2019 APSARD Annual Meeting Speaker Slides

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The Washington Marriott Wardman Park
Washington, D.C., USA

APSARD
The American Professional Society of ADHD and Related Disorders

Why are we (not) waiting? New perspectives from the neuroscience of impulsive choice in ADHD.

Edmund Sonuga-Barke

APSARD 2019

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RUNNING ORDER

- Impulsive choice: A motivational signature of ADHD?
- The pathophysiology of impulsive choice in ADHD
  - Plausible putative sources of impairment in ADHD
    - The usual suspects……
      - Deficient executive networks
      - Impaired reward circuits
    - …..and beyond
      - Affective hypersensitivity in limbic system
      - Default mode dysregulation
- What have we learnt about impulsive choice in ADHD?

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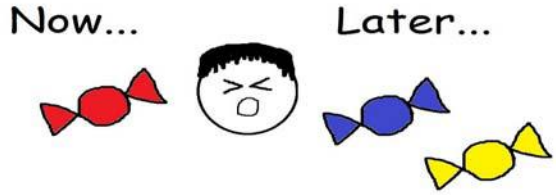
IMPULSIVE CHOICE: A MOTIVATIONAL SIGNATURE OF ADHD?



Present versus future reward choices are ubiquitous and important

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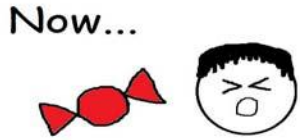
IMPULSIVE CHOICE: A MOTIVATIONAL SIGNATURE OF ADHD?



Is this the case for people with ADHD?

4

IMPULSIVE CHOICE: A MOTIVATIONAL SIGNATURE OF ADHD?

- People with ADHD respond differently to rewards (and punishers) compared to their peers – a longstanding idea.
- Inconsistent results - hard to pin down where the problem lies.
  - Diminished response to extrinsic reinforcement?
  - Impaired intrinsic reinforcement?
  - Deficits in linking actions to outcome (i.e. learning)?
  - Problems comparing different options (i.e., decision making)?
  - Problems with specific sorts of outcomes?

Sonuga-Barke, 2011

ADHD is associated in particular with problems dealing with delayed reward!

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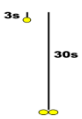
IMPULSIVE CHOICE: A MOTIVATIONAL SIGNATURE OF ADHD?

Marx et al. 2018

ADHD and the Choice of Small Immediate Over Larger Delayed Rewards: A Comparative Meta-Analysis of Performance on Simple Choice-Delay and Temporal Discounting Paradigms

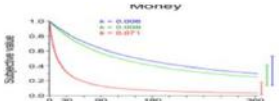
Ivo Marx[1], Thomas Hacker[2], Xue Yu[3], Samuele Cortese[4,5,6,7], and Edmund Sonuga-Barke[8]

Simple Choice Task



Always real delay (secs)– usually real rewards

Temporal Discounting Task



Often hypothetical delays (days)– sometimes real rewards.

Real time discounting delays in secs.

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IMPULSIVE CHOICE: A MOTIVATIONAL SIGNATURE OF ADHD?

Simple Choice Task
N=2666 (ADHD-1,425)

Temporal Discounting Task
N=1097(ADHD-561)

The two paradigms produced similar medium sized effect estimates.

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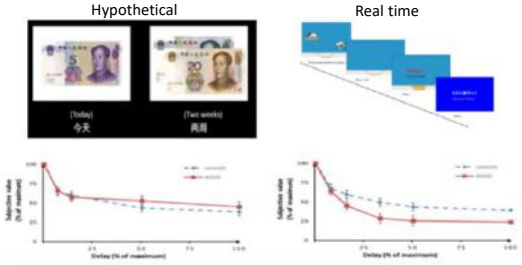
DIRECT COMPARISON OF HYPOTHETICAL AND REAL TIME DISCOUNTING

Yu et al. 2016

Hypothetical

Real time



There was no correlation between tasks.

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DIRECT COMPARISON OF SIMPLE CHOICE AND TEMPORAL DISCOUNTING

Yu et al. 2018

	Temporal discounting tasks		Single-choice tasks	
	TD-S	TD-L	SC-S	SC-L
Delays	0, 5, 10, 20, 30 s	5, 10, 20, 30, 60 s	13 s	25 s
Average delays	13 s	25 s	13 s	25 s
Size immediate reward	0, 2, 4, 6, 8, 10 cents	2, 4, 6, 8 cents	5 cents	5 cents
Block length	60 trials	40 trials	60 trials	40 trials
Total maximum gain	¥6	¥4	¥6	¥4

	ADHD (n = 17)		Controls (n = 24)	
	M	SD	M	SD
SC-L	26.3	23.3	44.3	28.5
TD-L	19.4	17.2	38.3	23.7
SC-S	80.1	37.9	54.2	33.1
TD-S	31.6	16.8	47.4	17.9

ADHD IC was limited to the long delay tasks.

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Impulsive choice in ADHD is a such A simple behaviour….

……It surely must have a simple pathophysiology

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But…….

…intertemporal choice is a complex multi-system and….

…ADHD is remarkably heterogeneous neuro-biologically.

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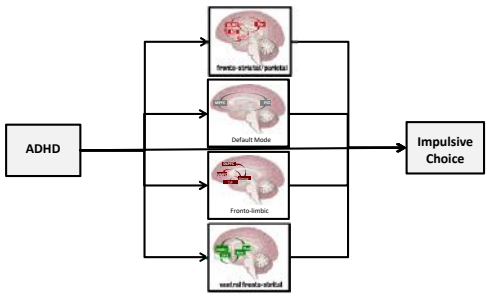
…AND BEYOND.



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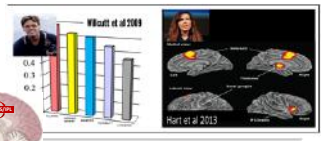
DEFICIENT EXECUTIVE NETWORKS – PLAUSIBLE TARGET

Necessary for LL choices

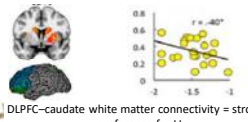
Required for -

- controlled evaluation of LL vs SS
- inhibition of pre-portent response to SS
- management of decision to delay

Deficient in ADHD

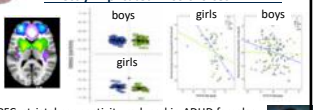


Directly implicated in LL choices



DLPFC–caudate white matter connectivity = stronger preference for LL
(van den Bos et al., (2014)

Directly implicated in SS choices in ADHD



DLPFC–striatal connectivity reduced in ADHD females and associated with stronger preference for LL – less so in ADHD (Rosch et al., 2018)

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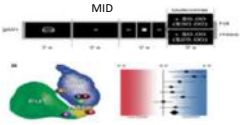
IMPAIRED REWARD CIRCUITARY – PLAUSIBLE TARGET

Necessary for LL choices

- Ventral striatum - Reward valuation and encoding
- Integration and computation of competing outcome value
- Integration motivation and emotion information
- OFC - Monitoring choice outcomes against expectations

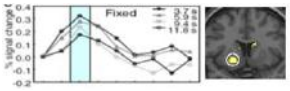
Deficient in ADHD

MID



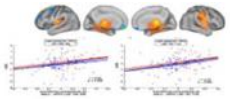
Hypoactivation to cues of delayed reward
(Plitcha et al. 2014)

Directly implicated in LL choices



VS BOLD declines with delay to future rewards
(Gregorios-Pippas, et al. 2009)

Directly implicated in SS choices in ADHD



Abberant VS connectivity is corelated with discounting (Dias, et al. 2013)

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THE INTERPLAY BETWEEN REWARD AND EXECUTIVE DEFICITS IN ADHD IC ONE OR TWO PATHWAYS?

- Empirical parsing of neuropsychological heterogeneity has led to multiple pathway models.
- The dual pathway model proposed that ADHD was underpinned by two dissociable patterns of impairment (Sonuga-Barke, 2002).
  - cognitive (underpinned by deficits in executive control)
  - motivational (underpinned by an aberrant response to delayed reward).
- Considerable neuropsychological support for variants of this model.
- Stevens et al (2018) set out to identify the neural markers of these pathways.

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REWARD AND EXECUTIVE DEFICITS IN ADHD IC ONE OR TWO PATHWAYS?

- Taxometrics identified three groups using data from TD and EF tasks.

