

ADHD: What We Know and What We Need to Learn

Stephen Hinshaw
University of California, Berkeley

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Objectives

- **Lot of ground to cover:**
 - **Facts and myths**
 - **Variation and policy**
 - **Models**
 - **Sex Differences and female manifestations**
 - **Development**
 - **Treatments in brief**

1. ADHD: Key Themes

■ Newsworthy

- Ritalin available without a prescription as of 2011 in Israel
 - But then retrenchment; opposite policies that only specialists can prescribe
 - How much neuronenhancement do we want?
- 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 opinion pieces:
 - Sroufe, Kareishi, Friedman, Brooks: Back to the past

■ Careful assessment crucial

- 10' office visit not sufficient for thorough evaluation
- But, remember: 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

- **Continuum, not category**
- **Syndrome, not disorder**
 - Multiple causal pathways; risk factors interact/transact
- **Sex differences: 3:1 in representative samples**
 - Girls relatively more likely to show Inattentive type
 - BUT, development crucial: closer to 1:1 in adult ADHD

Tidal Wide, Variation, Policy

- **Diagnostic prevalence and medicated prevalence up drastically in 1990s**
 - Medicaid changes
 - IDEA: ADHD as 'other health impaired' condition
- **Then, National Survey of Children's Health**
 - Visser et al. (2010), CDD
 - Rate of ADHD diagnosis went up 22% from 2003 to 2007
 - In a number of states, the increase was over 40%
 - North Carolina: > 60% in those 4 years
 - Low income rates now equal to middle class
 - African-American rates now equal to White
 - Hispanic lower (but fast growing)

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

ADHD Cross Culturally

- Appears in nearly all cultures (that feature compulsory education)
- Polanczyk et al. (2007), *AJP*:
 - Diagnostic prevalence strikingly similar across world regions: 5%
 - Disparities linked to dx practices (ICD vs. DSM; informants; etc)
- Hinshaw et al. (2011)
 - Within-country variation high in many nations
 - However, treatments and systems of care vary radically across regions and cultures
 - **MANY NATIONS 'CATCHING UP' WITH U.S. MEDICATION TRENDS**
 - *But some not: politics, history, penetration of Big Pharma*

2. Nature of ADHD: 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**

Table 2. Measures of Dopamine D₂/D₃ Receptor and Dopamine Transporter Availability^a

Left Hemisphere	Availability, Mean (SD)		Effect Size ^b	95% Confidence Interval ^b	P Value ^c
	Controls	ADHD			
Dopamine D ₂ /D ₃ receptor					
Accumbens (Motivation)	2.85 (0.31)	2.68 (0.28)	0.61	0.06 to 0.30	.004
Caudate (Attention)	2.80 (0.49)	2.47 (0.61)	0.60	0.10 to 0.56	.005
Midbrain	0.28 (0.14)	0.18 (0.19)	0.57	0.02 to 0.17	.01
Hypothalamic region	0.12 (0.13)	0.04 (0.12)	0.61	0.02 to 0.12	.004
Dopamine transporter					
Accumbens (Motivation)	0.71 (0.16)	0.63 (0.11)	0.59	0.03 to 0.13	.004
Caudate (Attention)	0.66 (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

^a Measures of receptor and transporter availability ($BP_{ND} = DVR - 1$) obtained using an independent region-of-interest analysis to corroborate the statistical parametric mapping findings.

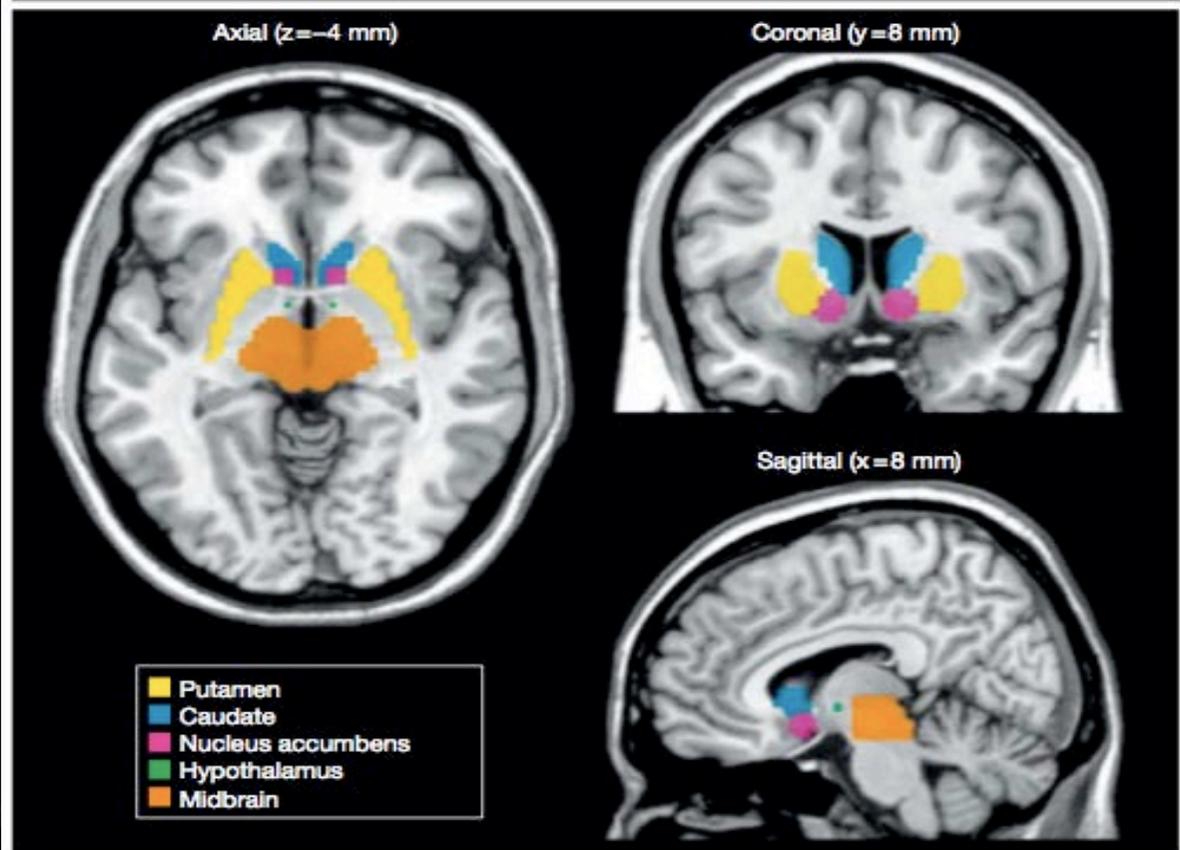
^b Mean differences and effect sizes for the comparisons between controls and participants with attention-deficit/hyperactivity disorder.

