of a problem to another as the condition demands
- Test
  - Trails Making (D-KEFS)
  - Intra-Extra Dimensional Shift Set (CANTAB),
- BRIEF examples
  - Tries the same approach even when it does not work
  - Has trouble moving from activity to activity
  - Resists accepting a different solution
  - Experiences anxiety, or extreme anger when things change

Roth, R.M., Isquith, P.K., & Gioia, G.A. (2005). Behavi*or rating inventory of executive function-adult version: Professional manual.* Lutz, FL: PAR Psychological Assessment Resources, Inc.

Trails Making

- Switch between connecting the numbers and letters
- Begin at number 1 and draw a line from 1 to A, A to 2, 2 to B, B to 3 and so on until you reach the end



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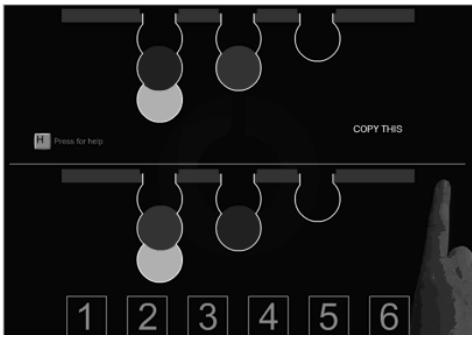
Planning/Organizing

- Ability to manage current and future oriented task demands within the situational context
- Test
  - Stockings of Cambridge (CANTAB), TOWER tasks
- BRIEF examples
  - Starts tasks without the right materials
  - Has trouble prioritizing or organizing activities
  - Starts homework or chores at the last minute
  - Underestimates the time to finish tasks

Roth, R.M., Isquith, P.K., & Gioia, G.A. (2005). Behav*ior rating inventory of executive function-adult version: Professional manual.* Lutz, FL: PAR Psychological Assessment Resources, Inc.

Stockings Of Cambridge

- Use the balls in the bottom to copy the pattern in the top



Fried, R. (2006). *Executive Functioning/Cognitive Performance Assessment: New Battery, Distinction of EFD, and Pilot CANTAB Results* [PowerPoint Slides]. Retrieved from Dr. Ronna Fried, Ed.D.

Task Monitoring

- Ability to check work and assess performance during or after finishing a task to ensure a goal is finished
- Test
  - Symbol Search (WAIS/WISC)
- BRIEF examples
  - Does not check work for mistakes
  - Makes careless errors
  - Fails to catch one's errors while completing a task
  - Does not problem solve during a task

Roth, R.M., Isquith, P.K., & Gioia, G.A. (2005). Behav*ior rating inventory of executive function-adult version: Professional manual.* Lutz, FL: PAR Psychological Assessment Resources, Inc.

Symbol Search

- One of these shapes is in this group of shapes over here, so draw a line through the shape
- Neither of these shapes is in this group of shapes over here, so draw a line through the NO box

		NO
		NO
		NO

Wechsler, D. (2008). Wechsler adult intelligence scale (wais). San Antonio, TX: Pearson Education.

Working Memory

- Ability to hold information in one's mind for purpose of generating a response or completing a task
- Test
  - Digit Span, Letter Number, and Arithmetic (WISC/WAIS)
- BRIEF examples
  - When given three things, remembers only the first or last
  - Forgets to hand in homework
  - Forgets what they are doing in the middle of things
  - Has trouble remembering things, even for a few minutes (

Roth, R.M., Isquith, P.K., & Gioia, G.A. (2005). Behav*ior rating inventory of executive function-adult version: Professional manual.* Lutz, FL: PAR Psychological Assessment Resources, Inc.

Working Memory

Letter Number

- I am going to say some numbers and letters and when I'm through, I want you to say the numbers first, in order, starting with the lowest number then tell me the letters in alphabetical order

7-N-2-P-6-F-9-A

Wechsler, D. (2008). Wechsler adult intelligence scale (wais). San Antonio, TX: Pearson Education.

Arithmetic

A post office sorts 20,000 pieces of mail in October. In November, the pieces of mail sorted increased by 10%. In December, the pieces of mail sorted increased by another 5%. How many pieces of mail are sorted in December after both increases?

Wechsler, D. (2008). Wechsler adult intelligence scale (wais). San Antonio, TX: Pearson Education.

Initiating

- Ability to begin a task and independently generate ideas, responses, or problem solving strategies
- Test
  - Coding, Symbol Search, and Matrix (WAIS/WISC), Color Word and Trails Making (D-KEFS)
- BRIEF examples
  - Lies around the house a lot (couch potato)
  - Has good ideas but does not get the job done
  - Needs extensive reminders to begin a task
  - Has trouble getting started on tasks

Roth, R.M., Isquith, P.K., & Gioia, G.A. (2005). Behav*ior rating inventory of executive function-adult version: Professional manual.* Lutz, FL: PAR Psychological Assessment Resources, Inc.

Self Monitoring

- Ability to keep track of the effect of one's behavior on others and attend to one's behavior in a social context
- TEST examples: careless errors (process approach)
- BRIEF examples
  - Does not notice when behavior causes negative reactions
  - Becomes too wild or silly
  - Does not notice when others get mad until it is too late
  - Makes inappropriate sexual comments

Roth, R.M., Isquith, P.K., & Gioia, G.A. (2005). Behav*ior rating inventory of executive function-adult version: Professional manual.* Lutz, FL: PAR Psychological Assessment Resources, Inc.

Emotional Control

- Ability to modulate one's emotional responses appropriately
- BRIEF examples
  - Has explosive, angry outbursts
  - Becomes tearful easily
  - Overreacts emotionally to minor events
  - Reacts more emotionally to situations than friends

Roth, R.M., Isquith, P.K., & Gioia, G.A. (2005). Behav*ior rating inventory of executive function-adult version: Professional manual.* Lutz, FL: PAR Psychological Assessment Resources, Inc.

