

Genetic, Biological, and Environmental Risk Related to Inattentive and Impulsive Behavior: Addiction and Self-Harm as Outcomes

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Objectives

- **Importance of inattention and impulsivity**
 - **At their extremes, diagnosis of ADHD**
- **Genetic and biological risk; environmental risk**
- **Multifinality and equifinality/transaction**
- **Models**
- **Sex differences and female manifestations**
 - **Self-harm**
- **Addiction**
- **Treatments**

Inattention/Disorganization

- Several forms of “attention”—
 - “Automatic”/spatial (what’s that in peripheral vision?)
 - Selective (talk or coffee break)
 - Sustained (will you be awake by the end?)
 - Capacity/load (how alert will you be with 500 slides?)
 - ****Each with different neural ‘location’**
 - Though few functions are completely localized
- ***Across all dimension of behavioral problems, this is the one with strongest link to (a) academic failure and (b) surprisingly, substance abuse (even though impulsivity is part of the path in some kids, too)***

Hyperactivity/Impulsivity

- More blatant and easier to detect than inattention/disorganization in terms of behavior ratings
 - These behaviors disrupt classrooms and homes
- Related to the construct of “response inhibition”
 - Ability to disengage from a previously rewarded response tendency
 - Think of spitballs in classroom, or unwrapping presents at birthday party (yet whose birthday?)
 - Considerable neuroscience research teasing apart the neural correlates and pathways underlying RI

Issues #1

Early temperament as precursor to both?

- **TEMPERAMENT:** early-appearing, persistent styles of behaving and showing emotion, presumably highly mediated biologically
- **1. HI as linked to activity level and part of “negative affect”**
- **2. Inattention/disorganization as linked to “effortful control,” an intriguing dimension that doesn’t come online until near age 1**

Issues #2

- **Linkage between RI and inattention/EF:**
 - **Hard to engage in a task, or to apply cognitive control/executive functions to planning for them, staying engaged, correcting mistakes, fighting interference, etc. etc., if you haven’t shown inhibitory control in the first place**
- **Thus, one model (see Barkley, 1997) is that poor RI is the “precursor,” paving the way toward disrupted task performance, because the individual never gets a chance to engage in EF**

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Issues #3

- Both dimensions exist on a bell curve in the population
- If you're at the extremes of either or both, you're likely to receive a diagnosis of attention-deficit/hyperactivity disorder (ADHD)
 - Inattentive presentation (high on one dimension)
 - HI presentation (high on the other)
 - Combined presentation (high on both)
 - "High": on absolute scale, or compared to age and sex norms?

ADHD: Key Themes

- Newsworthy
 - Cause of ADHD is SpongeBob Square Pants
 - Cause of ADHD is starting kindergarten at age 4
 - Stimulants lead to heart attacks
 - New York Times 2012/2013 opinion pieces:
 - Sroufe, Kareishi, Friedman, Brooks: Back to the past
- Careful assessment crucial
 - 10' office visit not sufficient for thorough evaluation
 - Original factor name: "Immaturity"

Impairment

- **Academic (school failure)/Vocational (low SES):**
 - \$130-220 billion annually over and above direct costs of treatment
- **Social/peer (most peer-rejected condition)**
- **Family (reciprocal chains of bidirectional influences)**
- **Accidental injury (across the age span)**
- **Lowered independence (mildly retarded range/normal IQ)**
- **Impairment often independent of comorbidity...AND key comorbidities don't respond optimally to ADHD tx**
 - E.g., LD, delinquency, depression

Themes - 2

- **Syndrome, not disorder**
 - Multiple causal pathways; risk factors interact/transact
- **Sex differences: 3:1 in representative samples**
 - "Naturally," as boys differ from girls, earlier in life, in terms of activity level and effortful control
 - Girls relatively more likely to show Inattentive type
 - BUT, development crucial: closer to 1:1 in adult ADHD