^c Comparisons correspond to independent samples 2-tailed *t* tests.



Transporter PET Image

Figure 1. Regions of Interest Used to Extract the D₂ / D₃ Receptor and Dopamine Transporter Measures



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

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“Combination models”

Beyond single cognitive functions...

- **Douglas: Self-regulation**
- **Sergeant: Cognitive energetic resources**
- **Barkley: response inhibition, leading to failure to invoke four core EFs**
- **Motivation/reward/cognitive process**
- **Greatly needed:**
 - **common language, tasks; dimensionalized look at symptoms; endophenotypes**

Neural profiles

- **Structural/anatomical: overall lowered cerebral volume; caudate, cerebellum...**
 - New findings with small samples regularly appearing
- **Key research: Shaw et al. (2006, 2009)**
 - Delayed patterns of cortical thickening/thinning in ADHD vs. comparison samples, longitudinally
 - Roughly 3 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

3. ADHD: Risk, Etiology

- **Heritability and Genes:**
 - **H² of ADHD 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 predict later ADHD**
 - **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

4. Developmental Paths

- **Infancy/temperament:**
 - Activity level (not major sex differences) vs. effortful control (end of first year of life; major sex differences)
- **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)

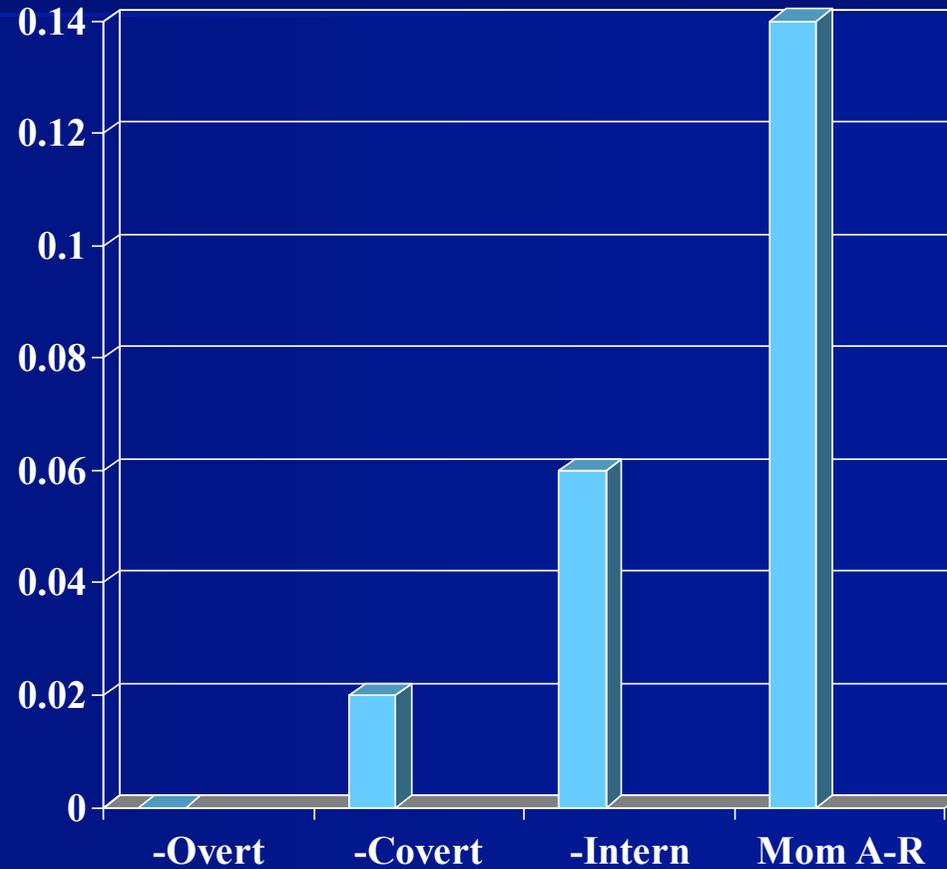
- **Aim: Predict peer acceptance from parenting**
 - Ideas About Parenting (Heming et al., 1989)
 - 3 factors = Authoritarian, Authoritative, Permissive

- **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

More on Developmental Paths: Long-term Outcomes

- ▣ Persistence of ADHD into adulthood = variable
 - Depends on measurement source
 - Barkley et al. (2002): < 5% to nearly 70%
 - ▣ Depends on informant...and developmentally sensitive criteria

- ▣ RESILIENCE: Does it exist?
 - Sobering data from Lahey and Hinshaw labs (Lee et al., 2008; Owens et al., 2009):
 - ▣ Very low percentages with good functioning across domains by adolescence (under 20% vs. close to 80% in comparisons)