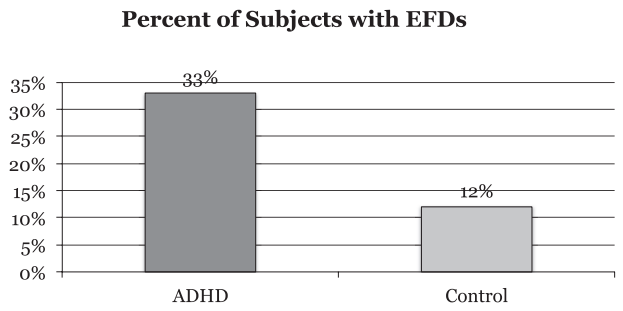
Impact of EFDs on Children with ADHD

- Examined psychometrically defined EFDs in children with and without ADHD and EFDs
- Included male and female (mean age=12.3-13.7 years old) probands from two longitudinal family studies of ADHD

	Control	ADHD
	N=125	N=159
Male	103	121
Female	122	138

Fried, R. (2010). *Deconstructing Attention and Cognition in ADHD: New Understandings for Improved Management* [PowerPoint Slides]. Retrieved from Dr. Ronna Fried, Ed.D.

Impact of EFDs on Children with ADHD



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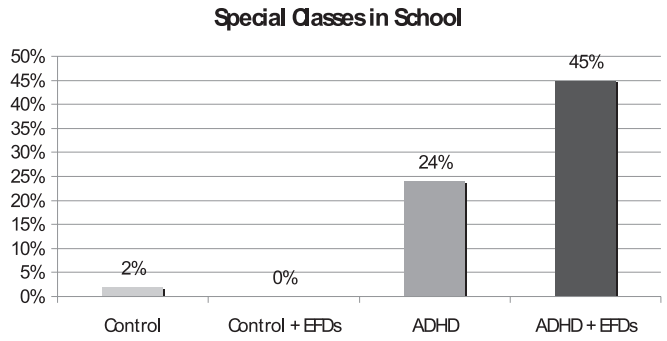
Impact of EFDs on Children with ADHD



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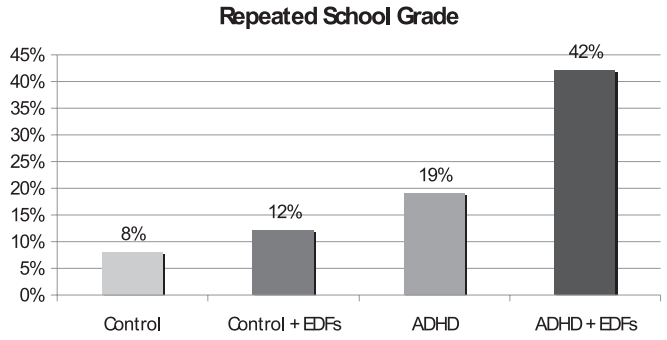

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Impact of EFDs on Children with ADHD

- Using the psychometrically defined method, significantly more children with ADHD had EFDs than controls
- Neuropsychological impairments in children with ADHD have implications for functional outcome above and beyond the diagnosis itself
- Children with ADHD and EFDs had an increased risk for grade retention and a decrease in academic achievement, relative to ADHD alone

Fried, R. (2010). *Deconstructing Attention and Cognition in ADHD: New Understandings for Improved Management* [PowerPoint Slides]. Retrieved from Dr. Ronna Fried, Ed.D.

Impact of EFDs on Adults with ADHD

- Examined psychometrically defined executive function deficits (EFDs) in adults using traditional neuropsychological tests

	Control	Control + EDF	ADHD	ADHD +EDF
	N=122	N=23	N=147	N=66
Age	29.3 ± 8.4	35.4 ± 8.8	34.6 ± 10.4	40.0 ± 10.3
Gender (% male)	55 (45%)	11 (48%)	80 (54%)	33 (50%)

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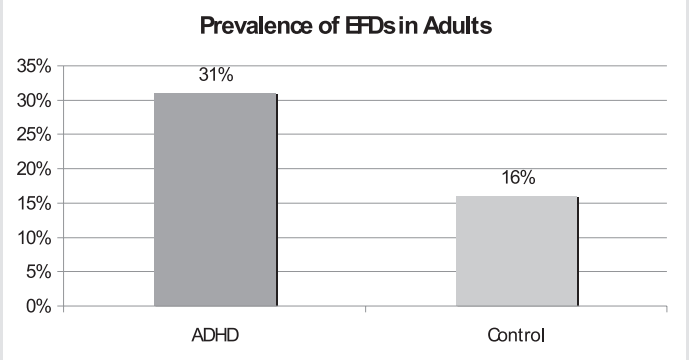
Impact of EFDs on Adults with ADHD



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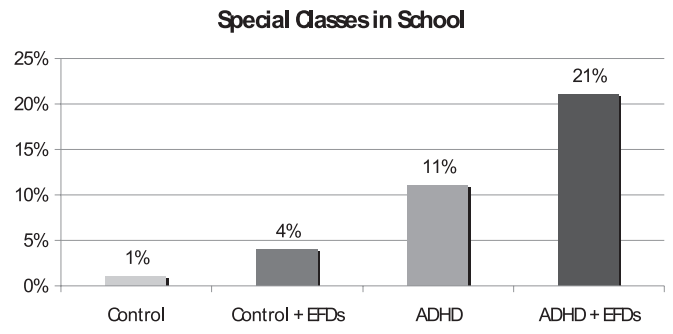

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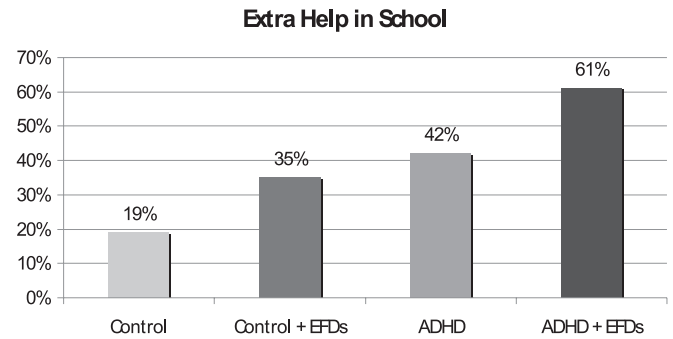

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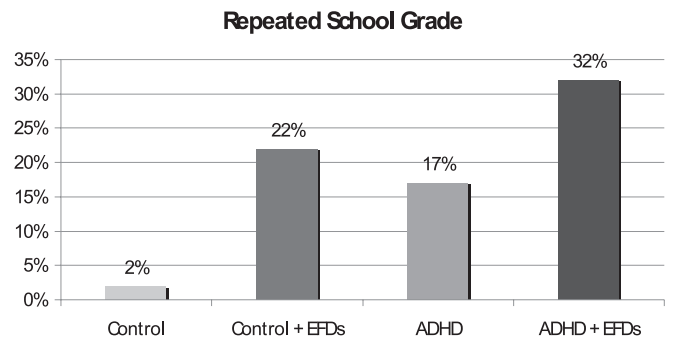
Impact of EFDs on Adults with ADHD