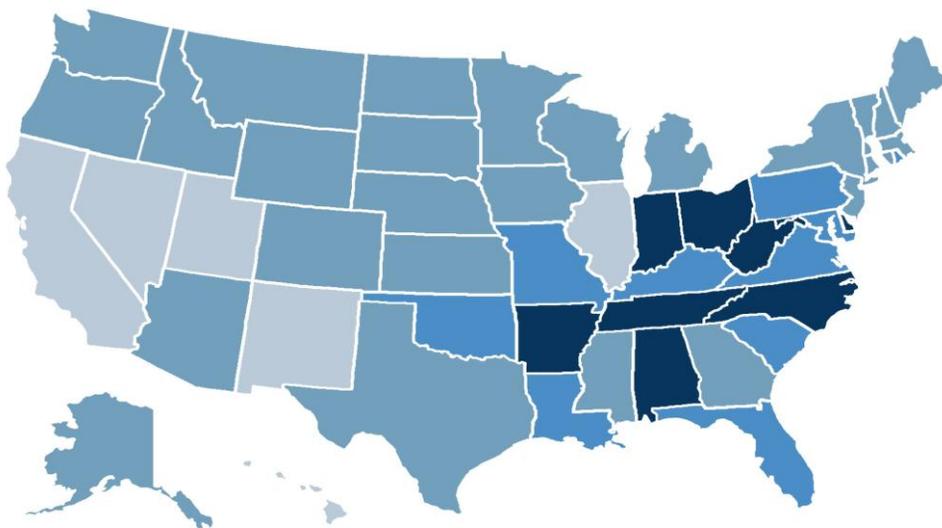
Tidal Wide, Variation, Policy

- **Diagnostic and medication prevalence up drastically in 1990s in US**
 - Medicaid changes
 - IDEA: ADHD = 'other health impaired' condition
- **Then, National Survey of Children's Health**
 - Visser et al.: CDC: parent-reported ADHD diagnosis in youth 4-17:
 - 2003: 7.8%
 - 2007: 9.5%
 - 2012: 11.0%
 - Low income rates now equal to middle class
 - African-American rates now equal to White
 - Hispanic lower (but fast growing)
- **Rates of medication higher, too:**
 - Over 2/3 currently diagnosed now receive medication
 - Largest medication increases: adolescents, adults

Diagnostic Prevalence:

5.60-7.11% (6) 7.54-9.96% (27) 10.14-12.41% (10) 13.08-15.52% (8)

United States Average: 9.47%

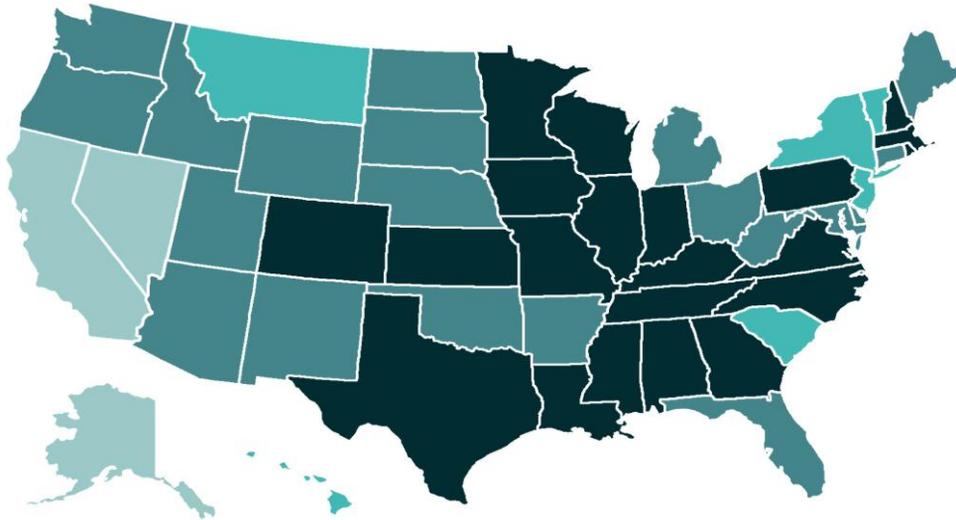


Source: 2007 NSCH, Children Aged 4-17

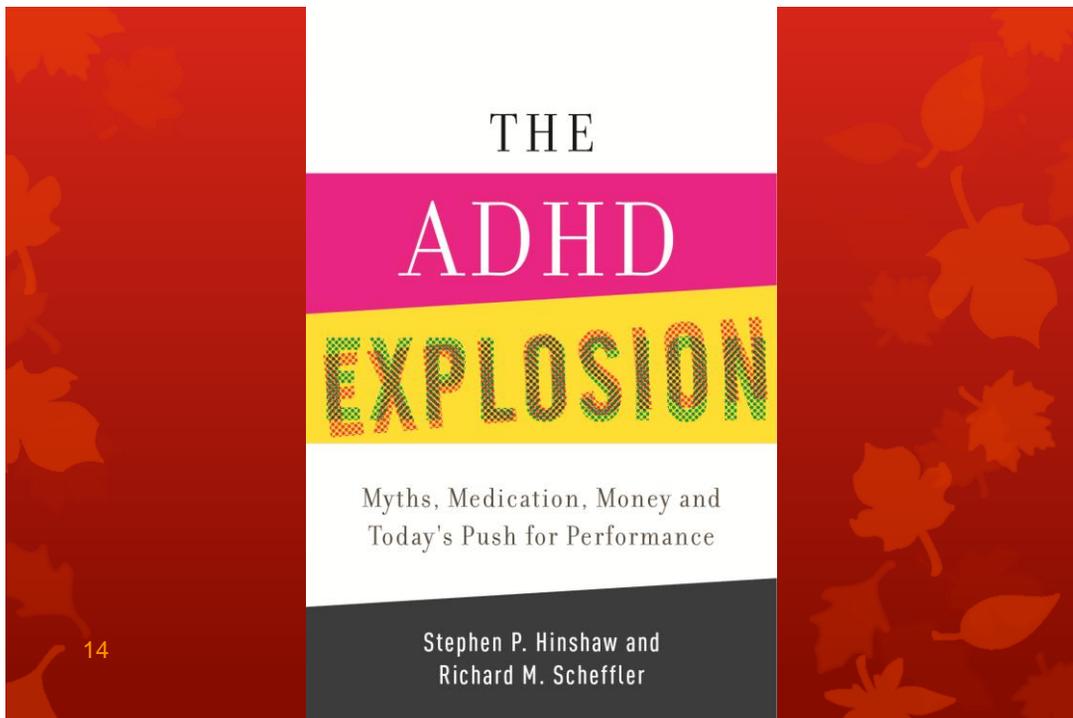
Medication Rate Given Current Diagnosis:

33.27-49.09% (3) 52.42-59.68% (7) 60.03-69.19% (19) 70.00-79.04% (22)

United States Average: 66.30%



Source: 2007 NSCH, Children Aged 4-17



**School Policy

- In rigorous analyses for the book, demographics and rates of health-care providers did NOT explain state differences
- But in states enacting early consequential accountability laws, children at or near poverty level showed **INCREASES** in ADHD diagnoses.
 - ****In states enacting high-school exit exam laws, same pattern, but for all teens, not just poor**
- **MECHANISM:** These accountability laws encourage ADHD diagnosis because (a) treatment may help achievement test scores, and (b) in some districts, diagnosed youth are excluded from the district's average test score!
- Where did such laws start: **SOUTH**

School and student accountability laws: most prevalent in the South

Region	Number of States	Consequential Accountability before NCLB	High School Exit Exam	Psychotropic Medication Law
Northeast	9	5	4	2
Midwest	12	5	3	2
South	17	15	13	5
West	13	5	8	5
United States	51	30	28	14

Sources: Investigators' Research, Dee & Jacob 2011, Dee & Jacob 2006, and Center for Education Policy

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Models

- **Multiple models**
 - Key issue: huge variability among and within individuals with ADHD
 - Intrasubject variability a major theme in current models
 - Including resting state/default mode imaging models
- **“Cognitive” models:**
 - Sustained attention, Response inhibition, Working memory...EF
 - BUT none is sufficiently sensitive or specific; apply only to subgroups
- **“Motivation” models: Reward undersensitivity**
 - E.g., Volkow et al. (2009): large medication-naïve adult sample, PET scans of transporters and receptors

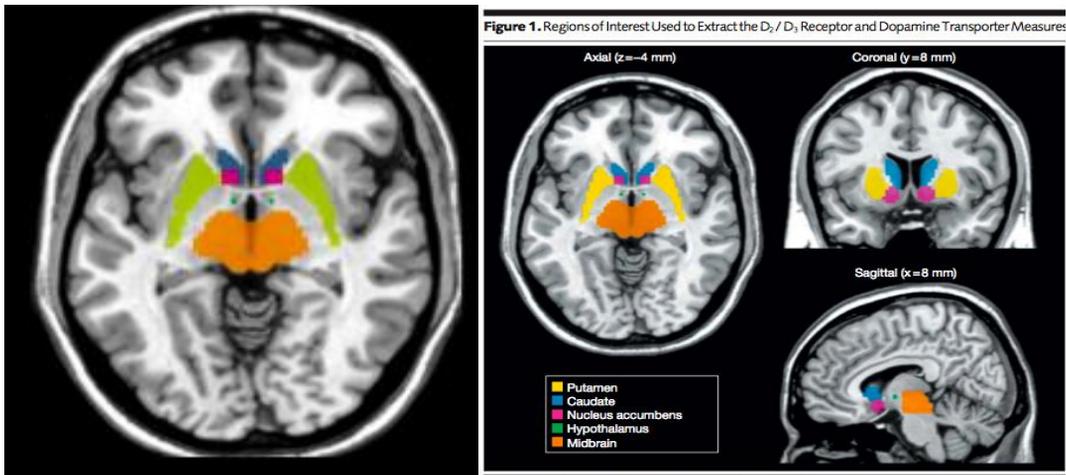


Figure 1. Regions of Interest Used to Extract the D₂/D₁ Receptor and Dopamine Transporter Measures