Table 1. Taxometric-Derived ADHD Subgroup Characteristics Compared With Non-ADHD Control Participants by One-Way ANOVA and Post Hoc Pairwise Group Comparison Results

	Control Subjects (n = 134)	ADHD-EF (n = 40)	ADHD-EF-REW (n = 31)	ADHD-NONE (n = 46)	p Value	Planned Comparison
Delay Discounting, AUC	0.386 (0.02)	0.318 (0.04)	0.374 (0.05)	0.353 (0.04)	.139	HC > ADHD-EF-REW
Experiential Discounting, AUC	0.838 (0.01)	0.882 (0.03)	0.858 (0.03)	0.886 (0.02)	.059	–
SKIP Average RT, s	13.375 (1.67)	6.943 (0.31)	2.445 (0.43)	11.682 (2.82)	.023	HC > ADHD-EF-REW
Stop Signal RT, ms	278.8 (5.96)	295.9 (10.72)	347.4 (12.24)	287.2 (10.09)	<.001	HC > ADHD-EF-REW
IMT Impulsivity, Ratio	0.506 (0.02)	0.674 (0.03)	0.806 (0.03)	0.532 (0.03)	<.001	HC > ADHD-EF-REW, ADHD-EF
DMT Impulsivity, Ratio	0.495 (0.03)	0.731 (0.05)	1.092 (0.06)	0.596 (0.05)	<.001	HC > ADHD-EF-REW, ADHD-EF
MMF Errors, n	16.993 (1.15)	33.771 (2.06)	36.954 (2.36)	23.537 (1.93)	<.001	HC > all 3 ADHD
CPT-II Commissions, n	20.426 (0.57)	23.536 (1.02)	26.61 (1.17)	18.529 (0.96)	<.001	HC > ADHD-EF-REW, ADHD-EF

- *No difference in symptom profiles between the different sub-groups.*
- *Compared groups' brain activity during GNG and adapted MID.*

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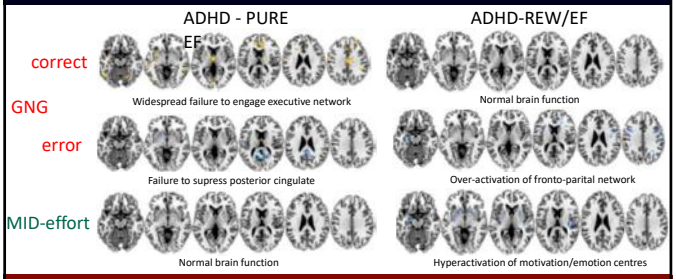
REWARD AND EXECUTIVE DEFICITS IN ADHD IC ONE OR TWO PATHWAYS?



Different neural sources of EF deficits in the two groups – suggesting a failure to regulate frontal activity during task performance marks the REW/EF group.

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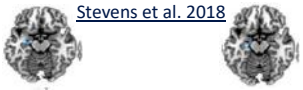
LIMBIC HYPERSENSITIVITY – A PLAUSIBLE CANDIDATE TO EXPLAIN IC IN ADHD

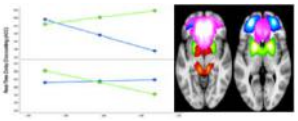
- ***Evidence implicating amygdala in ADHD IC keeps popping up.***

Stevens et al. 2018



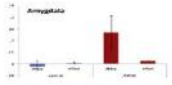
Hyperactivity during MID-effort and GNG errors

Rosche et al. 2018



Amygdala-DLPFC connectivity = more real time discounting in ADHD

Mies et al. 2018



Hyperactivated during delay but not effort discounting.

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A key function of the amygdala is processing and encoding aversive experiences to facilitate their avoidance

Could recent evidence relating TD to amygdala suggest that IC is driven more by the emotional response to delay than impaired executive control or altered reward processing?

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THE DELAY AVERSION HYPOTHESIS OF IC CHOICE IN ADHD

- For ADHD children the experience of waiting during the delay before outcomes or events is especially aversive.
- delay imposition is a negative reinforcer and delay escape a potent reinforcer.
- ADHD IC is a functional expression of aversion to delay – because it allows its avoidance.

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WHERE DID THE NOTION COME FROM?

We ran a series of choice experiments in the 1990s.

ADHD Individuals can wait for delayed rewards.

But they chose SS when it reduces overall delay.

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THE DELAY AVERSION HYPOTHESIS OF IC CHOICE IN ADHD

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Neurobiological Prediction

- Cues of delay elicit activation within the brain's emotional circuits which mediates delay aversion and IC.

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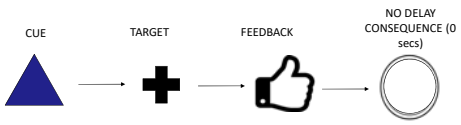
S AMYGDALA HYPER-RESPONSIVE TO CUES OF IMPENDING DELAY?

Van Desel et al. 2018

NO DELAY TRIAL



THE EDI (ESCAPE DELAY INCENTIVE TASK)

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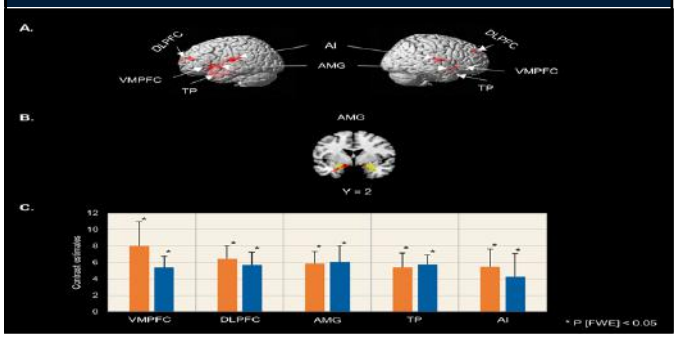
CERTAIN DELAY > NO DELAY CUES – ADHD VERSUS CONTROL



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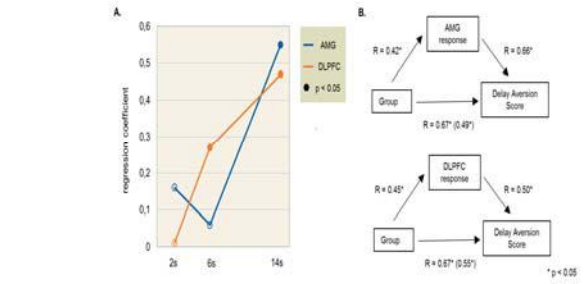
AMYGDALA AND DLPFC MEDIATE THE ADHD DELAY AVERSION PATHWAY.



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HOW SPECIFIC ARE THE EFFECTS? - DELAY AVERSION V LOSS AVERSION

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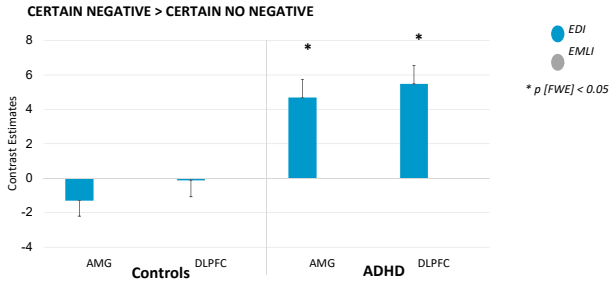
HOW SPECIFIC ARE THE EFFECTS? - DELAY AVERSION V LOSS AVERSION



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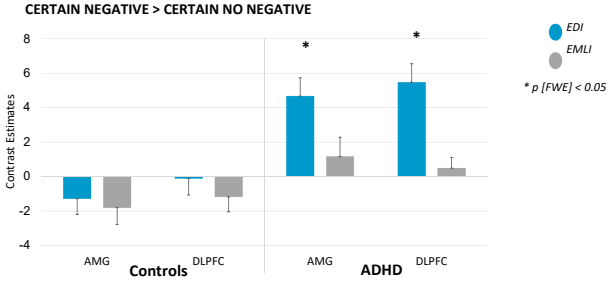
HOW SPECIFIC ARE THE EFFECTS? - DELAY AVERSION V LOSS AVERSION



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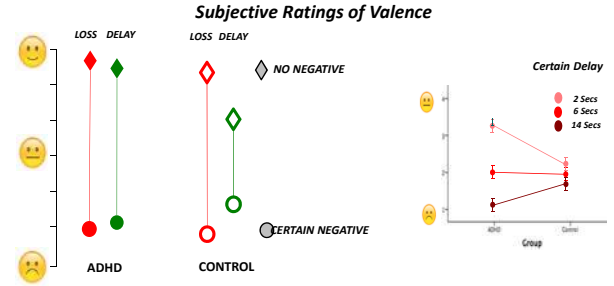

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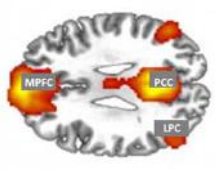
DEFAULT MODE DYSFUNCTION - A PLAUSIBLE CANDIDATE TO EXPLAIN IC IN ADHD