Sex Differences/Female Presentation

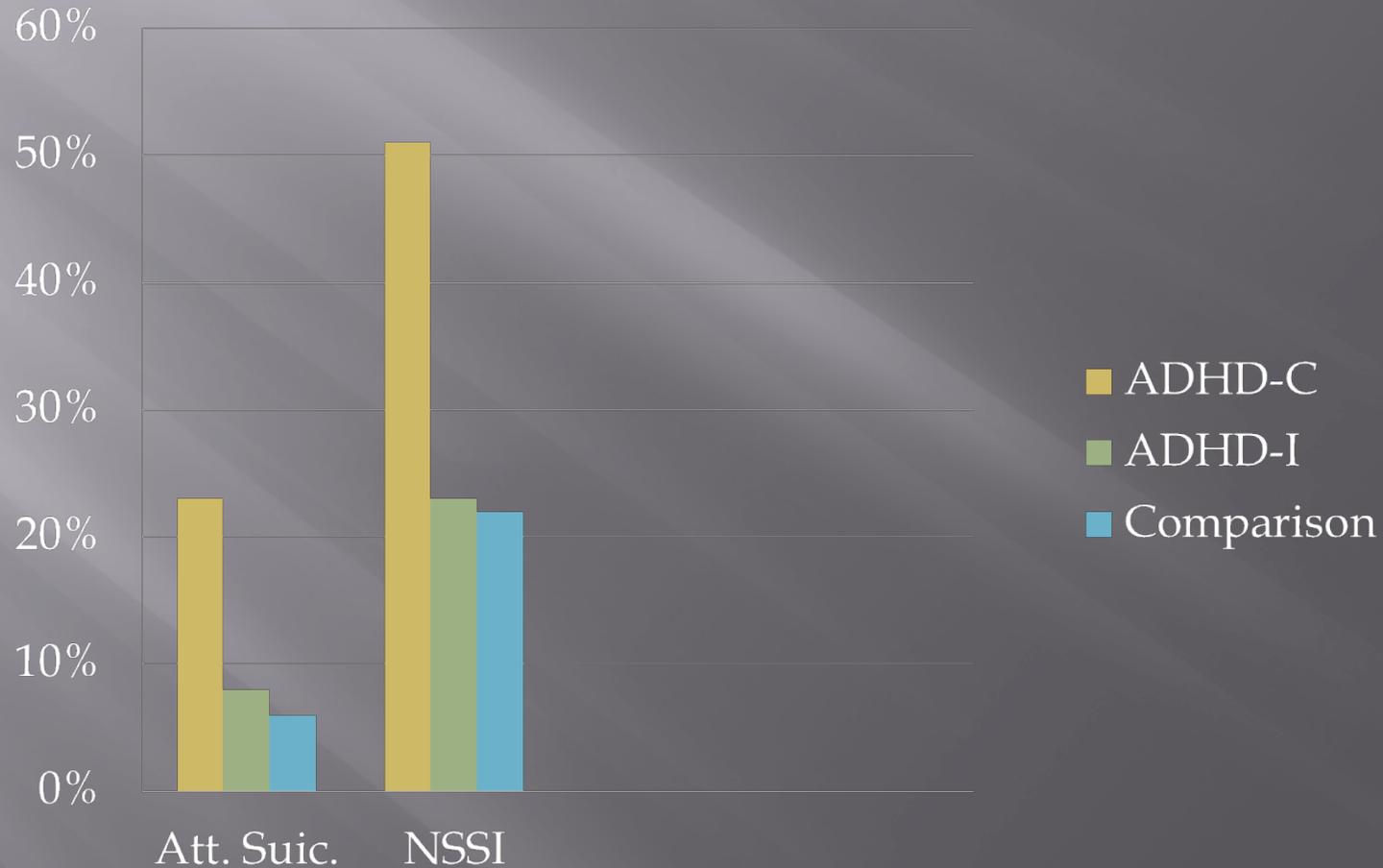
- ▣ Gender paradox?
 - Group (sex) with lower prevalence must have more and 'stronger' risk factors
- ▣ Our sample (BGALS):
 - Largest in existence of preadolescent girls with ADHD (140, with 88 matched comparison girls)
 - Baseline: marked impairments across symptoms, impairments, neuropsych measures
 - Impairments maintained at 5-year follow-up
 - ▣ 11/11 domains, with widening gap in math