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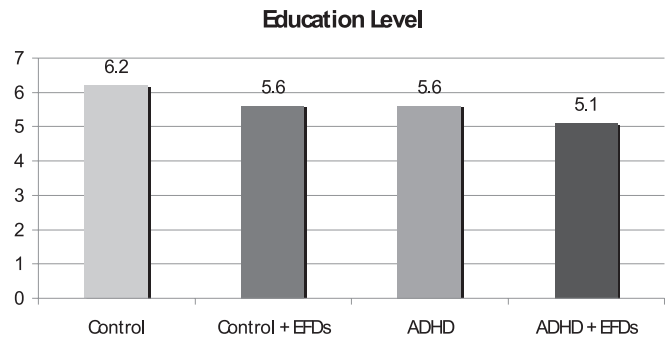

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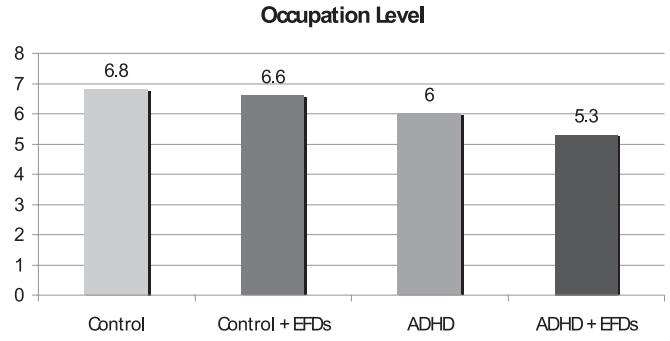

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Impact of EFDs on Adults with ADHD

- Using the psychometrically defined method, significantly more adults with ADHD had EFDs than controls
- Adults with ADHD and EFDs had significantly lower levels of education, occupation, and overall SES and more impaired interpersonal functioning
- EFDs in adults were associated with a decrease in academic achievement, irrespective of ADHD status

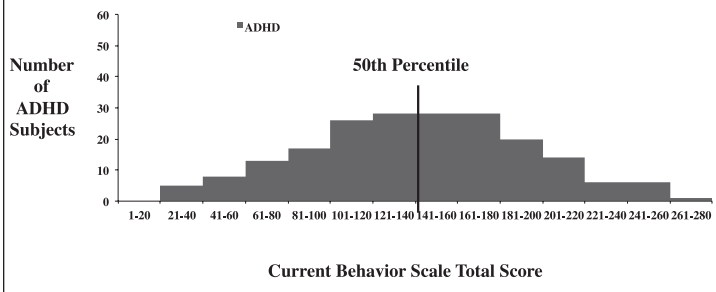
Fried, R. (2010). *Deconstructing Attention and Cognition in ADHD: New Understandings for Improved Management* [PowerPoint Slides]. Retrieved from Dr. Ronna Fried, Ed.D.

Self-reported EFDs

- Executive Function Domains
  - Set Shifting
    - not very flexible in my behavior or approach to a situation; overly rigid in how I like things done
    - slower to react to unexpected events
  - Planning/Organizing
    - have trouble planning ahead or preparing for upcoming events
    - trouble organizing my thoughts or thinking clearly
  - Working Memory
    - when shown something complicated to do, cannot keep the information in mind so as to imitate or do it correctly
    - can't seem to hold in mind things I need to remember to do
  - Inhibition
    - find it difficult to tolerate waiting; impatient
    - make impulsive comments to others

Self-reported EFDs

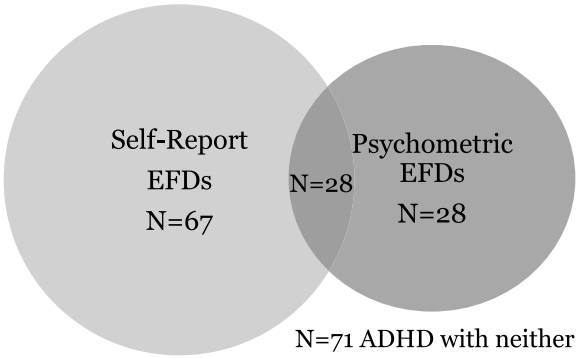
Distribution of CBS scores in Adults with ADHD



Biederman J, Petty C, Fried R, Fontanella J, Doyle AE, Seidman LJ, Faraone SV. Can Self-Reported Behavioral Checklist Be Used to Predict Functional Outcomes? *Journal of Nervous and Mental Disease*. 2007 Mar;195(3):240-6.

Can self-reported behavioral scales assess executive function deficits? A controlled study of adults with ADHD

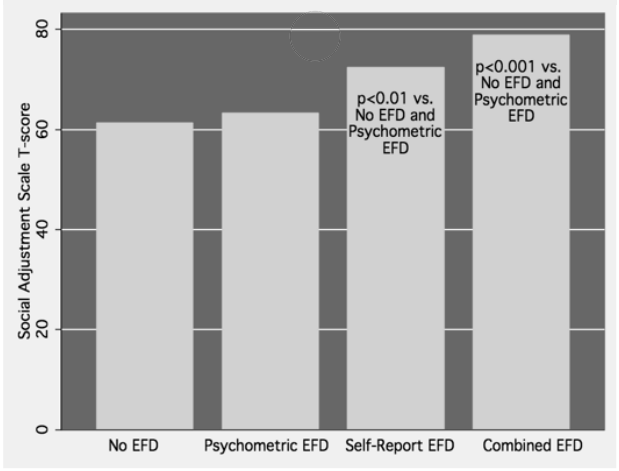
Prevalence of EFDs in 194 Adults with ADHD



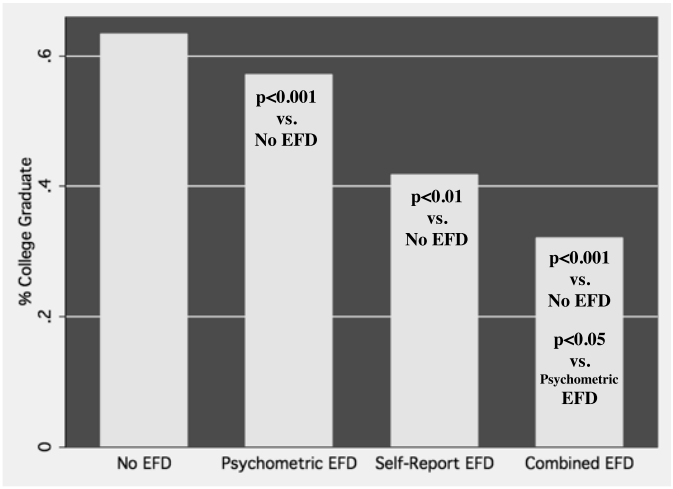
N=71 ADHD with neither EFD

Biederman, J., Petty, C.R., Fried, R., Black, S., Faneuil, A., Doyle, A.E., Seidman, L.J., & Faraone, S.V. (2007). Discordance between psychometric testing and questionnaire-based definitions of executive function deficits in individuals with adhd. *Journal of Attention Disorders, 12(1)*, 92-102.