PSYCHOLOGICALLY A DOUBLE EDGED SWORD

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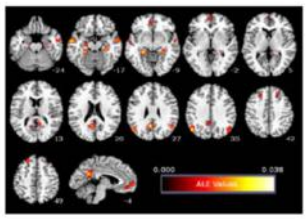
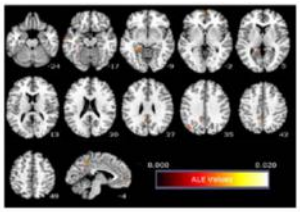
DEFAULT MODE DYSFUNCTION - A PLAUSIBLE CANDIDATE TO EXPLAIN IC IN ADHD

Stawarczyk et al. 2015

EPISODIC FUTURE THOUGHT



MIND WANDERING



STRUCTURED EPISODIC THOUGHT ACTIVATE SIMILAR DMN REGIONS

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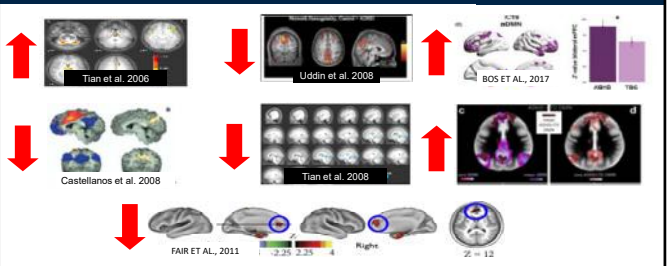
DISTURBED/IMMATURE DMN CONECTIVITY IN ADHD

Metin et al. submitted



Meta-analysis of 17 studies identified PCC as the source of dysconnectivity

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Given the plausibility that LL choice requires the effective imagining of future events we tested the relationship between ADHD, default mode connectivity, temporal discounting and mind wandering.

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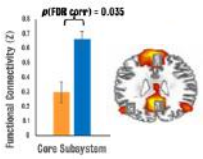
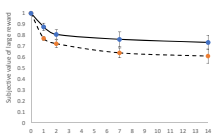
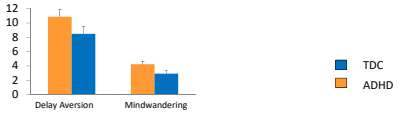
DOES REDUCED DEFAULT MODE INTEGRITY MEDIATE THE RELATION BETWEEN ADHD TEMPORAL DISCOUNTING AND MIND-WANDERING

Broulidakis et al. in prep



ADHD associated with less DMN FC, greater TD, more delay aversion and mindwandering





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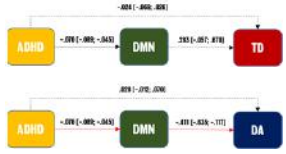
DOES REDUCED DEFAULT MODE INTEGRITY MEDIATE THE RELATION BETWEEN AND TEMPORAL DISCOUNTING AND MIND-WANDERING

Broulidakis et al. in prep

Reduced DMN FC is associated with greater TD (p=.02) and more delay aversion (p=.001) but not more mind-wandering (p=.54).



Reduced DMN connectivity appears to moderate the relationship between ADHD delay aversion but not temporal discounting.

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WHAT HAVE WE LEARNT ABOUT IMPULSIVE CHOICE IN ADHD?

- IC in ADHD is observed for both real and hypothetical choices – but only a sub-group are likely effected.
- Pathophysiologically it is likely to turn out to be a heterogeneous and complex phenomena – although little direct evidence so far.
- Disrupted reward and executive systems may play a role but perhaps not in the way predicted.
- Limbic system hyper-reactivity to delay appears central.
- Given its role in episodic prospection the DMN may play a role – although initial evidence suggests a strong link with delay aversion.

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APSARD 2019
Washington DC

Pills, Skills and Behaviours: Exploring the Psychopharmacology of Impulsivity

(or how can we help them wait)

David Coghill
Financial Markets Foundation
Chair of Developmental Mental Health

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Disclosures

Source	Consultant	Advisory Board	Speaker	Research
Lilly		X	X	X
Janssen		X	X	X
Medice			X	X
Shire / Takeda	X	X	X	X
Servier			X	
Australian Government				X
NHMRC				X
NHS				X
NIHR				X
EU FP7				X

2

Outline

What is impulsivity – slight recap

Medication effects on symptoms (and why never to trust your clinical impressions)

Medication effects on Impulsivity

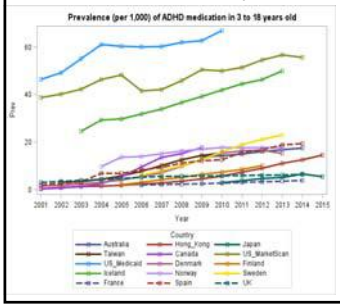
- Inhibitory Control
  - What are the relationships between symptoms and cognition?
- Impulsive choice
  - Delay discounting
  - Delay aversion
  - Head to head
- Decision making

Medication effects on the DMN

Where to from here?

3

There is considerable cross national variability in prescribing for ADHD

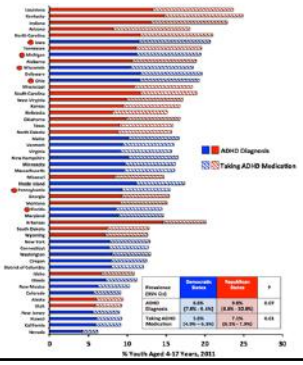


Country/Region	Cross sectional Prevalence (2010)
Australia	**1.4%**
United States	6.7%
Canada	1.8%
UK	0.6%
Northern Europe	1.9%
Western/Southern Europe	0.7%
Asia-Pacific	0.9%
Total	**1.9%**

4

Relative rates of parent-reported attention-deficit /hyperactivity disorder (ADHD) diagnosis and medication treatment in the US by political affiliation.

Prevalence (95% CIs)	Democratic States	Republican States	P
ADHD Diagnosis	8.1% (7.1% - 8.8%)	9.9% (9.3% - 10.6%)	0.0045
Taking ADHD Medication	5.1% (4.4% – 5.7%)	7.2% (6.5% - 7.8%)	0.0001



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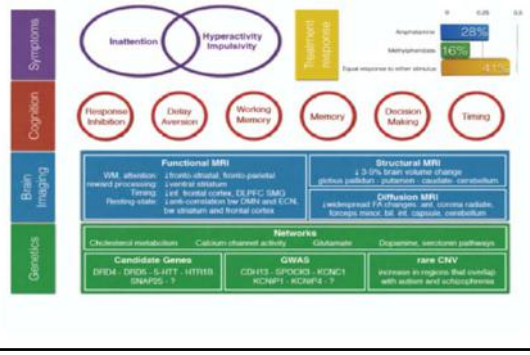

6

Impulsivity comes in may different colours and it is very unlikely that these disparate behaviours reflect a unifying underlying behavioural process (Ho et al, 1999)

The emission of premature responses in schedules in which reinforcement is made contingent upon pausing (Gordon 1979; Sagvolden and Berger 1996),

Premature termination of sequences of responses (Evenden 1998),

Emitting short latency incorrect responses in conditional discrimination tasks (Kagan 1966; Evenden 1999),

Failure of responding to decline in extinction schedules (Berger and Sagvolden 1998; Sagvolden et al. 1998),

Impaired temporal differentiation of responding (Walker 1982; van den Broek et al. 1992),

Choice of smaller earlier reinforcers in preference to larger delayed reinforcers (Ainslie 1975; Herrnstein 1981.

7

7

Impulsivity comes in may different colours and it is very unlikely that these disparate behaviours reflect a unifying underlying behavioural process (Ho et al, 1999)

Proposed Deficits

Behavioural Inhibition (Soubrié 1986)

Waiting Capacity (Thiébot et al. 1985)

Behavioural Switching (Ho et al. 1998)

Tolerance of delay of gratification (Mischel 1966; Logue 1988)

Timing (Siegman 1961; Barratt 1981)

8

8

Impulsivity in the clinical context

Criteria for ADHD Diagnosis: DSM-5

Inattention
- ❑ Lack of attention to details, makes careless mistakes
- ❑ Difficulty sustaining attention
- ❑ Does not listen when spoken to directly
- ❑ Trouble completing or finishing job tasks
- ❑ Problems organizing tasks and activities
- ❑ Avoids or dislikes sustained mental effort
- ❑ Loses and misplaces things
- ❑ Easily distracted
- ❑ Forgetful in daily activities

Emotional Lability – Emotional Impulsivity?