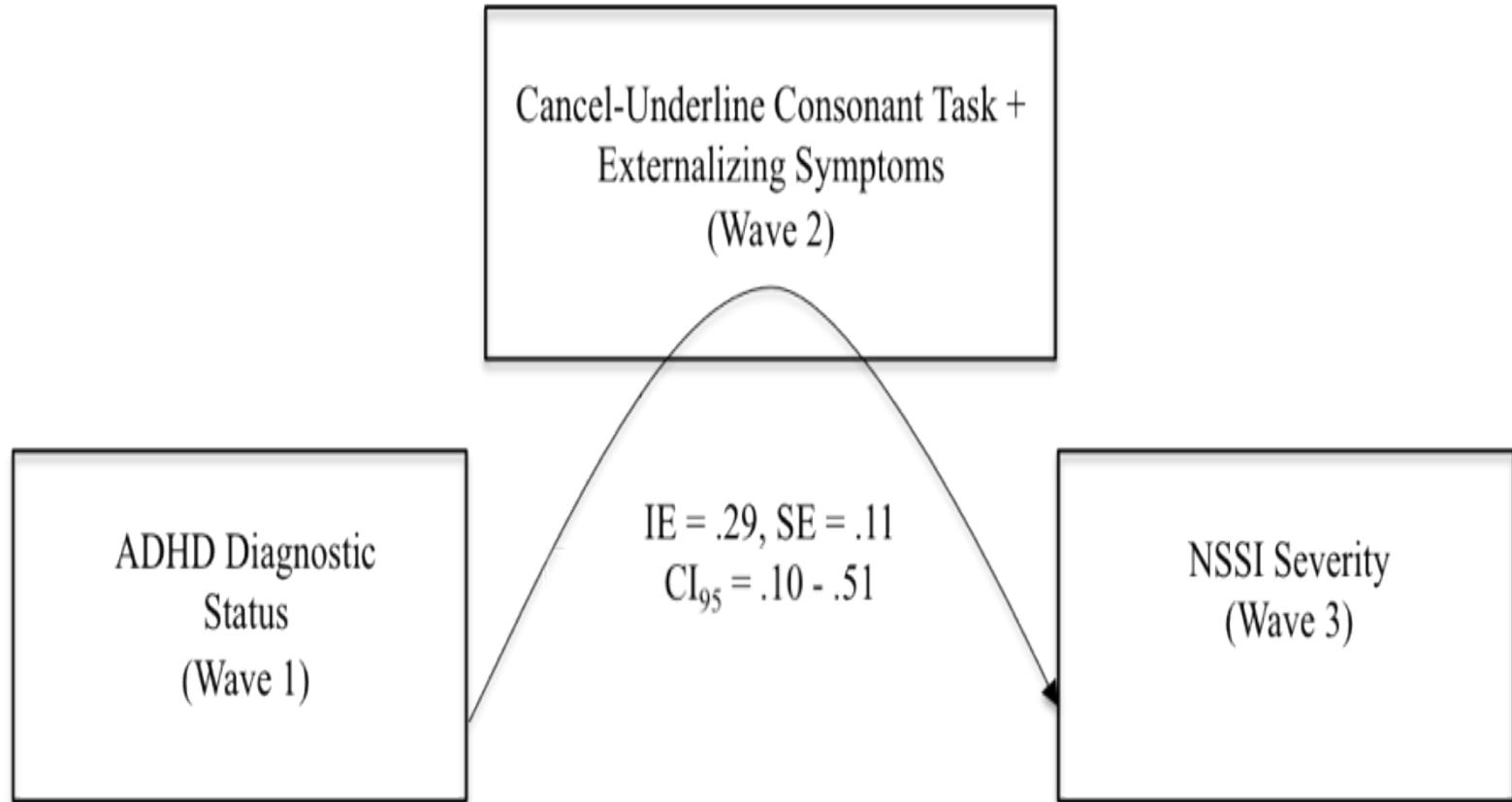
10-year follow-up

- ▣ **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 23% ADHD-I 22% comparisons**

BGALS Follow-up: Self-harm

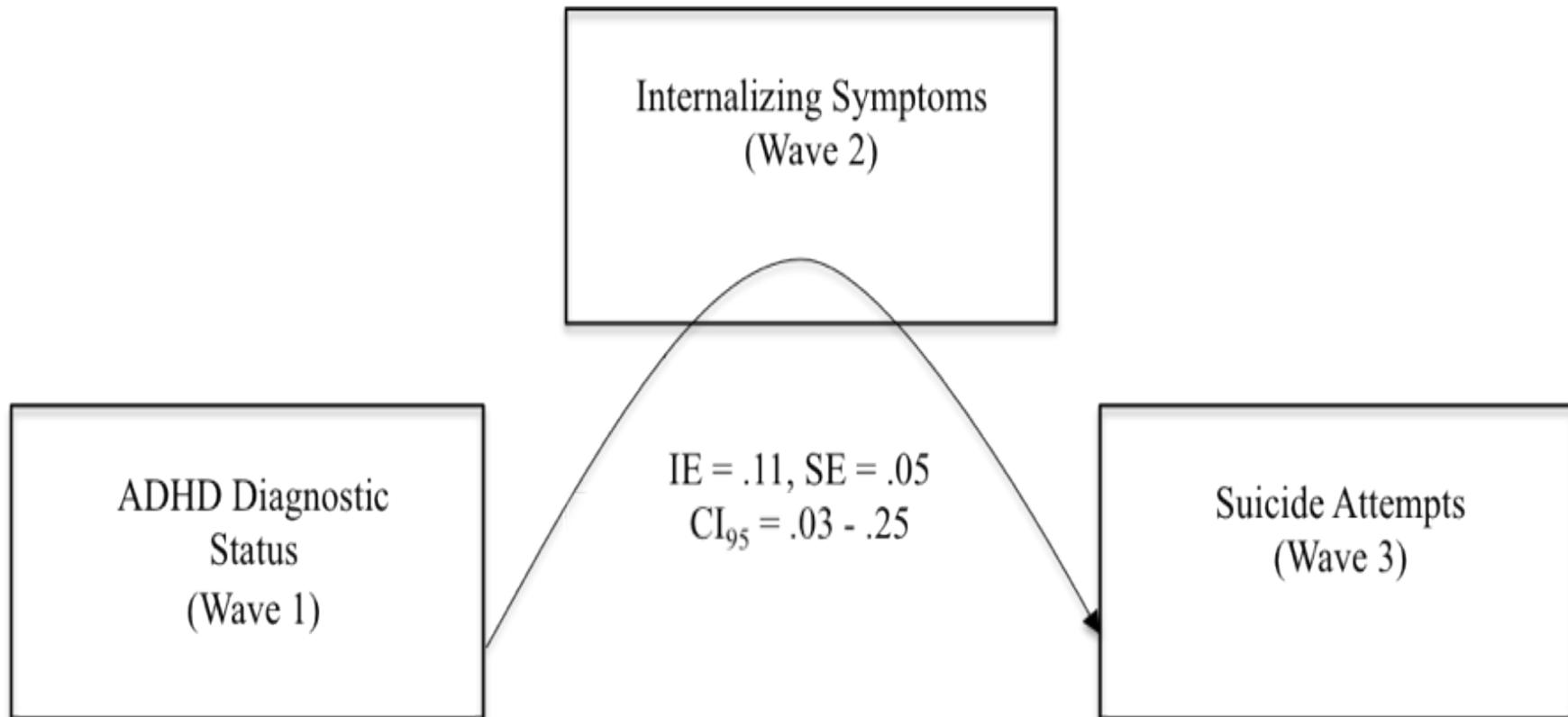
At 10-year follow-up





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.

Conclusions

- ▣ **ADHD: Not a static “entity”**
 - Didn't even delve into types (inattentive, HI, combined)
- ▣ **Dimensional/overlapping with normal distribution**
 - Need for translational research, linking research on basic attentional, inhibitory, cognitive, emotion processes to ADHD
- ▣ **Multiplicity of causal pathways: Equifinality**
 - Interactive in ways we are only beginning to know
 - Deprivation as well as DA genes as well as other neurobiological risks relevant for different cases

Conclusions - 2

- **Differential outcomes from early ADHD symptoms: Multifinality**
 - What predicts, moderates, mediates differential outcomes?
- **Need greater insights into peer deficits and social skills related to this population, as well as role of EF deficits for a subgroup; motivation making a major comeback**
- **Developmental, contextual factors crucial**
 - Parenting styles, which may not be causal, are important determinants of outcome, even for a condition with $h^2 = .7$
 - Systems, health-care, legislative, cultural, stigma-related factors related to underutilization and disparities in care

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**

Monitoring

- **Absolutely essential:**
 - **Must evaluate treatment effectiveness carefully!**
 - ***Medication:* Large range of effective dosages, little to predict which dose range will work for any given child**
 - ***Behavioral treatment:* Which rewards? Which punishments? Can tell only by monitoring...**
 - **Use narrow rating scales, with individualized items, to assess treatment responsiveness**