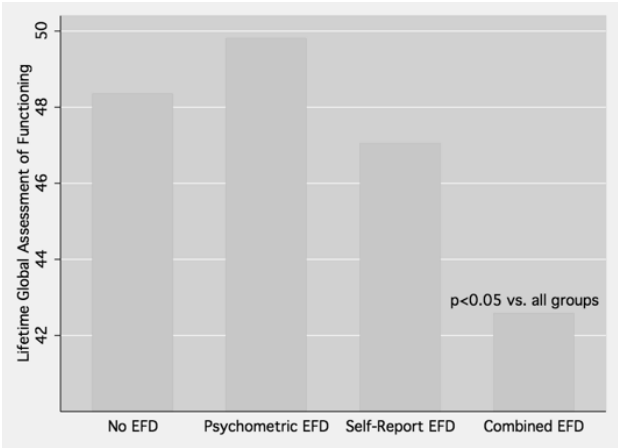
Social Adjustment Scale: >65 Significant Problem



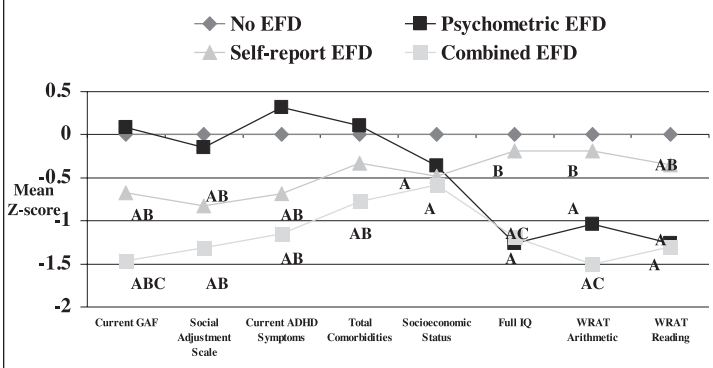
Educational Level



Lifetime GAF



Comparison of main outcomes between ADHD adults with no EFDs, psychometrically defined EFD, self-reported EFD, or both EFDs



A = p<0.05 vs. No EFD; B = p<0.05 vs. Psychometric EFD; C = p<0.05 vs. Self-report EFD

Outcomes of EFDs in ADHD

- ADHD is understood as both a behavioral and cognitive disorder
- EFDs are common but not ubiquitous in ADHD
  - 30-50% of individuals with ADHD have EFDs
- Testing and self-report checklists identify EFDs in different people
- ADHD can cause significant impairment in areas of academic, work, and social functioning

Biederman, J., Petty, C.R., Fried, R., et al. (2006). Impact of psychometrically defined deficits of executive functioning in adults with attention deficit hyperactivity disorder. *American Journal of Psychiatry*, 163, 1730-1738.

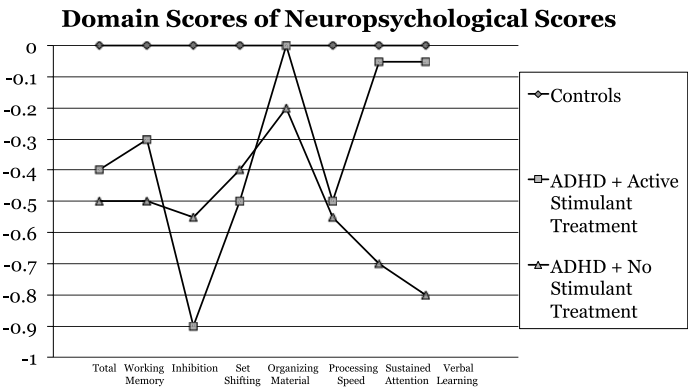
Medication Effects on EFDs

- Evaluated the impact of stimulant medication on EFDs in adolescents and young adults with ADHD
- Stimulant medication at the time of testing versus no stimulant medication in the past month
- All subjects completed a neuropsychological battery

Control	ADHD + Active Stimulant Treatment	ADHD + No Stimulant Treatment
N=26	N=94	N=133

Biederman, J., Seidman, L.J., Petty, C.R., Fried, R., Doyle, A.E., Cohen, D.R., Kenealy, D.C., & Faraone, S.V. (2008). Effects of stimulant medication on neuropsychological functioning in young adults with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry, 69(7)*, 1150-1156.

Medication Effects on EFDs



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Medication Effects on EFDs

- ADHD stimulant treatment group scored significantly higher on the sustained attention and verbal learning domains than ADHD no stimulant treatment group
- Differences were not found for other EF measures on Traditional Tests with standard medication regime

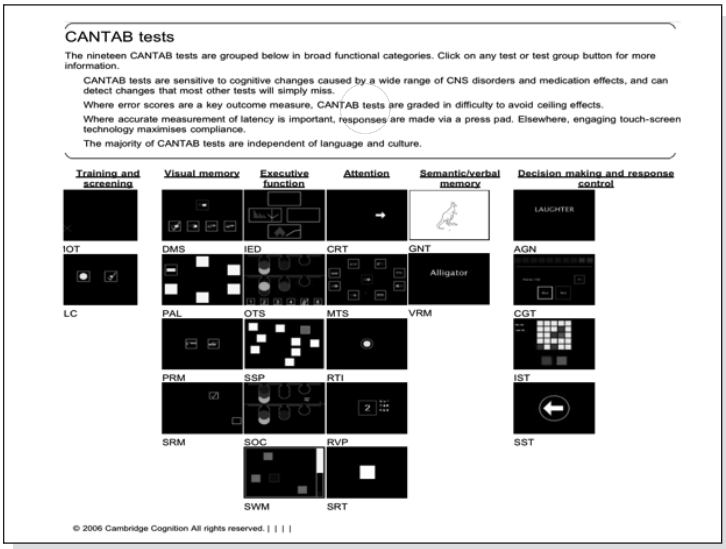
Biederman, J., Seidman, L.J., Petty, C.R., Fried, R., Doyle, A.E., Cohen, D.R., Kenealy, D.C., & Faraone, S.V. (2008). Effects of stimulant medication on neuropsychological functioning in young adults with attention-deficit/hyperactivity disorder. *Journal of Clinical Psychiatry, 69(7),* 1150-1156.