Transporter PET Image

The regions of interest for the midbrain are obtained in several planes, and the shadow is projected to the axial image shown in the figure, which explains why the third ventricle is covered by the region. The x coordinate maps the left-right position; the y coordinate, the anterior-posterior position; and the z coordinate, the superior-inferior position

Dopamine transporter						
<u>Accumbens</u>	(Motivation)	0.71 (0.16)	0.63 (0.11)	0.59	0.03 to 0.13	.004
<u>Caudate</u>	(Attention)	1.66 (0.23)	0.53 (0.19)	0.62	0.04 to 0.22	.003
Midbrain		0.16 (0.10)	0.09 (0.11)	0.66	0.03 to 0.12	<.001
Hypothalamic region		-0.01 (0.10)	-0.05 (0.12)	0.36	-0.01 to 0.09	.08

Neural profiles

- **Structural/anatomical: overall lowered cerebral volume; caudate, cerebellum...**
 - New findings with small samples regularly appearing
- **Key research: Shaw et al. (2006, 2007, 2009, 2012)**
 - Delayed patterns of cortical thickening/thinning in ADHD vs. comparison samples, longitudinally
 - 3.5-year delay for ADHD groups: Immaturity come to life
 - Complex patterns across later adolescence, too
- **Functional: most evidence relates to frontal-striatal paths in WM and response inhibition**
 - Until recently: must 'scan' during active cognitive performance
 - Default mode: reliable differences when S's not 'doing anything'; more 'intrusions' into task performance in ADHD

Risk, Etiology

- **Heritability and Genes:**
 - **H² of the two underlying dimensions, and of ADHD categorically, is near .8**
 - Such figures pertain to parent report of symptoms; but shared method variance/DZ twin contrast effects
 - Teacher ratings: Lower figures (still moderate to high)
 - **Given these estimates, common assumption that ADHD is 'fixed' and largely immutable**
 - I.e., "parenting can't matter"; parents as shepherds
 - Misreading of heritability

Other Risk Factors

- **Low birthweight**
 - Predicts ADHD, LD, Tourette's, CP, retardation
- **Teratogenic effects**
 - FAE: Many are nearly identical to ADHD symptoms
 - Smoking/nicotine: may be spurious
 - Biological + psychosocial effects of alcohol use in parents
- **Early parenting: No consistent evidence as causal**
 - Middle-class; few prospective studies from early years
- **Insecure attachment?**
 - Does NOT reliably predict later ADHD, independent of comorbid aggression
 - Re: aggressive behavior--interactions with temperament, later parenting, family structure/context, yield externalizing behavior

Risk Factors: Equifinality

- **Carlson et al. (1995):**
 - In low-income sample, early maternal insensitivity predictive of ADHD symptoms to a greater extent than early temperament
 - Need genetically informative design
- **Institutional deprivation (Kreppner et al., 2001)**
 - English and Romanian Adoptive Study Team: Inattention/overactivity associated with length of severe institutional deprivation in first 4 years
 - *Specific* effect: Conduct problems and internalizing symptoms not similarly associated with deprivation
 - Yet, different "feel" from typical ADHD presentation
 - AND, EF deficits may be distinct from 'typical' ADHD presentation
- Hence, *equifinality* apparent

Ultimate cause?

- The “real” cause of ADHD has to be compulsory education (same as for LD)
- Certainly, ‘attention’ or ‘impulse control’ genes have been around for the history of our species, but extremes not salient until we made children sit and learn to read
- Entirely possible to posit genetic, neurobiological, AND cultural forces as responsible

Developmental Paths

- **Preschool Manifestations (S. Campbell)**
 - Careful evaluations of 3 and 4 year olds
 - Prospective predictions to mid-late childhood:
 - PPP = .5! Hence, *multifinality* apparent
 - That is, suggestions of (a) “he’ll grow out of it” and (b) “medicate today” are each fraught with error
 - Predictors of continuation:
 - (a) severity of early ADHD
 - (b) negativity of early parent/child interaction, controlling for severity of child’s ADHD

Parenting Influences on Positive Peer Status

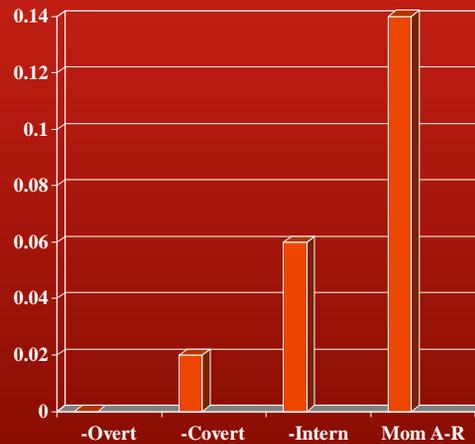
Hinshaw, Zupan, et al. (1997)