Hyperactivity
- ❑ Fidgetiness (hands or feet) or squirming in seat
- ❑ Leaves seat when not supposed to
- ❑ Restless or overactive
- ❑ Difficulty engaging in leisure activities quietly
- ❑ Always 'on the go'
- ❑ Talks excessively

Impulsivity
- ❑ Blurts out answers before questions have been completed
- ❑ Difficulty waiting in line or taking turns
- ❑ Interrupts or intrudes on others when they are working or busy

American Psychiatric Association. Diagnostic and Statistical Manual (DSM) of Mental Disorders. 5th Edition 2013

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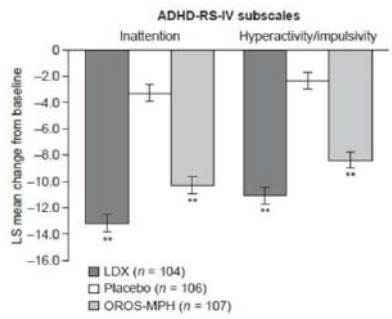
Study 325: LDX vs Placebo vs Concerta LS mean change (± SE) from baseline to endpoint for ADHD-RS-IV inattention and hyperactivity/ impulsivity subscale scores



Coghill et al 2013 European Neuropsychopharmacoloy

10

10

"Clinical Experience" is often misleading

ADHD RS impulsivity ADHD RS hyperactivity * Appointment type

Appointment type		ADHD RS impulsivity	ADHD RS hyperactivity
Hello	Mean	1.8039	2.2533
	Std. Deviation	.82548	.92009
Total	Mean	1.5725	1.7301
	N	1589	1669
	Std. Deviation	.86672	1.00604

Correlations

		Drug 1 - Daily amount (mg)	ADHD RS impulsivity	ADHD RS hyperactivity
Drug 1 - Daily amount (mg)	Pearson Correlation	1	-.205**	-.256**
	Sig. (2-tailed)		.000	.000
	N	1041	671	703
ADHD RS impulsivity	Pearson Correlation	-.205**	1	.742**
	Sig. (2-tailed)	.000		.000
	N	671	672	661
ADHD RS hyperactivity	Pearson Correlation	-.256**	.742**	1
	Sig. (2-tailed)	.000	.000	
	N	703	661	704

** Correlation is significant at the 0.01 level (2-tailed).

Hyperactivity
- ❑ Fidgetiness (hands or feet) or squirming in seat
- ❑ Leaves seat when not supposed to
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- ❑ Difficulty engaging in leisure activities quietly
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Impulsivity
- ❑ Blurts out answers before questions have been completed
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11

11

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Tolerance of delay of gratification (Mischel 1966; Logue 1988)

Timing (Siegman 1961; Barratt 1981)

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12

Medication effects on inhibitory control (behavioural inhibition, deficits in executive functioning)

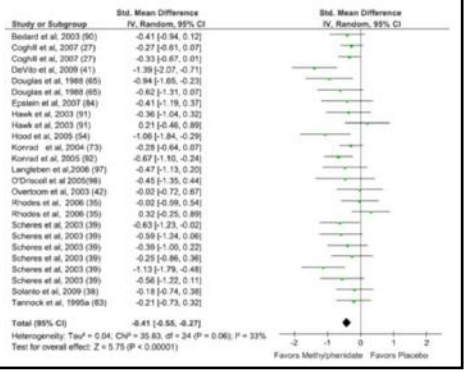
13

Effects of Methylphenidate on Cognitive Functions in Children and Adolescents with ADHD Evidence from a Systematic Review and a Meta-Analysis

Coghill et al (2014)

Biological Psychiatry

SMD -0.41 (-0.55, -0.27)



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Effects of methylphenidate on executive functioning in attention-deficit/hyperactivity disorder across the lifespan: a meta-regression analysis Tamminga et al 2016

Very similar conclusions to the Coghill (2014) meta analysis

No linear or quadratic age-dependencies were observed, indicating that effects of MPH on executive functions are independent of age in children and adults with ADHD.

However, adolescent studies are lacking and needed to conclude a lack of an age-dependency across the lifespan.

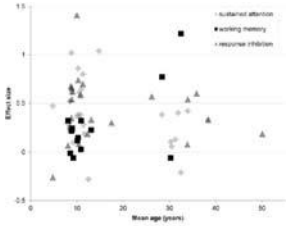

Fig. 3. Overall age–response relationship.

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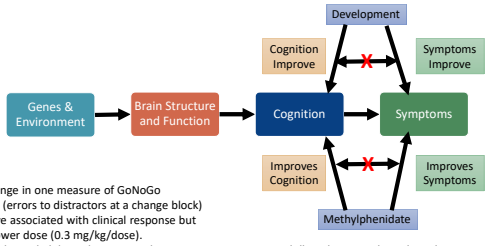
Coghill et al 2014 Psychological Med.



Actually: Change in one measure of GoNoGo performance (errors to distractors at a change block) was predictive associated with clinical response but only at the lower dose (0.3 mg/kg/dose). Interestingly this task did not discriminate between ADHD and health controls at baseline

Coghill et al 2007 Biological Psychiatry

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Predicting Response to Methylphenidate: Variables included in the prediction

	Responders (N=30)	Non-responders (N=13)	
BPVS Percentile rank	40.27 (30.58)	32.15 (28.84)	n.s.
decimal age	11.19 (2.39)	11.26 (2.99)	n.s.
diagnosis of oppositional defiant disorder	21/30	9/13	n.s.
diagnosis of conduct disorder	14/30	2/13	n.s.
deprivation score	4.27 (1.72)	4.08 (1.32)	n.s.
t-score baseline Parents ADHD Conners	78.07 (4.25)	80.08 (4.03)	n.s.
Go/NoGo - type 1 RTT	441.61 (91.85)	504.37 (108.07)	n.s.
Go/NoGo - type 2 RTT	457.48 (70.20)	497.13 (116.15)	n.s.
Go/NoGo - type 1 ERD	2.85 (1.54)	1.92 (1.50)	n.s.
Go/NoGo - type 2 ERD	2.63 (1.81)	1.85 (1.49)	n.s.
Pattern recognition z score*	-1.12 (1.66)	-0.56 (1.48)	n.s.
Spatial recognition z score*	-0.97 (0.89)	-0.55 (1.17)	n.s.
DMtS total percent correct z score*	-1.07 (1.23)	-0.66 (0.96)	n.s.

*adjusted for age and BPVS

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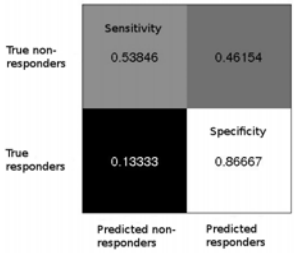
SVM classification: 77% (p<0.01)



Johnston *et al.*, under review

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SVM classification: 77% (p<0.01)

	Frequency of variable selection	Percentage of leave-one-out loops variable selected
BPVS Percentile rank	2	0.05
decimal age	0	0
presence of oppositional defiant disorder	0	0
presence of conduct disorder	43	1
deprivation score	0	0
t-score baseline Parents ADHD Conners	24	0.56
Go/NoGo - type 1 RTT	38	0.88
Go/NoGo - type 2 RTT	2	0.05
Go/NoGo - type 1 ERD	43	1
Go/NoGo - type 2 ERD	9	0.21
Pattern recognition z score*	12	0.28
Spatial recognition z score*	1	0.02
DMtS total percent correct z score*	0	0

*adjusted for age and BPVS

Johnston *et al.*, under review

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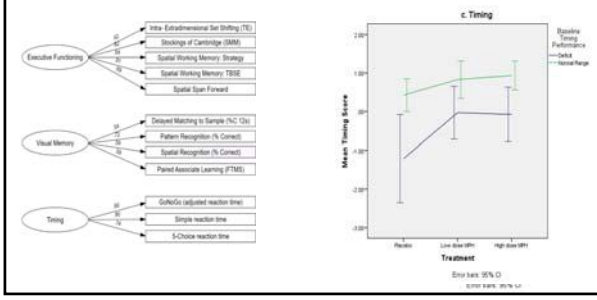
Presence of a baseline deficit does not impact on medication response



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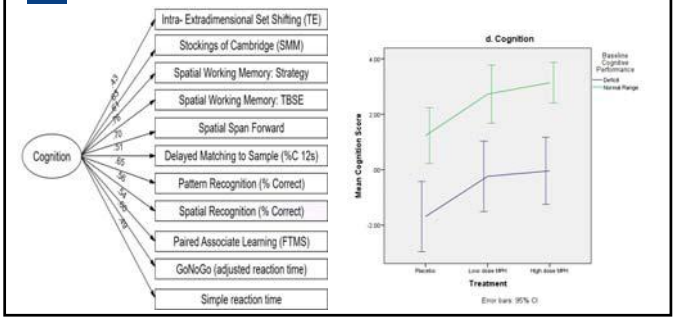
Presence of a baseline deficit does not impact on medication response



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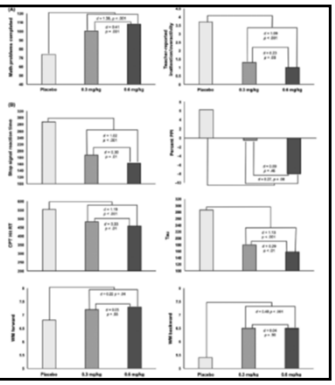
How do stimulant treatments for ADHD work? Evidence for mediation by improved cognition – Hawk et al 2018

Methylphenidate improved seatwork productivity and teacher ratings (ES = 1.4 and 1.1) and all domains of cognition (ES = 0.3–1.1).