The CANTAB

- Cambridge Neuropsychological Test Automated Battery
- Advantages over standardized clinical tests:
  - Separation of mnemonic and strategic components of working memory
  - Data linking performance deficits to focal brain abnormalities
  - Easier administration methods
  - Less vulnerable to practice effects

Advantages of the CANTAB over traditional testing

- It is differentially sensitive to specific brain regions
  - Useful in imaging studies examining the neural underpinnings of EFDs
- Computerized format makes testing administration highly reliable
  - Allows for more streamlined comparisons across studies examining EFDs in children with ADHD
- Can be administered by trained psychometricians
  - Can be utilized in places where neuropsychology services are limited



CANTAB Assessment vs. Neuropsychological Test

Domain of Executive Functioning	CANTAB Tasks	Traditional Neuropsychological Test
Planning	Stockings of Cambridge (SOC)	Tower of Hanoi; Tower of London
Shifting	Intra-Extra Dimensional Set Shift (IED)	Wisconsin Card Sort (WCST) Trailmaking
Spatial Working Memory	Spatial Working Memory (SWM)	Corsi Blocks
Working Memory	Rapid Visual Information Processing (RVP)	Digit Span; Wechsler Arithmetic; Letter-Number
Reaction Time	Reaction Time (RTI)	CPT (ISI)
Inhibition/Vigilance	Affective Go/No-go (AGN)	CPT (Commission/Omission)
Verbal Memory	California Verbal Learning Test (CVLT)	Verbal Recognition Memory (VRM)

Effect Size in Domain of EFD in CANTAB and Traditional Tests

Domain of Executive Functioning	CANTAB Tasks (Present Study) Effect Size	Traditional Neuropsychological Tests (Wilcutt Meta-Analysis) (Wilcutt et al., 2005) Effect Size
Planning	.41	.62
Shifting	.36	.46
Spatial Working Memory	.58	.63
Working Memory	.63	.75
Reaction Time	.39	.61
Inhibition/Vigilance	.54	.60

Method: Subjects

- Children & Adolescents: 6-16 years
  - With ADHD: n=107
  - Without ADHD: n=45
- Both sexes
- ADHD status determined by structured diagnostic interview: Schedule for Affective Disorders and Schizophrenia for School Aged Children-Epidemiological Version (KSADS-E)

Results

- ADHD and Control Subjects did not significantly differ on age or sex

	ADHD (N=107)	Control (N=45)	Test Statistic	p-Value
N (%) Male	84 (79)	31 (69)	$\chi^2_{(1)}=1.59$	0.21
	Mean ± SD	Mean ± SD		
Age	11.9 ± 3.0	12.2 ± 3.4	$t_{(150)}=-0.72$	0.47
Socioeconomic Status	2.0 ± 1.0	2.0 ± 1.0	z=0.35	0.73

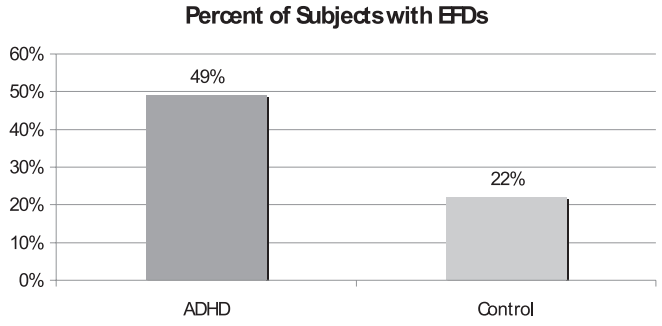
Method: CANTAB Assessment

- Subjects were administered 7 subtests from the CANTAB.
  1. Verbal Recognition Memory (VRM)
  2. Intra-Extra Dimension Set Shift (IED)
  3. Spatial Working Memory (SWM)
  4. Stockings of Cambridge (SOC)
  5. Reaction Time (RTI)
  6. Rapid Visual Information Processing (RVP)
  7. Affective Go/No-go (AGN)
- Each domain was compared to traditional neuropsychological test

Results

- ADHD subjects significantly more impaired on all measures of the CANTAB when compared to Controls.
  *exception: AGN total omissions
- Effect sizes for individual CANTAB test: medium range
- Largest effect sizes seen in Spatial Working Memory total and between errors (f=0.33)

Percent EFD with CANTAB



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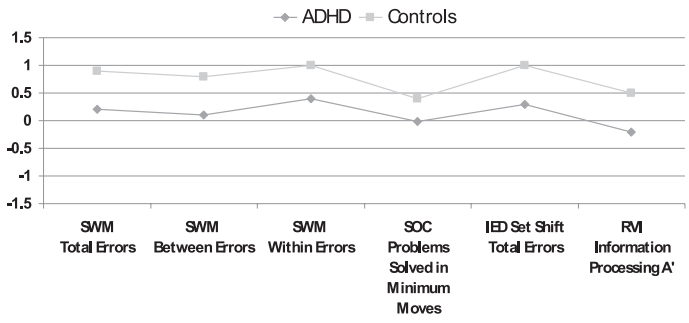
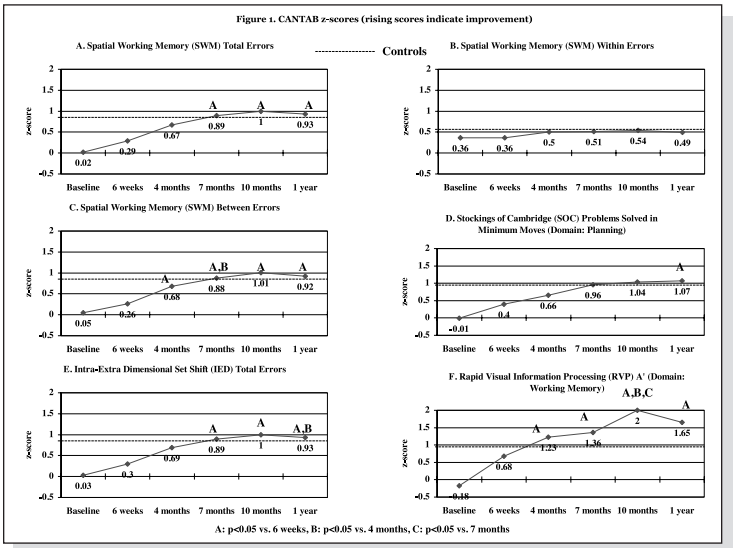
CANTAB Scores: ADHD vs. Controls