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**

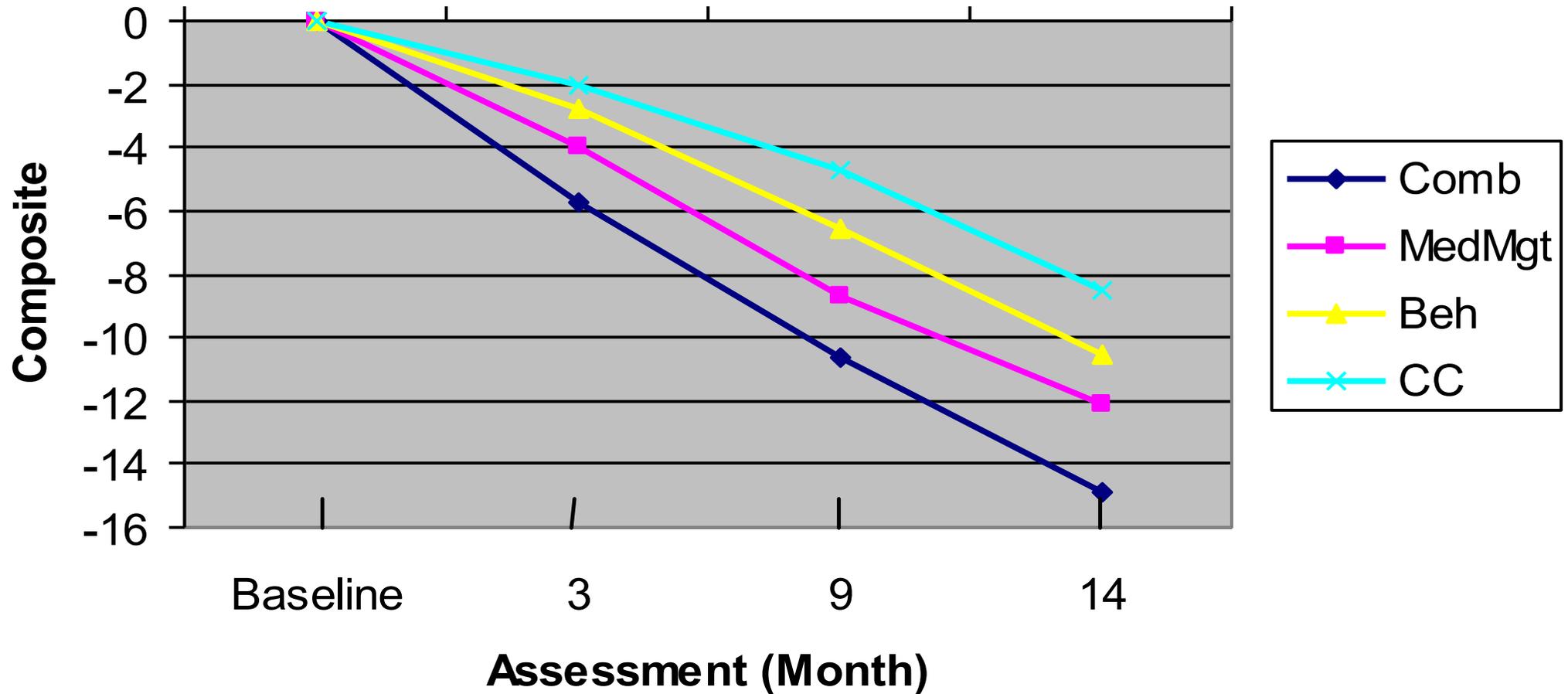
MTA Study - Design Summary

- **579 youth with ADHD-Combined, 7-10 yrs**
- **4 randomly assigned groups: 14 months of tx**
 - Medication management (MedMgt)
 - Intensive behavioral treatment (Beh)
 - Both treatments in combination (Comb)
 - Community care (tx as usual; CC)
- **Assessed at baseline, 3, 9, and 14 months**
- **Diverse sample, 7 sites in US/Canada**

MTA Study – Initial Findings

- **For symptoms of ADHD:**
 - MedMgt, Combined > Beh, CC
- **For impairments:**
 - Comb > CC, consistently
- **For getting youth close to “normal range”:**
 - Comb superior
 - 67% COMB
 - 55% MEDMGT
 - 34% BEH
 - 25% CC

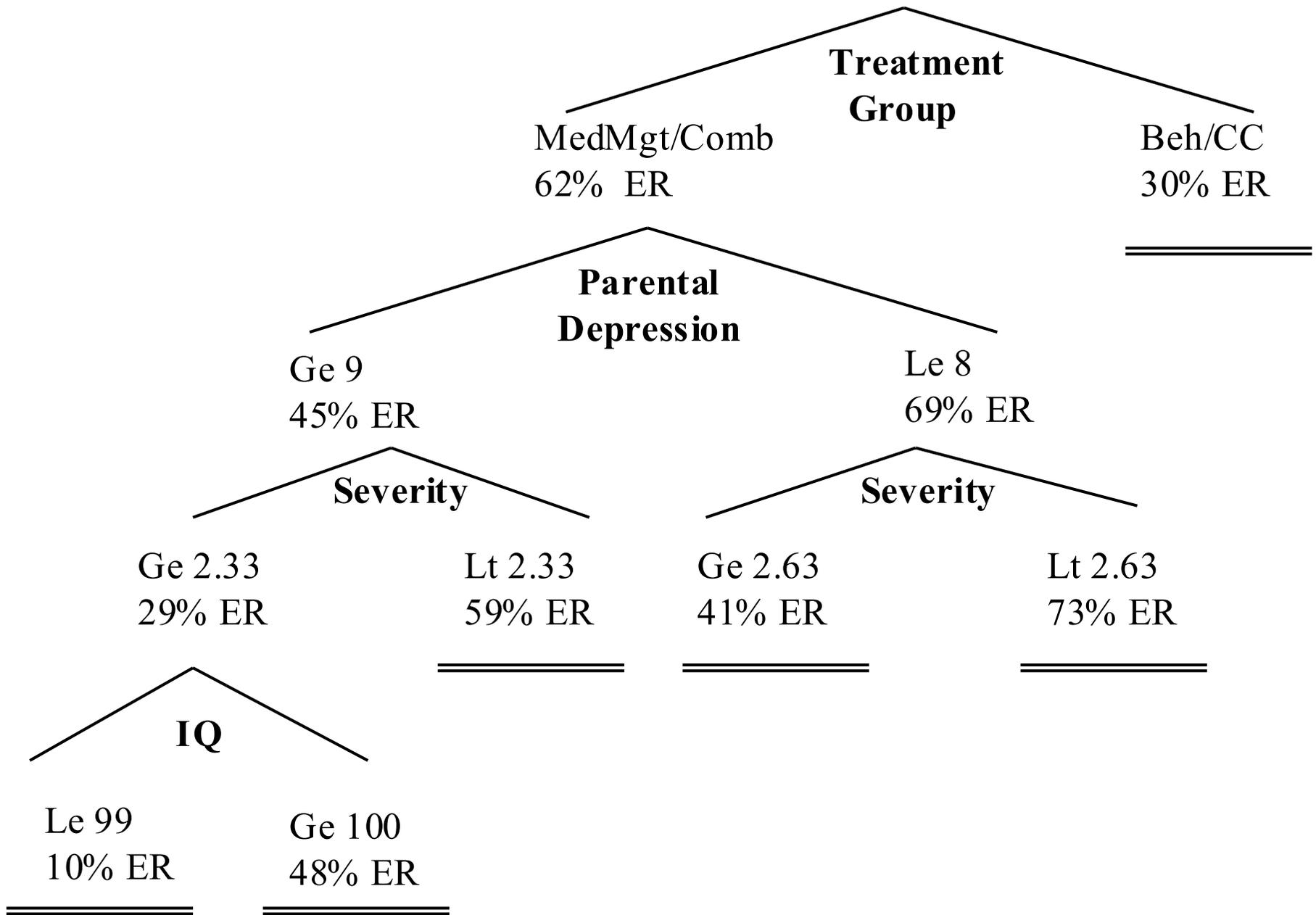
Composite Score Adjusted for Baseline Conners et al., 2001