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How do stimulant treatments for ADHD work? Evidence for mediation by improved cognition – Hawk et al 2018

Classroom Productivity

Table 2 Mediation results for classroom productivity

	MPH versus placebo				Low (0.3 mg/kg) versus high (0.6 mg/kg)			
	a (b, SE)	b (b, SE)	Indirect Effect (b, SE)	95% CI	a (b, SE)	b (b, SE)	Indirect Effect (b, SE)	95% CI
SSRT	104.3 (9.3)***	0.1 (0.03)**	8.2 (3.2)** R^2 = .10	2.5, 15.0	22.3 (7.9)**	0.01 (0.03)	0.3 (0.7) R^2 = .002	−1.2, 1.7
Percent PPI	−7.4 (4.2)*	0.2 (0.1)*	−1.4 (1.0) R^2 = .08	−3.5, 0.3	−2.9 (5.0)	−0.1 (0.06)*	0.3 (0.7) R^2 = .07	−0.7, 2.0
CPT Hit RT	81.3 (7.0)***	0.03 (0.04)	2.3 (3.4) R^2 = .03	−4.2, 9.3	20.6 (6.7)**	−0.001 (0.03)	−0.02 (0.3) R^2 = .01	−1.7, 1.4
XO Tau	115.8 (9.4)***	0.03 (0.02)	3.1 (2.7) R^2 = .02	−2.2, 8.6	18.6 (6.8)**	0.07 (0.03)*	1.2 (0.8)* R^2 = .08	−0.04, 2.9
WM Forward	0.4 (0.2)*	2.5 (1.3)*	1.1 (0.8) R^2 = .09	−0.1, 3.0	0.1 (0.2)	1.2 (0.8)	0.1 (0.3) R^2 = .02	−0.4, 0.9
WM Backward	1.1 (0.2)***	2.7 (1.1)*	2.8 (1.2)* R^2 = .10	0.6, 5.4	−0.1 (0.2)	1.0 (1.2)	−0.08 (0.3) R^2 = .02	−0.9, 0.5

Inhibitory control (Stop Signal Task, SST) and working memory backward uniquely mediated the effect of MPH (vs. placebo) on productivity.

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How do stimulant treatments for ADHD work? Evidence for mediation by improved cognition – Hawk et al 2018

Teacher Rated Behaviour

Table 3 Mediation results for teacher ratings

	MPH versus Placebo				Low (0.3 mg/kg) versus High (0.6 mg/kg)			
	a (b, SE)	b (b, SE)	Indirect effect (b, SE)	95% CI	a (b, SE)	b (b, SE)	Indirect effect (b, SE)	95% CI
SSRT	104.3 (9.3)***	0.00 (0.003)	−0.03 (0.3) R^2 = .10	−0.5, 0.5	22.3 (7.9)**	0.004 (0.002)	0.1 (0.1) R^2 = .06	−0.002, 0.2
Percent PPI	−8.0 (4.5)*	0.01 (0.02)	−0.1 (0.2) R^2 = .13	−0.5, 0.1	−2.3 (5.2)	0.003 (0.004)	−0.01 (0.03) R^2 = .07	−0.1, 0.1
CPT Hit RT	81.3 (7.0)***	0.003 (0.004)	0.3 (0.3) R^2 = .03	−0.3, 0.9	20.6 (6.7)**	0.002 (0.003)	0.04 (0.1) R^2 = .01	−0.1, 0.2
XO Tau	115.9 (9.4)***	0.003 (0.003)	0.4 (0.3) R^2 = .09	−0.2, 1.0	18.6 (6.8)**	0.002 (0.002)	0.04 (0.1) R^2 = .01	−0.04, 0.2
WM Forward	0.4 (0.2)*	0.2 (0.1)	0.1 (0.1) R^2 = .06	−0.03, 0.2	0.1 (0.2)	0.04 (0.1)	0.003 (0.02) R^2 = .02	−0.03, 0.1
WM Backward	1.1 (0.2)***	0.3 (0.1)**	0.4 (0.1)** R^2 = .16	0.1, 0.7	−0.1 (0.2)	0.1 (0.1)	−0.01 (0.03) R^2 = .02	−0.08, 0.04

Only working memory backward mediated the impact of MPH on teacher-rated behavior.

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Atomoxetine Improved Response Inhibition in Adults with Attention Deficit/Hyperactivity Disorder – Chamberlain et al 2007

Table 1. Neuropsychological Performance of Adults with ADHD on and off Atomoxetine and Comparison with Healthy Control Subjects

	ADHD Patients (n = 20)				CS (n = 20)		Main Effect of Drug (Atx vs. Plc)[a]	Main Effect of Group (ADHD vs CS)[a]	
	Atx		Plc		Unt				
Test and Measure	Mean	SD	Mean	SD	Mean	SD	p	p	p
Stop-signal									
SSRT (msec)	185.81	59.59	235.10	73.89	186.30	41.14	.021	.997	.009
Median go reaction time (msec)	440.55	63.91	422.35	55.33	421.35	79.43	.148	.411	.963
Go reaction time variability[c] (msec)	164.42	82.38	156.94	72.47	131.12	44.11	.742	.120	.173
P(inhib)	.47	.10	.49	.17	.55	.14	.758	.063	.234
Rapid Visual Information Processing									
Proportion of targets detection	.64	.20	.67	.26	.73	.19	.350	.164	.374
Commission errors	.80	.65	1.50	1.40	.85	1.31	.043	.886	.137
Spatial Working Memory									
Total between-search errors	18.85	15.20	22.65	13.33	11.70	11.36	.235	.031	.025
Strategy scores	32.95	6.28	32.15	5.26	29.55	6.24	.304	.058	.273
Three-dimensional set shifting									
Total errors	16.73	7.48	18.47	9.29	20.88	9.83	.432	.142	.432
Total reversal errors	6.16	3.00	7.47	6.75	5.51	3.49	.380	.536	.256
Extra-dimensional shift errors	8.80	7.61	9.37	9.41	12.27	9.57	.456	.210	.339

ATX reduced SSRT on Stop Task and Commission Errors on Rapid Visual Information Processing

Note: Acute single dose challenge

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Impulsive Choice

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Effects of medication on delay discounting

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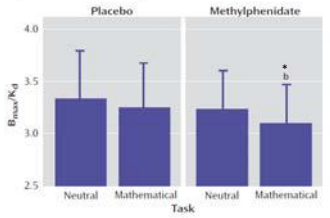
Evidence That Methylphenidate Enhances the Saliency of a Mathematical Task by Increasing Dopamine in the Human Brain Volkow et al 2004

Methylphenidate significantly increased extracellular dopamine, when coupled with the mathematical task but not when coupled with the neutral task.

The mathematical task did not increase dopamine when coupled with placebo.

Subjective reports about interest and motivation in the mathematical task were greater with methylphenidate than with placebo and were associated with dopamine increases

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



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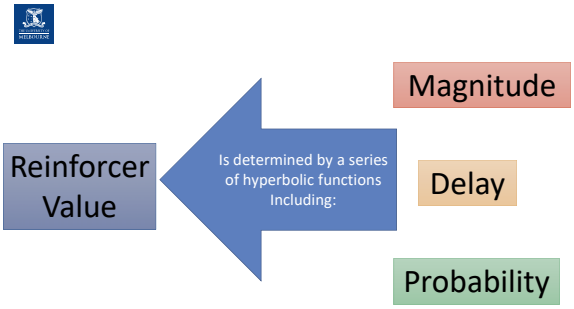

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Multiplicative hyperbolic model of choice Ho et al 1999

Postulate 1: The value of a positive reinforcer presented immediately following an operant response is assumed to be an increasing hyperbolic function of its physical magnitude or quantity (V_i)

Postulate 2: The value of a positive reinforcer whose delivery is delayed for some time after an operant response is assumed to be a decreasing hyperbolic function of that delay (V_d)

Postulate 3: The value of a positive reinforcer that occurs with a probability p following an operant response is assumed to be a decreasing hyperbolic function of the "odds-against" that probability (V_p)

Postulate 4: The overall value of a positive reinforce is jointly determined by the above three hyperbolic functions: $V^* = V_i + V_d + V_p$

Postulate 5: It is postulated that an equivalent set of equations describe the (negative) values of aversive events

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Multiplicative hyperbolic model of choice
Ho et al 1999

Postulate 6:

It is assumed that discounting parameters are relatively stable properties of individual organisms, which reflect their sensitivity to particular features of reinforcing stimuli.