Medication Effect on CANTAB

- Statistically significant improvements in multiple cognitive domains were observed in a sample of adolescents with ADHD over the course of 12 months of **robust treatment with extended release methylphenidate**

Adult ADHD

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NOTES:

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Pharmacology of Adults with ADHD

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Neurobiology of Dyslexia

Bennett A. Shaywitz, MD

and

Sally E. Shaywitz, MD

www.MGHCME.org

Massachusetts General Hospital
Psychiatry Academy

NEUROBIOLOGY OF DYSLEXIA

ADHD Across the Life Span
March 17, 2013

Sally E. Shaywitz, M.D.
Bennett A. Shaywitz, M.D.
Yale Center for Dyslexia & Creativity

Disclosures

Bennett A. Shaywitz, MD
Dr. Bennett Shaywitz is Co-PI on a grant sponsored by Eli Lilly, "A double-blind placebo controlled study of atomoxetine for the treatment of attention deficit/hyperactivity disorder (ADHD) in children and adolescents with ADHD and comorbid dyslexia, Eli-Lilly B4Z-US-LYEB" and PI on a second grant sponsored by Eli Lilly, "Neurophysiology of Attention-Deficit/Hyperactivity Disorder(ADHD) and Comorbid Dyslexia: functional Magnetic Resonance Imaging (fMRI) Measures of Brain Activation During Attention and Reading Tasks Pre-and Post-Atomoxetine Treatment B4ZUS-LYEI."

Sally E. Shaywitz, MD

Dr. Sally Shaywitz is PI on a grant sponsored by Eli Lilly, "A double-blind placebo controlled study of atomoxetine for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents with ADHD and comorbid dyslexia, Eli-Lilly B4Z-US-LYEB"and Co-PI on a second grant sponsored by Eli Lilly, "Neurophysiology of Attention-Deficit/Hyperactivity Disorder (ADHD) and Comorbid Dyslexia: functional Magnetic Resonance Imaging (fMRI) Measures of Brain Activation During Attention and Reading Tasks Pre-and Post-Atomoxetine Treatment B4Z-US-LYEI."

Dyslexia – represents >80% of all LD
Often un-diagnosed
Associated with ADHD

Historical Background

1896 - W. Pringle Morgan: 14-year-old boy who was "bright and intelligent" but whose "great difficulty has been--and is now--his inability to read."

Definition

Dyslexia is an *unexpected difficulty* in reading, unexpected in relation to: intelligence, motivation, education, professional status
Empiric support: In typical readers, reading and IQ development are dynamically linked over time; In dyslexia developmental uncoupling between IQ and reading
Sea of Strengths Model

Epidemiology
Connecticut Longitudinal Study: 1 in 5, 10 million children nationally
Universal, occurs in every language, affects both boys and girls
Dyslexia persists: not simply lag in development that children will outgrow

Etiology
Multi-factorial model - multiple genetic and environmental risk and protective factors
Less than 1% of risk related to genetic variants
Dyslexia best explained by *multiple* genes, each contributing a *small* amount of the variance

Why print has meaning
Difference between spoken and written language
Phoneme: smallest unit of speech distinguishing one word from another; basic unit of spoken language, e.g., word "cat" composed of three separate phonemes: k aaa t

Alphabetic Principle
Words not whole envelopes of sound: segments represent sounds
Printed word has same number and sequence of sounds as spoken word

Neurobiologic Mechanisms in Dyslexia: fMRI & psychopharmacology

Neural Systems in Reading: fMRI in dyslexic readers
"A neural signature for dyslexia"
Inefficient functioning of neural systems for skilled, fluent reading
Made "visible" previously hidden disability
Similar neural systems in all alphabetic and logographic languages

Pharmacotherapy as Potential Adjunct Treatment in Dyslexia
Atomoxetine improved reading in children with dyslexia only and ADHD+D.

Translating Research into Policy and Practice

Diagnosis
Dyslexia puts all the pieces together
No longer just a collection of psychological test scores

<u>Spoken language</u>
Delayed speech, lacks verbal fluency, mispronunciations, not glib,
Word retrieval difficulties – needs time to summon verbal response when questioned; struggle to retrieve words, "on tip of my tongue"
Avoids saying words that may mispronounce
Spoken vocabulary < listening vocabulary
Dyslexic knows what s/he wants to say, but can't find/retrieve the right sounds to form the spoken word that represents that word.

Reading
Trouble learning letters, letter-sounds, sounding out words
Lacks strategy for reading new words
Avoids reading aloud
Slow reading, lacks fluency

Other problems
Poor spelling
Poor handwriting
Problems with attention
Difficulty learning foreign language
Problems with self-esteem

Diagnostic Criteria
Clinical Diagnosis
History
Observation of spoken language and reading
Disparity between reading and intelligence, education or professional status
Assessment of fluency critical
Management of Dyslexia:
Reading interventions
Accommodations

Accommodations
by themselves do not produce success
only act as catalyst that allows success to happen
Extra time – dyslexia robs a person of time: accommodations return it.
Neurobiological evidence for requirement for extra time
Oral exams may not allow demonstration of knowledge and skills, especially if in artificial, anxiety-provoking setting ➠ minimize factors exacerbating anxiety

Practical Consequences
Dyslexic speakers:
word retrieval difficulties, lack of glibness; pauses, um's; mispronunciations
particularly penalized by oral exams when put on the spot – interacts with anxiety
Dyslexic readers: require more time to read
Young adults with dyslexia: in college, graduate and professional schools:
access often determined by high stakes tests

Long Term Outcome
High level conceptualizers
New insights – "out of the box thinking"
Specialization – automaticity
High accomplishment
Leaders in science, medicine, law, business, writing/literature, poetry
Disproportionately high number of dyslexics leaders in medicine and science;
Nobel Laureates

References

Ferrer, E. et al. (2010) Uncoupling of Reading and IQ Over Time: Empirical Evidence for a Definition of Dyslexia. Psychological Science, 21(1) 93–101.