- **Aim: Predict peer acceptance from parenting**
 - Ideas About Parenting (Heming et al., 1989)
 - 3 factors = Authoritarian, Authoritative, Permissive
- **Authoritative Factor: 15 items**
 - *Warmth, Limits, Autonomy Encouragement--e.g.,*
 - "I encourage my child to be independent of me"
 - "I expect a great deal of my child"
 - "I have clear, definite ideas about childrearing"
 - "Raising a child is more pleasure than work"
 - "When I am angry with my child, I let him know"
 - "I reason with my child regarding misbehavior"

Results

- **Mothers of ADHD boys: lower on Authoritative (ES = .75)**
 - Yet variance in ADHD group equivalent to comparison group's
- **Tested predictive power of parenting factors, observed overt and covert behavior, and internalizing score (CDI, observed withdrawal) via hierarchical regressions**
 - Neither Authoritarian nor Permissive beliefs predicted peer nominations, but Authoritative beliefs did so (beta = .3), even with diagnostic group controlled

Explained Variance in Positive Nominations



Moderation and Implications

- Prediction applies only to ADHD group (beta = .30); for comparisons, beta = .00.
- Key theme: "firm yet affirming" parenting style
- Moral: forces that shape 'initial paths' may not be the same as those that maintain or exacerbate – or protect – later in development

Sex Differences/Female Presentation

□ Gender paradox?

- Group (sex) with lower prevalence must have more and 'stronger' risk factors

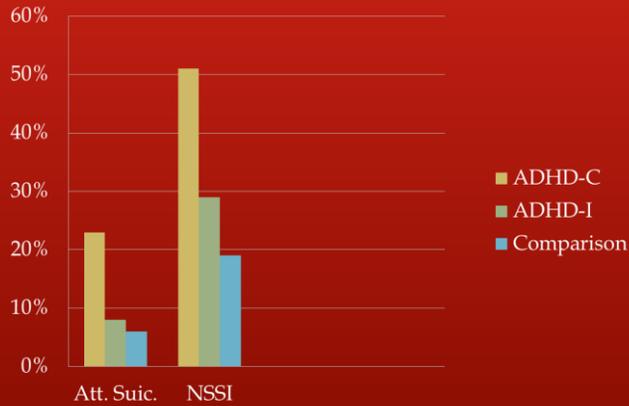
□ Our sample (BGALS):

- Largest in existence of preadolescent girls with ADHD (140, with 88 matched comparison girls)
- Baseline: marked impairments across symptoms, impairments, neuropsych measures
- Impairments maintained at 5-year follow-up
 - 11/11 domains, with widening gap in math

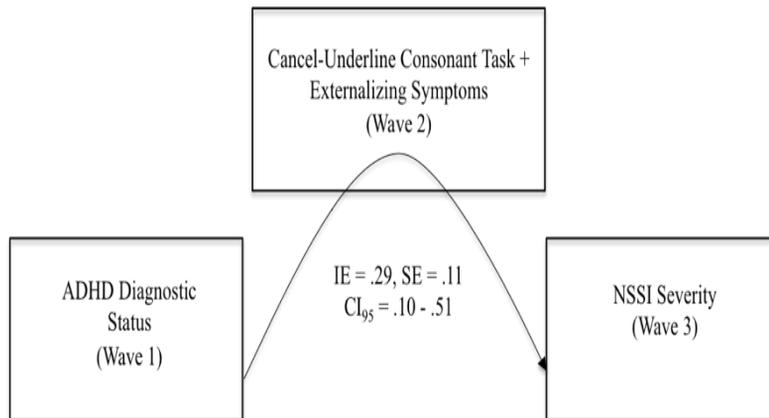
10-year follow-up

- 95% retention rate (vs. 92% at 5 year)
 - How? Facebook, relentless staff
- Despite 'losing' ADHD status majority of time, impairments maintain in academics, comorbidities, social functioning.
- Yet, self-harm findings:
 - *Suicide attempts*: 22% ADHD-C 8% ADHD-I 6% comparisons
 - *NSSI*: 51% ADHD-C 29% ADHD-I 19% comparisons