To the extent to which they may vary between individuals of the same species, they may be regarded as "personality dimensions"

However, unlike most other personality dimensions, they are amenable to study in animals, and are susceptible, or so we assume, to experimental manipulation using biological interventions.

Is it a change in sensitivity to delay or to the subjective sensitivity to the magnitude of reinforcement?

This methodology can then be used to identify individual differences in sensitivity to the magnitude, delay and probability of reinforcement.

It is also suitable for the quantitative evaluation of the effects of some pharmacological interventions on discounting parameters and can provide a bridge between animal and human studies.

Where K^+ refers to the discounting parameter (sensitivity to delay) for that organism

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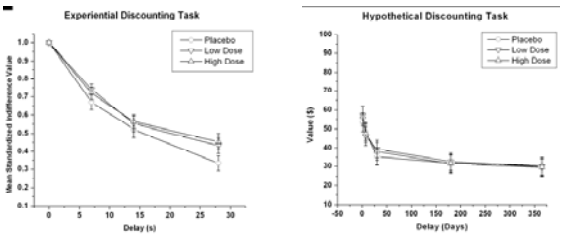
The Effects of Methylphenidate on Discounting of Delayed Rewards in ADHD Shiels et al 2009



Relative to placebo, methylphenidate reduced discounting of delayed experiential rewards, but not hypothetical rewards.

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Effects of medication on delay aversion

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Delay Aversion and Executive Functioning in Adults With ADHD: Before and After Stimulant Treatment Low et al 2018

Measure	ADHD v Control Diff at Baseline?	ADHD v Control Diff at Follow-up?	Group x Session Effect
Quick Delay Questionnaire	✓	✓	✓
BRIEF-A	✓	✓	✓
Delay Frustration Task	✓	✓	×
Digit span subtest	✓	✓	×
Rapid Visual Information Processing Task	✓	✓	×
Stockings of Cambridge	✓	✓	×
Spatial Working Memory Task	✓	✓	×

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Direct comparison of medication effects across different aspects of impulsivity

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Acute Effects of Methylphenidate on Impulsivity and Attentional Behavior among Adolescents Comorbid for ADHD and Conduct Disorder Dougherty et al 2016

3 x 1 week methylphenidate (placebo, 20mg, 40mg)

Process	Task	Treatment effects
Response initiation	Immediate Memory Task	Increased correct detections (40 > 20 & placebo) Increased commission errors (40 > 20 but not placebo)
Response Inhibition	GoStop Impulsivity Paradigm	NONE
Consequence Sensitivity (preference for SS)	2 choice Impulsivity Paradigm	NONE

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Effects of medication on Decision Making

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The Effects of Methylphenidate on Decision Making in ADHD DeVito et al 2008

Methylphenidate reduces the amount bet by ADHD group without ameliorating risk adjustment deficits relative to control subjects.

No impact of methylphenidate on other CGT Measures

Although amount bet does not separate healthy controls from ADHD

CGT Measures	ADHD vs Controls	Drug effect
Rational Choices	✓	×
Deliberation Time	×	×
Amount Bet	×	✓
Impulsivity Index	✓	×
Risk Adjustment	✓	×

Percentage Bet

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Other studies of Cambridge Gambling Task

Methylphenidate normalised decision-making behaviour of patients with Frontal Variant of Frontotemporal Dementia (but no effects on working memory, set shifting, reversal learning)

Methylphenidate had no effect on decision making in healthy medical students

Methylphenidate had no impact on performance of chess grand masters under timed chess conditions but improved their play in untimed games

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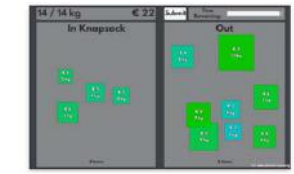
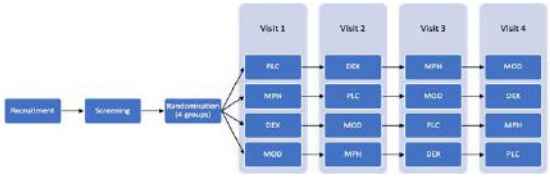


Distinguish:
- Value attained
- How close to optimum in item space



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Conclusions

Drugs have no significant effect on value attained (as % of optimum) or distance (in items) from optimum
- This masks a rich shift in behavior from the drugs, though.

MPH, and to lesser extent, MOD, create regression to mean for both value and distance
- This means that drugs can have a significant negative effect for better performers, and a positive one for underperformers

MPH and DEX have significant effects on search properties:
- MPH *increases* speed, DEX *decreases* speed
- MPH generates regression to mean; DEX does not
- Productivity of search decreases substantially for both

MOD is different in that:
- It does not significantly increase effort (time & moves)/speed/productivity
- There is some mild mean reversion

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Big Picture

"Smart drugs" *motivate* people just like complexity does

But *smartness of moves overall goes down*

Though worse-than-average do better because they spent more time and/or move more

Better-than-average decrease quality of moves and hence tend to end up worse off

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Effects of medication on the Default Mode Network

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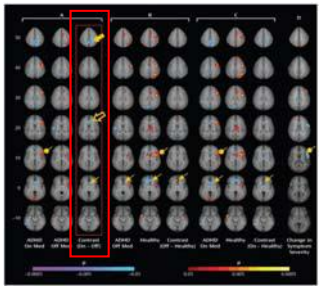
An fMRI Study of the Effects of Psychostimulants on Default-Mode Processing During Stroop Task Performance in Youths With ADHD – Peterson et al 2009

Section A shows activations in children with ADHD compared across the medicated and unmedicated states.

The red box indicates images that are testing the a priori hypothesis that medication would produce changes in brain activation within regions that subserve attention and impulse control.

Stimulant medication significantly improved suppression of default-mode activity in the ventral anterior cingulate cortex in the ADHD group.



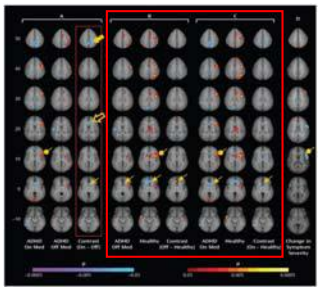
44

An fMRI Study of the Effects of Psychostimulants on Default-Mode Processing During Stroop Task Performance in Youths With ADHD – Peterson et al 2009

Sections B is a comparison between ADHD off meds and controls

Section C is a comparison between ADHD off meds and controls

When off medication, youths with ADHD were unable to suppress default-mode activity to the same degree as comparison subjects, whereas when on medication, they suppressed this activity to comparison group levels.

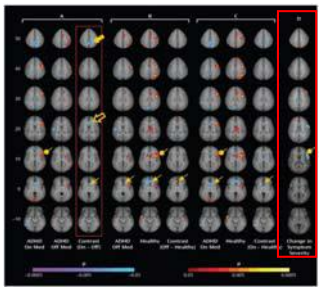


45

An fMRI Study of the Effects of Psychostimulants on Default-Mode Processing During Stroop Task Performance in Youths With ADHD – Peterson et al 2009

Column D shows correlations between change in symptoms and activation of DMN when off medication

Activation of the left lateral prefrontal cortex at baseline strongly predicted medication responsiveness (r=−0.73, df=16, p<0.001).



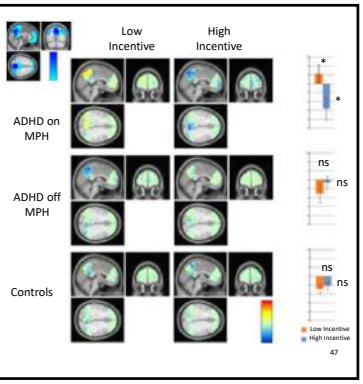
46

Task-related default mode network modulation and inhibitory control in ADHD: effects of motivation and methylphenidate Liddle et al 2011

Phasic DMN deactivation in each motivational condition of the Go/nogo task for ADHD participants (off and on methylphenidate) and controls

DMN deactivation was significantly modulated by motivational incentive only in the ADHD participants off-methylphenidate.