Faust, M. & Sharfstein-Friedman, S. (2003) Naming difficulties in adolescents with dyslexia: Application of the tip-of-the-tongue paradigm. Brain & Cognition, 53, 211-217.

Finn et al. (2013) Disruption of functional networks in dyslexia: a whole-brain, data-driven analysis of connectivity, submitted.

Shaywitz, S. (2005). *Overcoming Dyslexia: A new and complete science-based program for reading problems at any level*. New York, NY: Vintage.

Shaywitz, S., & Shaywitz, B. (2005). Dyslexia (Specific Reading Disability). *Biological Psychiatry*, *57*, 1301-1309.

Shaywitz, SE & Shaywitz, BA. (2008) Paying attention to reading: The neurobiology of reading and dyslexia, Development and Psychopathology 20, 1329–1349.

Shaywitz et al., (2012). Effects of Atomoxetine on Reading Abilities in Children with Dyslexia and Children with Attention Deficit/Hyperactivity Disorder and Comorbid Dyslexia, Annals of Neurology 72, Supplement 16, 5204.

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Legal Issues in Treating Individuals with ADHD Disorders

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Massachusetts General Hospital
Psychiatry Academy

Legal Issues and ADHD: Selected Topics

Ronald Schouten, MD, JD
Associate Professor of Psychiatry
Harvard Medical School
Director, Law & Psychiatry Service
Massachusetts General Hospital

Disclosure

Neither I nor any member of my immediate family has a significant financial interest or affiliation with any manufacturer of commercial product(s) or provider(s) of commercial services discussed in my educational presentations for MGH Psychiatry Programs in 2013.

ADHD and the Law: Multiple Issues

- Civil issues
  - Treatment
  - Disability
  - Constitutional
  - Child abuse/Custody
  - Fitness for duty
- Criminal issues
  - ADHD and criminal behavior
  - Competency to stand trial and criminal responsibility

Treatment Issues: Informed Consent

- Definition: A process by which one individual agrees to allow another individual to intrude upon his bodily integrity or other rights where the agreeing party is competent to consent and the consent is given voluntarily and with a reasonable degree of knowledge of the situation.

Elements of Informed Consent

- Information
- Voluntary
- Competence

Information

- Professional (Physician-based) standard, e.g. New York
- Materiality (Patient-based) standard, e.g. Massachusetts
  - Objective/Reasonable patient
  - Subjective/This patient

Information

General Requirements: Harnish v. Children's Hospital (Mass. 1982)

- Nature of condition and procedures
- Nature and probability of material risks
- Reasonably expected benefits
- Inability to predict results
- Potential irreversibility of the procedure
- Likely results, risks, & benefits of no treatment and alternative treatments

Voluntary

- Free of coercion by the treater. What about parents/guardian?
- Special issues with children and adolescents
  - Assent vs. consent
  - What basis for treatment refusal?
  - Clinical impact of parental coercion

Competent

- When is the child competent to decide?
- General rules:
  - Minors are incompetent; parents or guardians decide
  - Minors may decide if
    - Emancipated minors
    - Mature minors
    - Allowed by statute

Are the Parents Competent?

Incompetence constitutes a status of the individual that is defined by functional deficits (due to mental illness, mental retardation, or other mental conditions) judged to be sufficiently great that the person currently cannot meet the demands of a specific decision-making situation, weighed in light of its potential consequences.

Exceptions to Informed Consent

- Emergency
- Implied waiver
- Waiver
- Therapeutic privilege, e.g. New York

Off-Label Use of Medications

FDA Approval

- Approval given to marketing information based on research-proven efficacy and safety
- Not intended to interfere with doctor/patient decisions regarding use of medication

Physician May Use Professional Judgment

- Lack of FDA approval not a material risk
- Use of professional judgment provides basis for malpractice claim
- Protection from claims = documented studies of safe use + similar practice in community
- Black Box Warnings:
  - Pay attention
  - Not necessarily a major change in the approach to informed consent

HIPAA: Health Insurance Portability and Accountability Act

- Primary purposes
  - Ensure portability of health insurance when changing employers
  - Prevent unauthorized disclosures of medical information
  - Facilitate the exchange of medical information to improve the efficiency of care

HIPAA: Health Insurance Portability and Accountability Act

- Applies to most clinicians
  - Bill electronically or affiliated with an organization that uses electronic billing
  - Even if not applicable, will likely set the standard for confidentiality/privacy
- Numerous requirements, but
  - Fundamental concepts of confidentiality are unchanged
  - Disclosure without consent, for the public good, allowed in 13 situations, including
  - Risk of harm to self or others
  - Child abuse and other mandated reporting
  - Public health reporting
  - Judicial proceedings
  - Law enforcement needs

HIPAA: Health Insurance Portability and Accountability Act

- Does not override state privacy laws
- Minimum necessary rule applies in all cases
- Enforced by office of Civil Rights of DHHS; no private right of action.

Risk Management and Malpractice

Elements of a Malpractice Claim

- Elements of Proof: The Four Ds
  - **D**ereliction of a
  - **D**uty which
  - **D**irectly causes
  - **D**amages

The Four Ds

- Dereliction
  - Improper departure from accepted practice, or
  - Inept application of accepted practice

The Four Ds

- Duty
  - To possess and employ such reasonable skill and care as are commonly had and exercised by respectable, average clinicians in the same or similar community
  - Specialists held to higher standard
  - The School Rule
  - Duty to consult
  - To whom is the duty owed?
    - Tarasoff
    - McKenzie v. Hawaii Permanente Medical Group (2002)

The Four Ds

- Direct or proximate causation
  - Causation in fact: The But For Test
  - Proximate or legal causation = forseeability of harm
  - *Res ipsa loquitur:* The thing speaks for itself

The Four Ds

- Damages
  - Must be proven
  - Types
    - Physical
    - Emotional
    - Economic

Reducing Malpractice Risk

Role of the Therapeutic Alliance

Malpractice = bad outcome + bad feeling

Role of the Therapeutic Alliance: Russell's Rule

$$\text{Probability of suit} \propto \frac{\text{Physician's arrogance}}{\text{Physician's competence}}$$

Informed Consent and the Therapeutic Alliance

- Sharing uncertainty: what we know and don't know
- Includes uncertainty about the future
- Shared decision making as the model