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)...**



Longer-term 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**

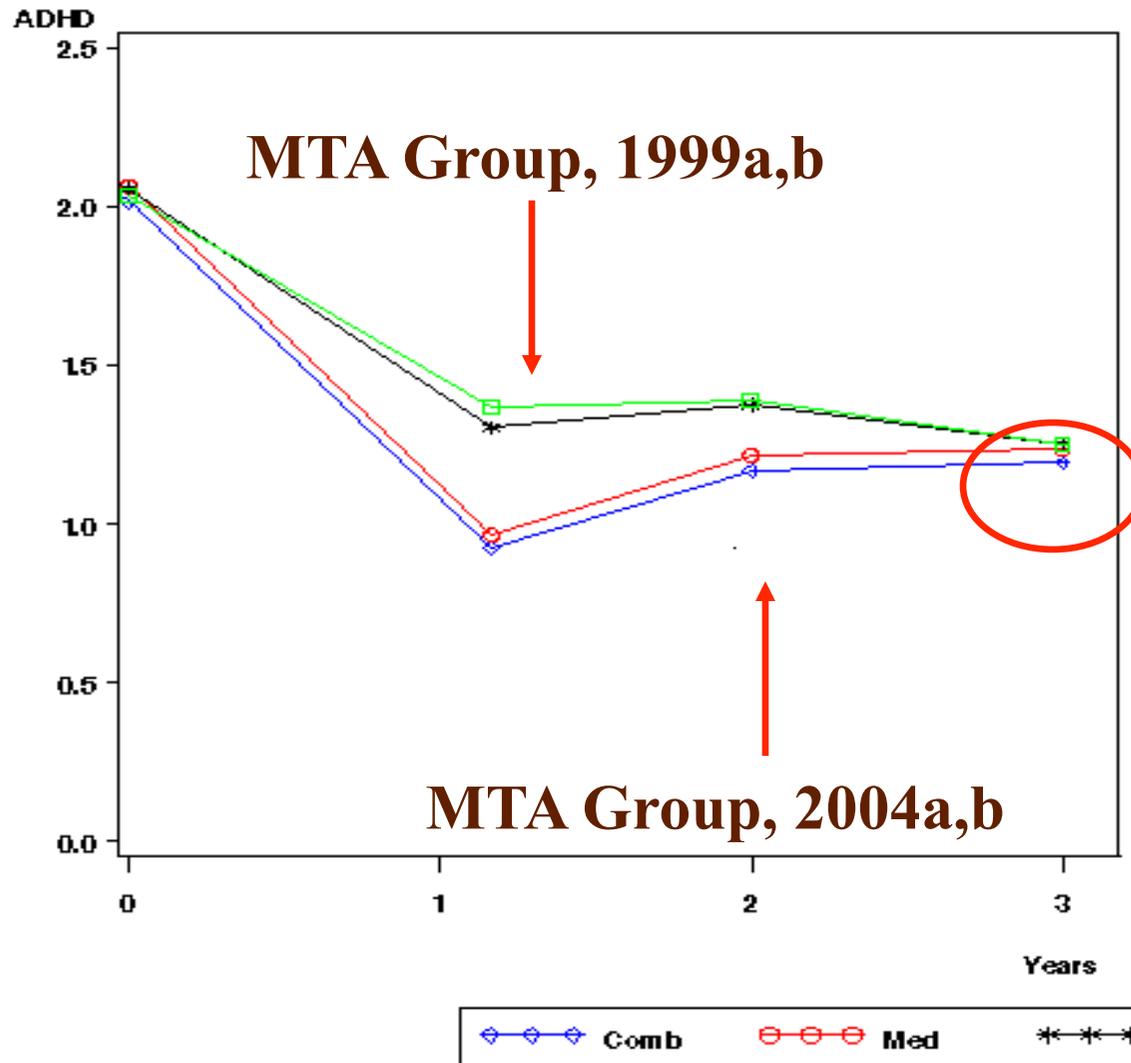
Does medication reveal 'late tolerance' ?