BGALS Follow-up: Self-harm At 10-year follow-up

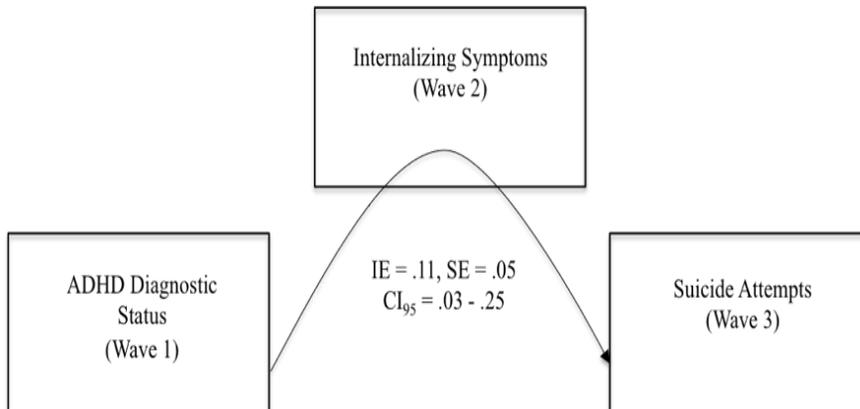


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MEDIATION: WAVE 1 ADHD STATUS TO WAVE 3 NSSI

Data represent indirect effect and standard errors using 10,000 bootstrap samples to obtain bias-corrected and accelerated 95% confidence intervals.



MEDIATION: WAVE 1 ADHD STATUS TO WAVE 3 SUICIDE ATTEMPTS

Data represent indirect effect and standard errors using 10,000 bootstrap samples to obtain bias-corrected and accelerated 95% confidence intervals.

Substance Use/Addiction as Outcomes

- **Well-documented that kids with ADHD are at high risk for substance use/abuse outcomes in adolescence**
 - Boys more so than girls (tobacco main risk for latter)
- **Mechanisms**
 - Inattention as strong a predictor as HI, intriguingly
 - School failure a potential mediator
 - Comorbid oppositionality and aggression a core path, too
 - "Self-medication" hypothesis?

Conclusions

- ADHD not a static “entity”/entirely related to underlying dimensions of Inattention and HI
- Different pathways lead to ADHD: Equifinality
- Differential outcomes from early ADHD symptoms: Multifinality
- Developmental, contextual factors crucial
 - Parenting styles, which may not be causal, are important determinants of outcome, even for a condition with $h^2 = .7/.8$
 - Systems, health-care, legislative, cultural, stigma-related factors related to underutilization and disparities in care
- Genes/biology, parenting/schooling, and cultural values INTERACT

Treatment Issues

- Only two empirically supported txs for ADHD:
 - Stimulant medication, behavioral intervention
 - CBT for adults getting close
- Exploratory/questionable/marginal treatments:
 - Diet: Restriction of additives may help especially with preschoolers; results disappointing with children > 6 years; sugar = reverse directionality
 - Biofeedback/Neurofeedback: Promising; better tested every year; expensive; will any 1:1 tx generalize beyond clinic?
 - Supplements (blue-green algae, etc.): Caveat emptor
 - Chiropractic, etc.: No shred of evidence for ADHD

Diversion

- Rates extremely high
- How effective are stimulants as 'neuroenhancers' for general population?
 - Smith & Farah (2011), *Psychological Bulletin*
 - Ilieva et al. (2013), *Neuropharmacology*
- Policy implications

Medication Treatment

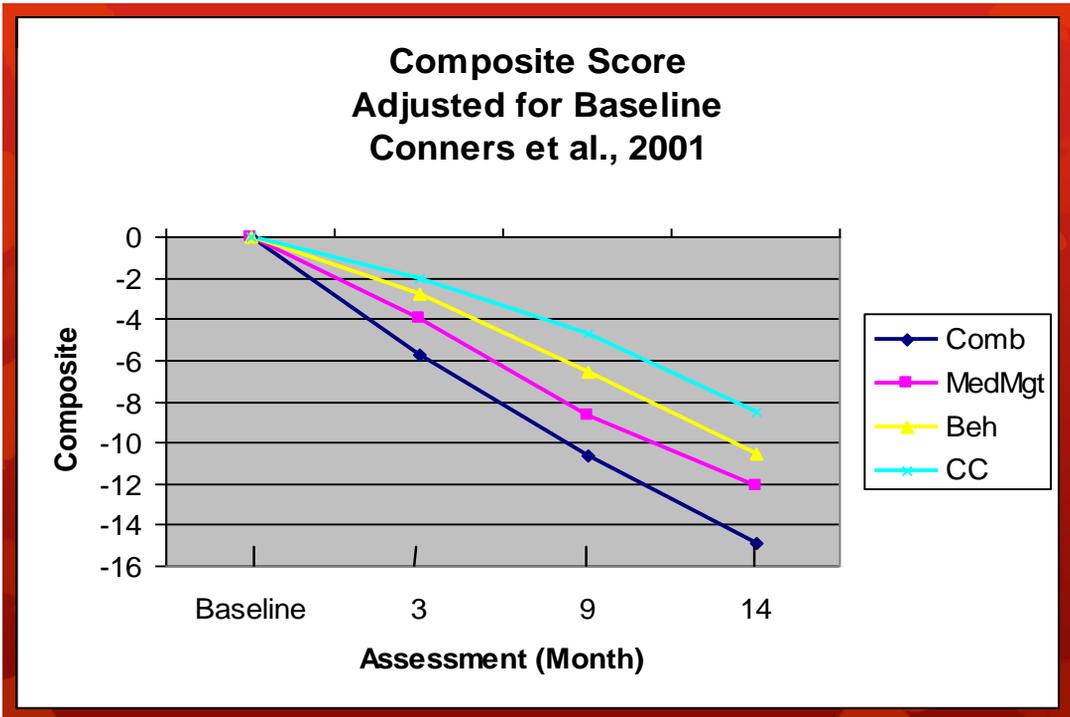
- **Stimulant medication: Best evidence**
 - Myth of "paradoxical" response
 - But, can be drugs of abuse, so use only when needed
 - Children do not appear to develop tolerance
- **Until a decade ago, limitation = 3-4 hr coverage**
 - Now, a range of longer-acting formulations
- **Alternatives to stimulants**
 - Atomoxetine
 - Antihypertensives
- **Low adolescent motivation**
 - At same time, stimulants as performance enhancers means that there's a real market