Informed Consent and the Therapeutic Alliance

- Example: the off-label use issue
  - Approved for other uses
  - Safe under these circumstances
  - Rationale for using in this way
  - Risks of use, including future risks not yet known
  - Questions
  - Choice

Prevention Plus Defense

- Assessment
- Consultation
- Documentation
- Don't make promises you can't keep
- The role of apologies and apology statutes
  - Impact on the relationship
  - Reduces payout by an average of $32,000
  - Most value: obstetrics & anesthesia, cases involving infants, improper management, and missed diagnoses

ADHD and Disability

Education of the Handicapped Act, 1982

- Protection of those with disabilities in the educational system.
- Minimal brain dysfunction is covered.
- Embodies Constitutional Due Process and Equal Protection provisions

Individuals with Disabilities Education Act, Amended 1995

- Originally passed in 1975
- Designed to ensure that children with disabilities get free appropriate public education
- IEP: Individualized Education Plan
- Education in least restrictive setting
- Procedural safeguards
- Attorney's fees to prevailing party in Federal Court

Behavioral Problems Under IDEA

- ADHD is covered; what about ODD?
- IEP meeting must be held prior to removal for more than 10 days
  - Court can enter TRO
  - Disruptive child may be returned pending IEP
  - Services while suspended?
- Relationship between rules violation and disability must be considered when determining punishment
- School authorities may make decisions on a case by case basis

Behavioral Problems Under IDEA

- School authorities may remove students who have "inflicted serious bodily injury upon another person while at school, on school premises, or at a school function", as well as those who carry or possess a weapon or knowingly possess or use illegal drugs or sell or solicit the sale of a controlled substance
- Courts split on whether services have to be provided after a child is suspended

Behavioral Problems Under IDEA

- Regulatory changes in 1999
  - Unilateral short suspensions up to 10 days
  - Expanded ability to remove for drugs/weapons
  - Codifies procedures for removal
  - Services provided after child expelled

The Americans with Disabilities Act

- Protection against discrimination based on disability in employment (Title I) and public accommodations (Title II and III)

The Americans with Disabilities Act

- No covered entity shall discriminate against a qualified individual with a disability because of the disability of such individual in regard to job application procedures, the hiring, advancement, or discharge of employees, employee compensation, job training, and other terms, conditions, and privileges of employment.

The Americans with Disabilities Act

- No individual shall be discriminated against on the basis of disability in the full and equal employment of of the goods, services, facilities, privileges, advantages, or accommodations of any place of public accommodation.

Qualified Individual with a Disability

- An individual with a disability who, with or without reasonable accommodation, can perform the essential functions of the job.
- Consideration given to employer's judgment regarding essential elements
- Written job description in existence before job advertised or hire serves as evidence of essential elements.

The ADA and School

- Axelrod v. Phillips Andover Academy (D. Mass. 1999)
  - Student with ADHD asked to withdraw in 3rd trimester of senior year
  - Court found disability
  - Student failed to request reasonable accommodation
  - Even with reasonable accommodation, student was not otherwise qualified, i.e. could not prove he could meet all the academic requirements in spite of handicap

Adult ADHD and the ADA

- Does ADHD explain/excuse poor performance?
- Work rules apply to everyone, regardless of disability status
- Wright v. CompUSA (1st Cir. 2003): Ee whose treatment for ADHD had been successful and whose symptoms were exacerbated by a new supervisor's management style did not present sufficient evidence that he was substantially limited in major life activities. Must prove:
  - Suffers from a disability
  - Nevertheless able to perform essential functions
  - Er took adverse action because of the disability

Disability Insurance

- ADHD and requests for disability
  - Short and long term
  - Any occupation vs. own occupation
- "New onset" ADHD in adults: Suddenly discovered/developed disorder or alternative explanation for other problems?
- SSDI
- Clear connection between ADHD and disability, see: Gjervan at al. J. Attention Disorders (16)7:544-552 (2012)

Constitutional Issues: Forced Medication of School Children

- State interest in maintaining classroom order vs. right of parental control
- Less restrictive alternatives
- Violation of right to privacy
- Violation of Due Process and Equal Protection clauses

Other Civil Issues

- Mandatory reporting of abuse and neglect
  - Risk of abuse/neglect in ADHD
  - Failure to provide necessary treatment
- Shared custody: Who decides?
  - Legal custody generally controls
  - Parent with physical custody can make immediate decisions
  - Resolve these issues beforehand
- Fitness for duty: blue and white collar jobs

Criminal Issues

- ADHD and criminal behavior
  - Prevalence of antisocial behavior in children with ADHD
  - Disinhibitory psychopathology: substance use, ODD/ conduct disorder, adult APD
    - High comorbidity
    - Share *externalizing*:
      - Heritable personality trait
      - Low constraint
      - Impulsivity
      - Negative emotionality
      - Predisposes to excessive reward seeking and risk-taking, hostility, poor impulse control

ADHD as a Criminal Defense

- Diminished Capacity
  - Altered mental state which falls short of qualifying for an insanity verdict, but which provides evidence of diminished capacity to understand wrongfulness or conform conduct
  - Can result in reduction to next lower charge

The Insanity Defense: Model Penal Code

- A person is not responsible for criminal conduct if, at the time of such conduct as a result of mental disease or defect, he lacks substantial capacity either to appreciate the wrongfulness of his conduct or to conform his behavior to the requirements of the law
- Must be a link between behavior and illness

The Insanity Defense: Federal Standard

- It is an affirmative defense to a prosecution under any Federal statute that, at the time of the commission of the acts constituting the offense, the defendant, as a result of a severe mental disease or defect, was unable to appreciate the nature and quality or the wrongfulness of his acts.

ADHD and Competency to Stand Trial

- Whether the defendant "has sufficient present ability to consult with his lawyer with a reasonable degree of rational understanding, and whether he has a rational as well as a factual understanding of the proceedings against him." Dusky v. US (US 1960)
- Fifth Amendment/self incrimination issues

The Clinician as Expert Dilemma

- A continuum from "return to work/disability" to risk of violence and criminal responsibility
- As you move along the continuum, it becomes a worse idea.
  - Lack of objective data
  - Danger to the relationship
  - Bias
- Beware the Siren's call

Conclusion

- Lots of legal issues with ADHD
- Good clinical care is good risk management, and vice versa
- Potential impact in criminal matters may lead to the treating clinician being drawn in to the legal process