- **Acute tolerance with stimulants?**
 - Yes, with abuse; but what about oral dosing with kids
- **Long-developing tolerance**
 - Literature underdeveloped here
 - Stimulant use DOES decrease DA receptors, transporters
 - So, does that mean that, clinically, we reach a point where the meds don't work any more?
- **Another perspective: so what if there IS 'late tolerance' — treat during sensitive periods**

Convergence of Symptoms by 3/8 Years

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

Average ADHD Over Time



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

Family discipline as mediator

Hinshaw et al., 2000, JACP

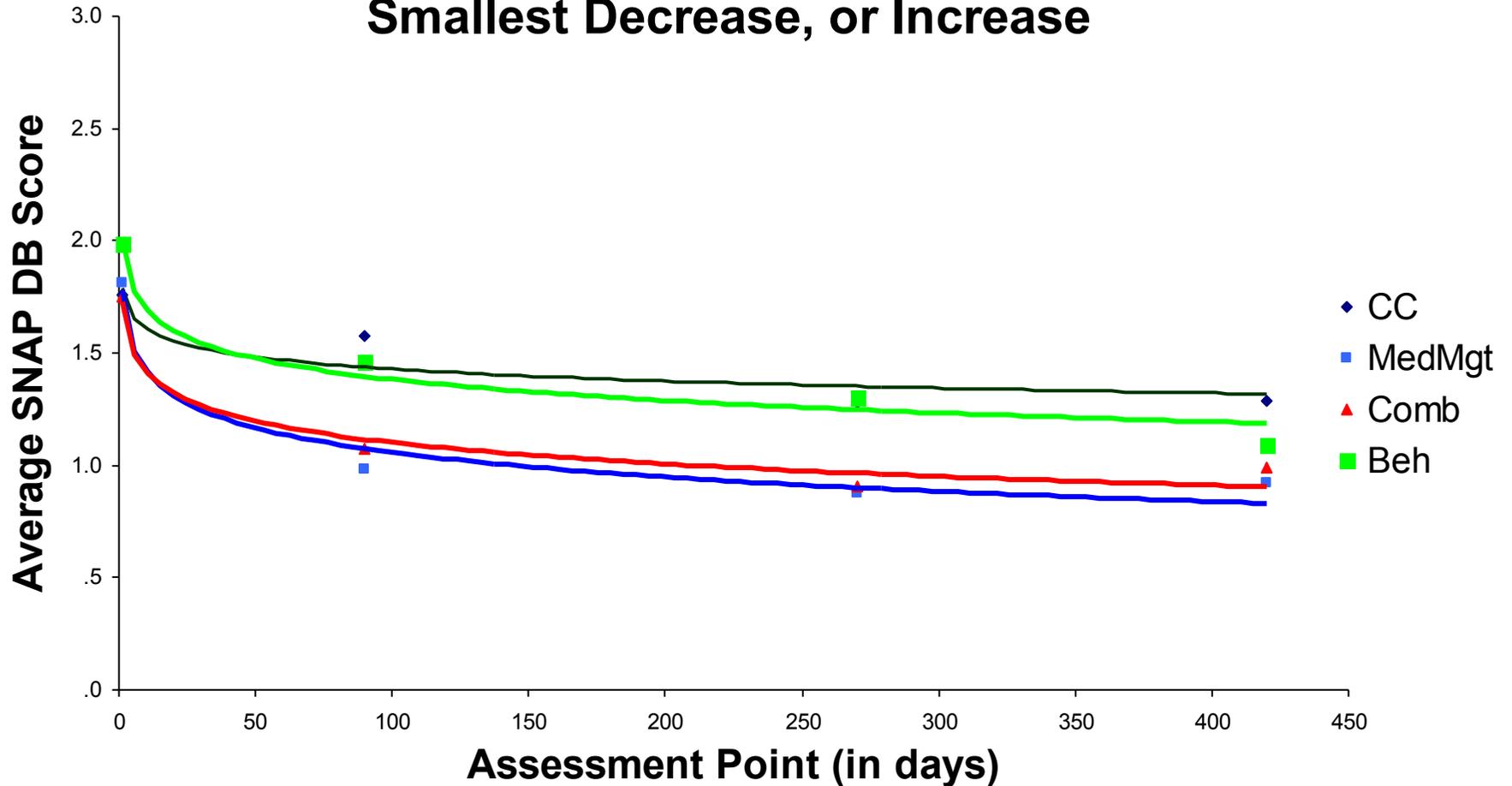
■ Theory:

- Family discipline has direct, causal influence on children's externalizing behavior patterns, through coercion, modeling, attachment failure
- Apply to ADHD, with high heritability?

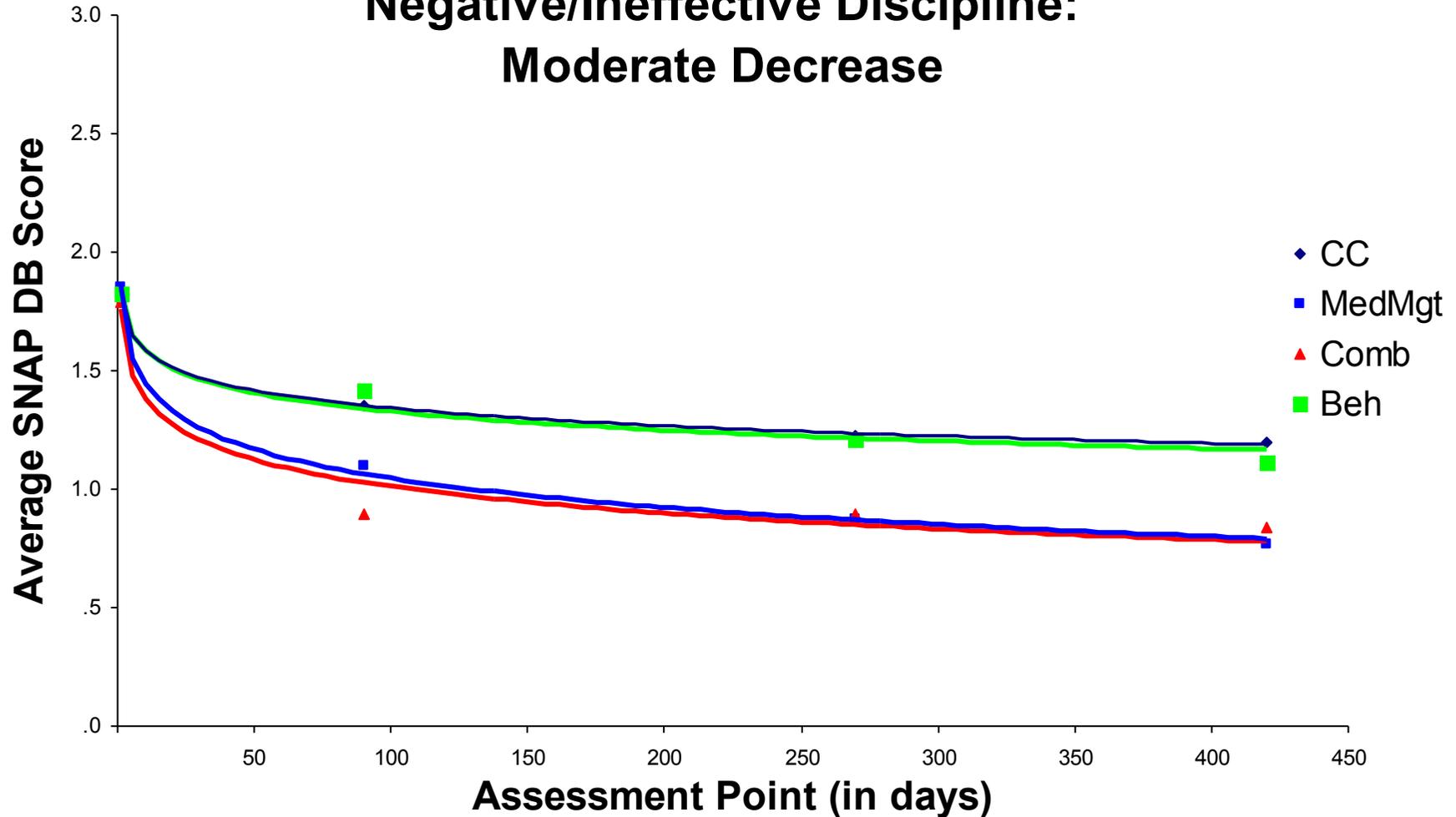
Prediction:

- Change in discipline style will serve as mediator of school outcomes--social skill and disruptive behavior--for behavioral tx components
- Negative/ineffective discipline passes mediator tests
 - Positive parenting and poor monitoring do not

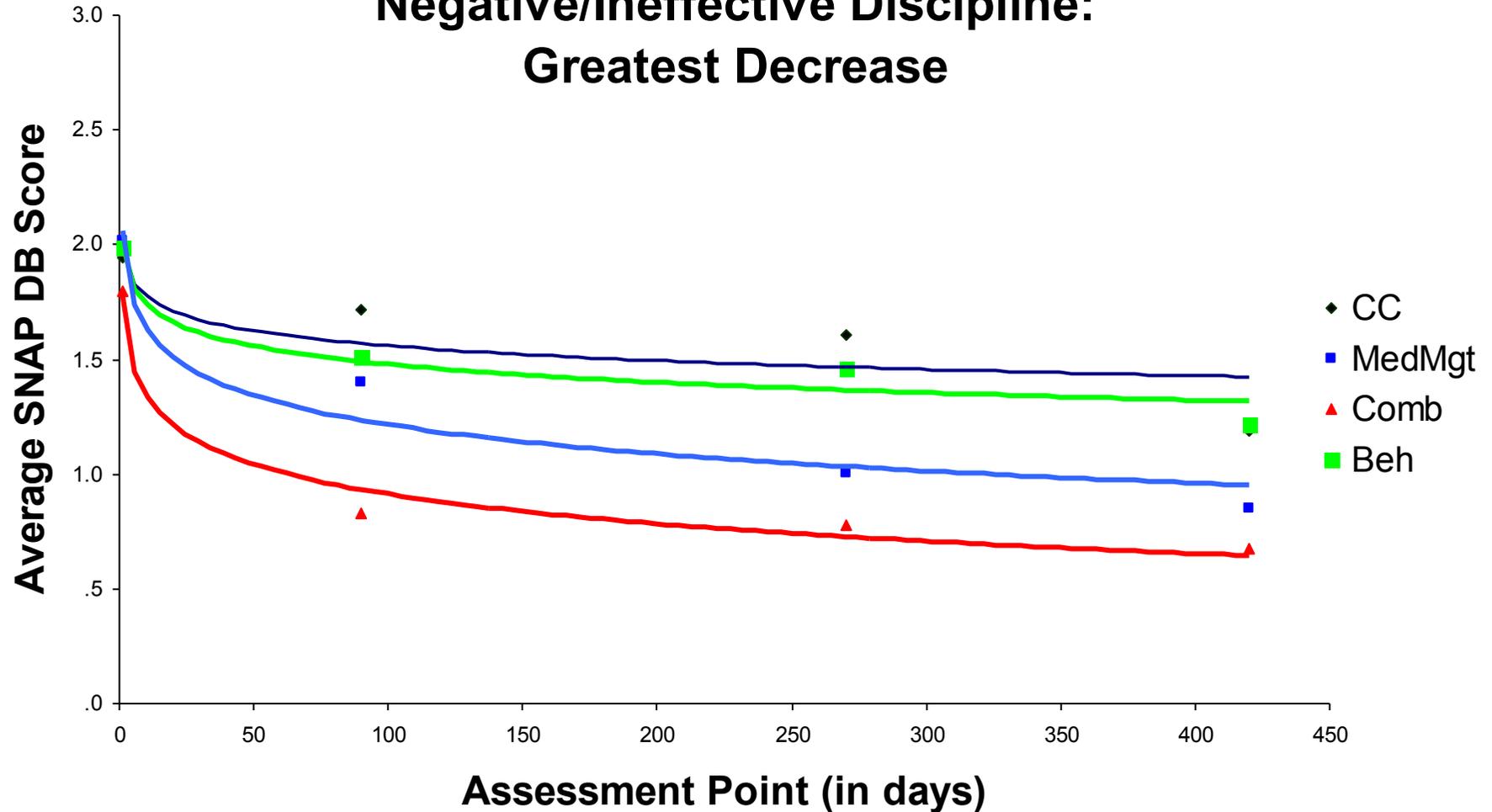
**Outcomes Across 14 Months
Teacher SNAP DB
Negative/Ineffective Discipline:
Smallest Decrease, or Increase**



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



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



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- **Help Group organizers**