Behavioral Treatment

- **Integration of home and school components, along with child components (e.g., social skills)**
- **Need for parents and teachers to collaborate**
- **Manageable goals--Rome wasn't built in a day!**
- **Reasonable expectations and extrinsic rewards**
- **"Prudent" negative consequences (without anger) > positive consequences alone**
- **Gradual fading of extrinsic rewards**

Social Skills

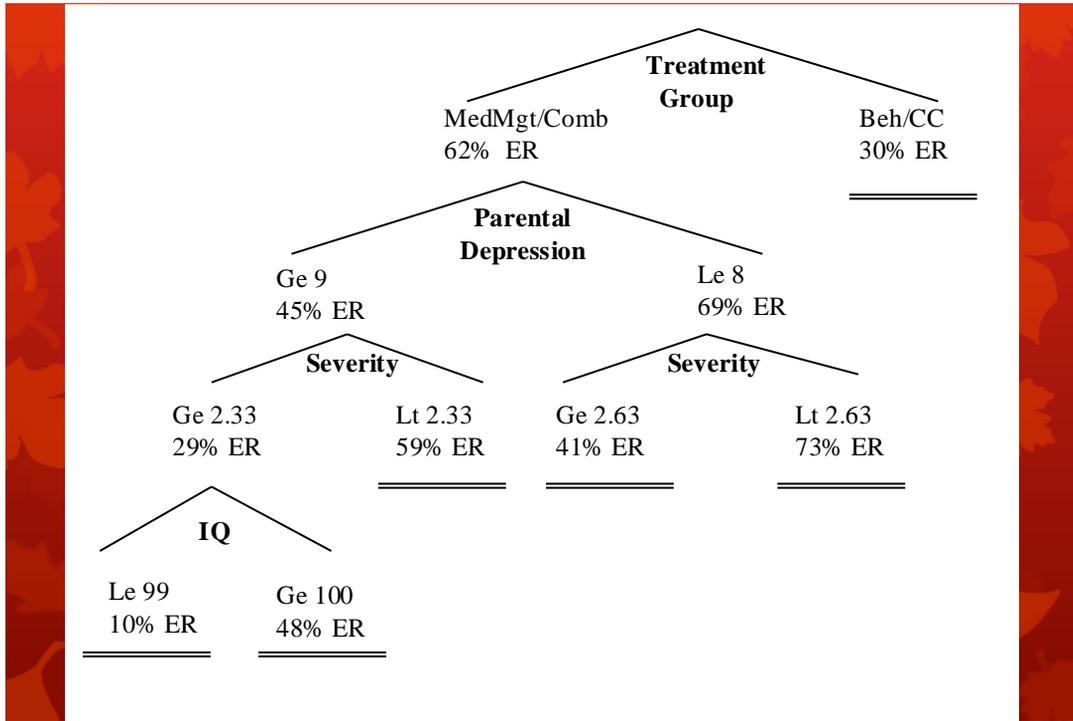
- **Paradox:**
 - **Can't teach peer-related skills 1:1 in adult treatment models, but potential for 'deviancy training' if groups of externalizing youth brought together**
- **Resolution:**
 - **Social skills intervention can work, but groups must be structured, leaders must provide clear incentives, and practice/rehearsal are crucial**



Moderators of Outcome

Owens, Hinshaw et al., 2003, *JCCP*

- What happens when multiple moderators tested simultaneously?
- ROC analyses of multiple moderators considered together (Kraemer software)...