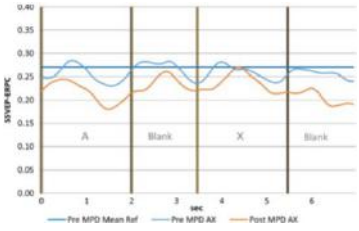
On-methylphenidate, there was no significant difference between diagnostic groups, nor any significant effects of motivational incentive



47

Dopaminergic modulation of default mode network brain functional connectivity in ADHD Silberstein et al 2016

Brain functional connectivity was estimated using an elcectrophysiological method known as steady-state visual evoked potential partial coherence before and after the administration of a methylphenidate dose to 42 stimulant drug-naïve boys newly diagnosed with ADHD while they performed the A-X version of the continuous performance task

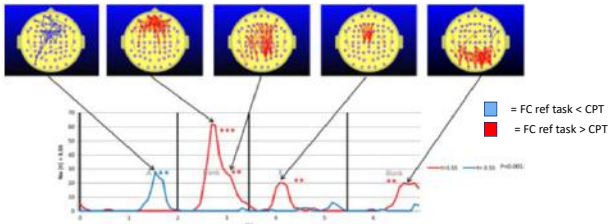


Measures of functional connectivity (FC) during continuous performance task A-X demonstrated a reduction in connectivity in the post-MPH condition

48

Dopaminergic modulation of default mode network brain functional connectivity in ADHD Silberstein et al 2016

Before MPH



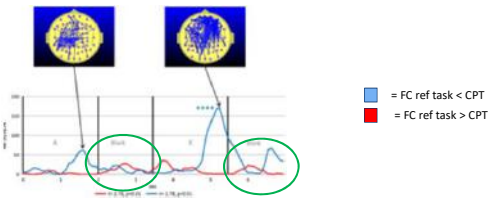
Student's t-frequency graph illustrating the number of electrode pairs where the Student's t test comparing ADHD group functional connectivity (FC) during the continuous performance task A-X task with the mean of the reference task

49

49

Dopaminergic modulation of default mode network brain functional connectivity in ADHD Silberstein et al 2016

Controls



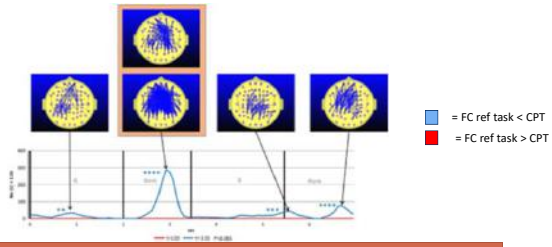
Student's t-frequency graph illustrating the number of electrode pairs where the Student's t test comparing ADHD group functional connectivity (FC) during the continuous performance task A-X task with the mean of the reference task

50

50

Dopaminergic modulation of default mode network brain functional connectivity in ADHD Silberstein et al 2016

Post MPH



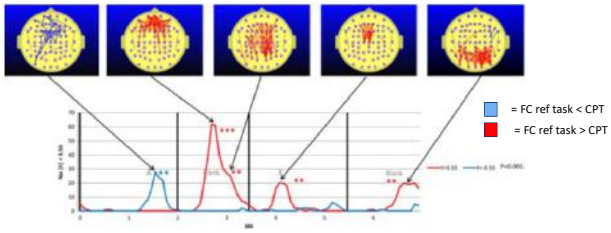
Student's t-frequency graph illustrating the number of electrode pairs where the Student's t test comparing ADHD group functional connectivity (FC) during the continuous performance task A-X task with the mean of the reference task

51

51

Dopaminergic modulation of default mode network brain functional connectivity in ADHD Silberstein et al 2016

Before MPH



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52

52

Dopaminergic modulation of default mode network brain functional connectivity in ADHD Silberstein et al 2016

Interpretation of findings

"Findings suggest that methylphenidate suppresses the increased functional connectivity observed in ADHD and that such suppression is associated with improved performance.

Our findings support the suggestion that the increased functional connectivity we have observed in ADHD is associated with abnormal DMN activity. "

53

53

Pattern Classification of Working Memory Networks Reveals Differential Effects of Methylphenidate, Atomoxetine, and Placebo in Healthy Volunteers Marquand et al 2011

Combined event-related fMRI with multivariate pattern recognition to characterize the effects of MPH and ATX in **healthy volunteers** performing a rewarded working memory (WM) task.

The effects of MPH and ATX on WM were strongly dependent on their behavioral context.

During non-rewarded trials, only MPH could be discriminated from placebo (PLC), with MPH producing a similar activation pattern to reward.

During rewarded trials both drugs produced the opposite effect to reward

- They attenuated WM networks
- Enhancing task-related deactivations (TRDs) in regions consistent with the default mode network (DMN).
- **The drugs could be directly discriminated during the delay component of rewarded trials: MPH produced greater activity in WM networks and ATX produced greater activity in the DMN.**

54

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Sumary

- As Edmund has already said the study of impulsivity is complex and challenging
- It seems likely (to me at least) that most if not all of the different aspects of impulsivity play a role in (some cases) of ADHD
- I note the lack of correlation performance on different tasks
- And am not surprised about the poor correlation between tasks and questionnaires
- Medication effects have been shown for many different aspects but evidence is much stronger for some that others with a lot of work still to do
- However the relationship between these effects and core symptom reduction is not yet well established
- In my personal view we should be very wary of studying impulsivity in isolation from other aspects of cognition
- Oh and I was wrong about the impact of meds on impulsive symptoms in my clinic! (but this does make be pleased that we record symptom outcomes as routine)

55

55

Where do we go from here?

1. Animal studies have demonstrated positive effects of several other drug classes on aspects of impulsivity

These include

- Donepezil (cholinesterase inhibitor)
- Memantine (NMDA antagonist)
- GluN2B antagonists (NMDA receptor subunit)
- Granisetron and Ondansetron (5-HT3 receptor antagonists)

2. Stronger designs that bring together the best features of current studies
   - chronic challenges
   - head to head (medications and models)
   - better understanding of relationship between symptoms and cognition
   - Collaboration to standardise methods where appropriate

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Catecholamine Regulation of Prefrontal Cortex: Relevance to Etiology and Treatment of ADHD

Amy F.T. Arnsten, Ph.D.
Professor of Neuroscience, Psychiatry, Psychology,
and the Yale Child Study Center
Yale University School of Medicine
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1

Disclosures

AFTA and Yale University receive royalties from Shire Pharmaceuticals from the US sales of Intuniv™ (extended release guanfacine) for the treatment of ADHD and related disorders. They do not receive royalties from international sales or generic Intuniv.

Dr. Arnsten consults with Lundbeck Pharmaceuticals on the development of superior atypical antipsychotic medications, and with Blackthorn Pharma on the development of kappa opioid antagonists.

2

Symptoms of ADHD

3

Symptoms of ADHD

Attention Deficit Hyperactivity Disorder-

Impaired regulation of:
- **attention**
- **impulse control, often manifesting as hyperactivity**
- **evident at early age, often continues into adulthood**

4

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Common, co-morbid diagnoses:

Oppositional Defiant Disorder or Conduct Disorder (inappropriate aggression)

Tourette's Syndrome (inappropriate movements- tics)

5

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Disorders with symptoms that can mimic ADHD:

Stress or Post-traumatic stress disorder-
e.g. from a family going through a divorce, or more gravely, from child abuse or witnessing traumatic events

Bipolar disorder (mania)

Lead poisoning

6

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Lead poisoning

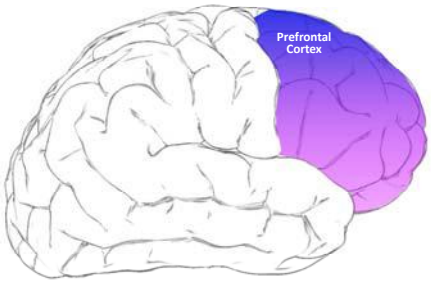
ALL OF THESE DISORDERS INVOLVE DYSFUNCTION OF THE PREFRONTAL CORTEX (especially right hemisphere)

7

Prefrontal Cortex: Function and Topography

8

The Functions of the Prefrontal Cortex

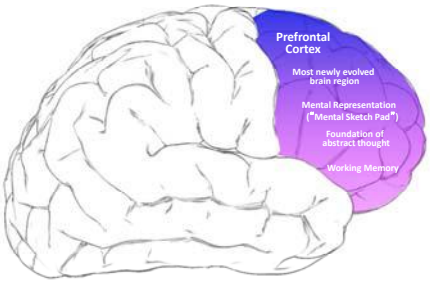


https://www.youtube.com/watchv=7BUNI1UHs8E&feature=youtu.be

amy.arnsten@yale.edu

9

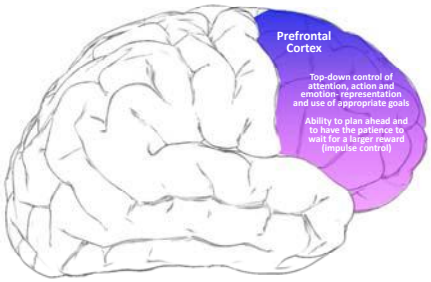
The Functions of the Prefrontal Cortex



Arnsten (2010) *Expert Rev Neurother* 10: 1595-605; Arnsten et al (2012) *Neuron* 76:223-39