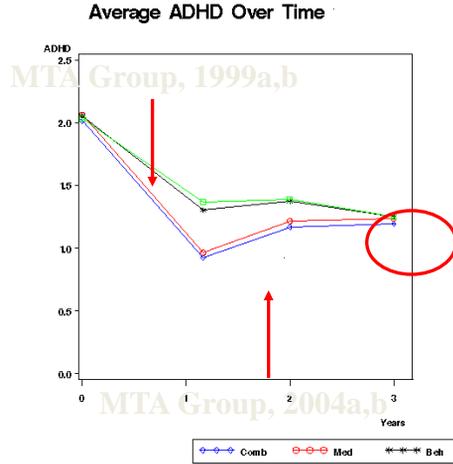


Follow-up: Beyond 14 months

- By 24 months, Beh and CC hold their own, but MedMgt and Comb worsen some
- By 3 years and now 6-8-10 years post-random assignment, the 4 treatment groups are equal
- Moral: Treatment needs to be sustained in order to continue benefits
 - ADHD more like diabetes than chronic illness
- GROWTH: Those on moderate-high doses, continuously, grow less rapidly (about 1 inch), but this effect may be subject to slight rebound
- Trade-off here

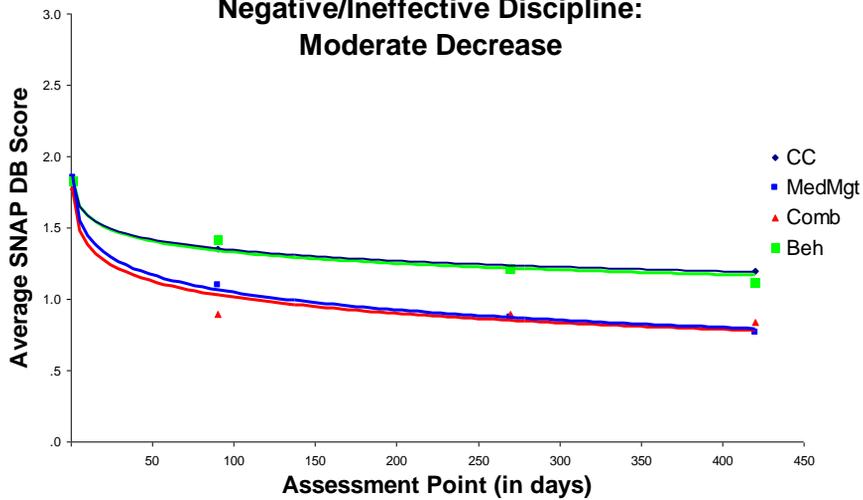
Convergence of Symptoms by 3/8/14 Years

Jensen et al. (2007), Swanson et al. (2007), Molina et al. (2009)

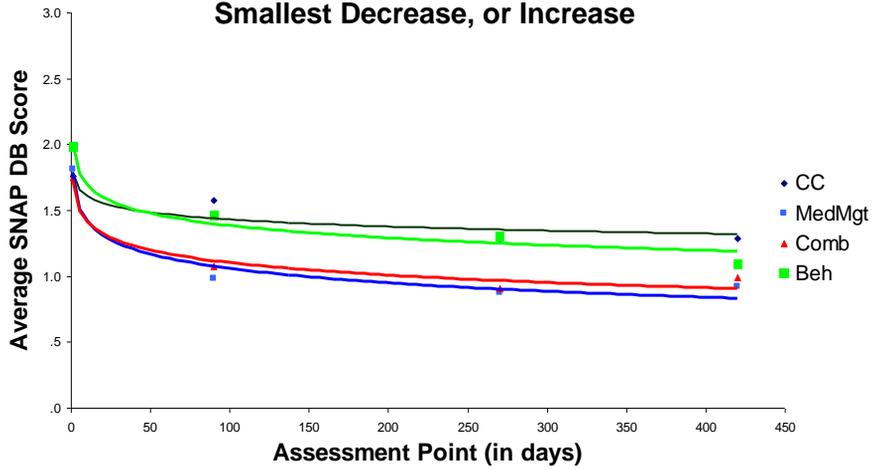


Randomized
Clinical Trial at
14-month
assessment:
Transition to
Naturalistic
Follow-up at
the 24-month &
36-month
Assessment

Outcomes Across 14 Months Teacher SNAP DB Negative/Ineffective Discipline: Moderate Decrease



**Outcomes Across 14 Months
Teacher SNAP DB
Negative/Ineffective Discipline:
Smallest Decrease, or Increase**



**Outcomes Across 14 months
Teacher SNAP DB
Negative/Ineffective Discipline:
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