10

The Functions of the Prefrontal Cortex



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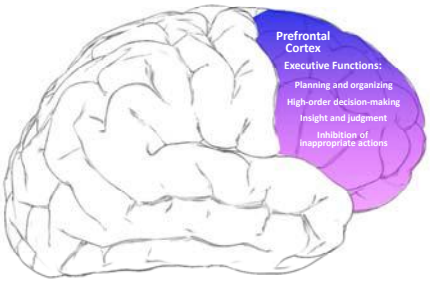
11

The Functions of the Prefrontal Cortex

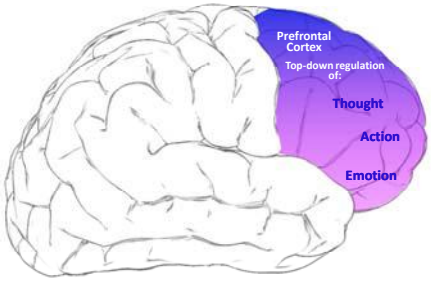


Arnsten (2010) *Expert Rev Neurother* 10: 1595-605; Arnsten et al (2012) *Neuron* 76:223-39

12

Connections and Topography

Dorsal and lateral vs. Ventral and Medial Topography



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13

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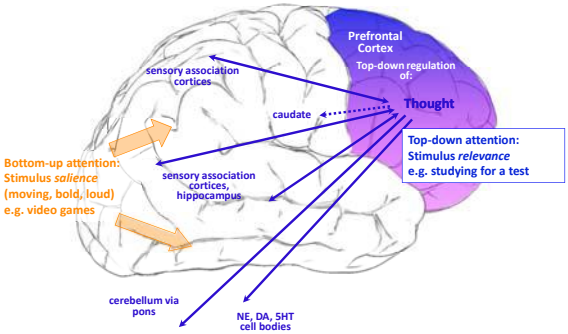

14

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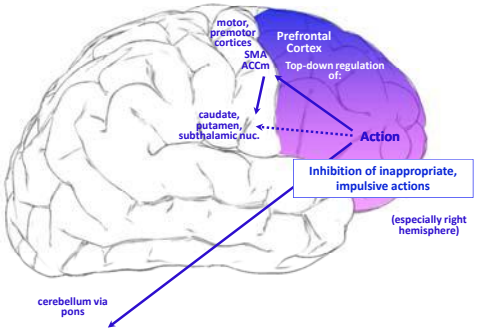

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15

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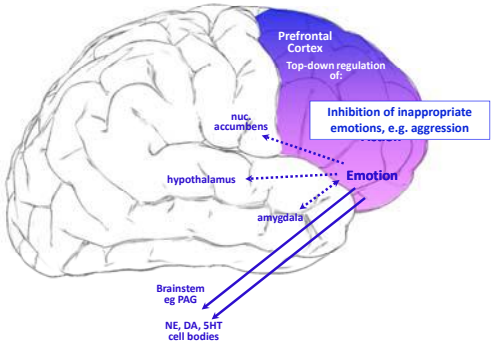

16

Connections and Topography

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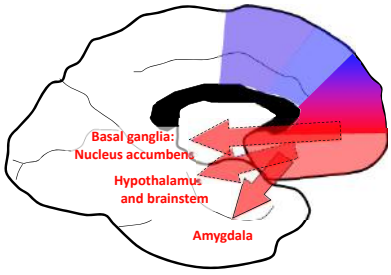
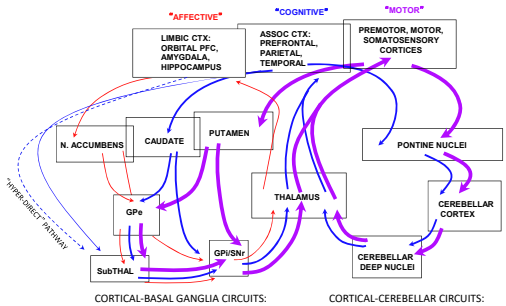


The Ventromedial Prefrontal Cortex Is Specialized for Emotional Regulation

17



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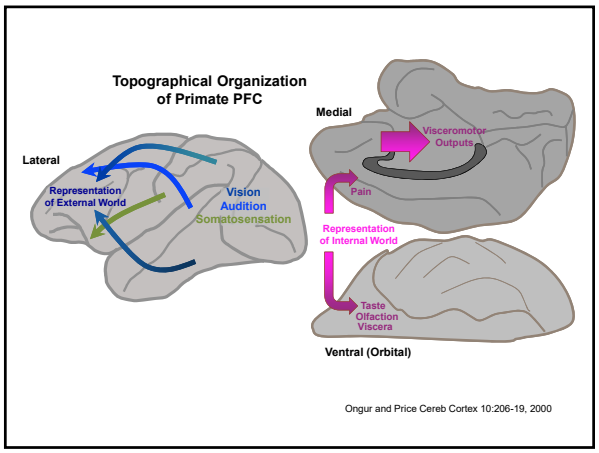
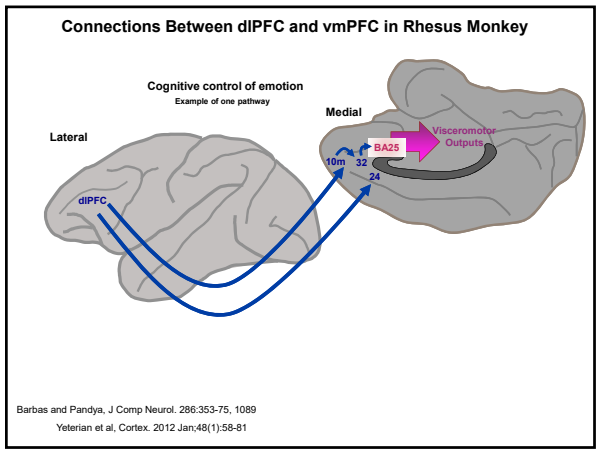


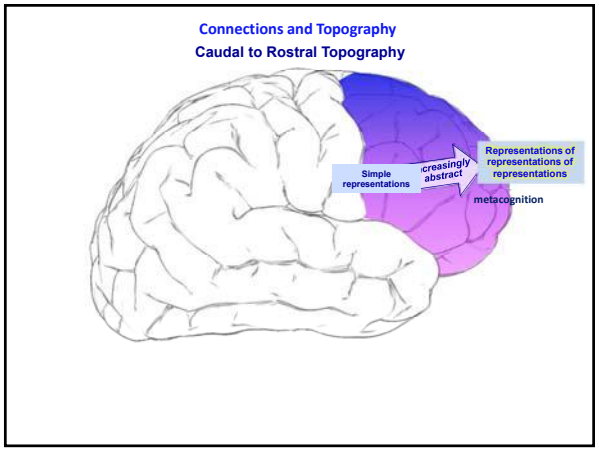
Ongur and Price Cereb Cortex 10:206-19, 2000

19



Barbas and Pandya, J Comp Neurol. 286:353-75, 1089
Yeterian et al, Cortex. 2012 Jan;48(1):58-81

20



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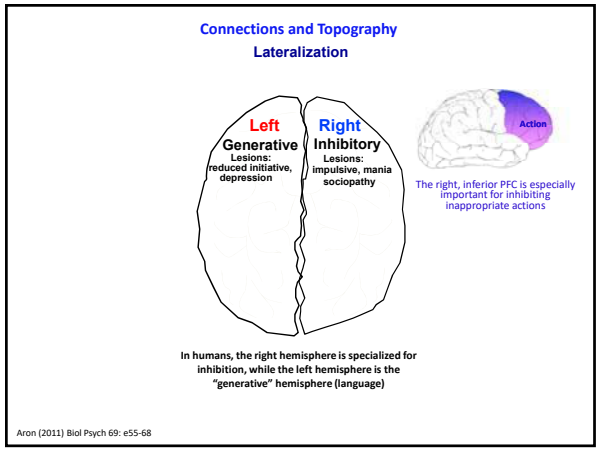
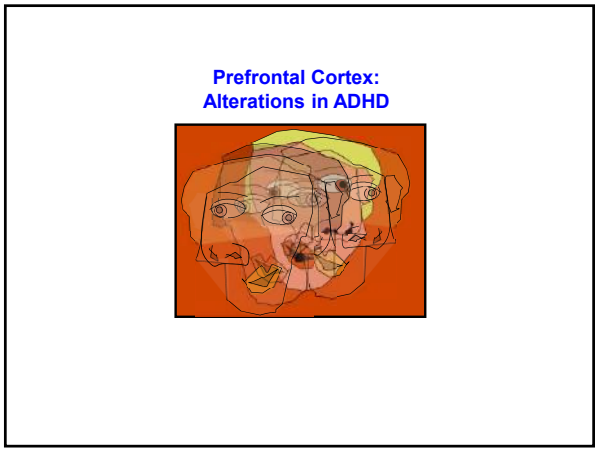


Aron (2011) Biol Psych 69: e55-68

22



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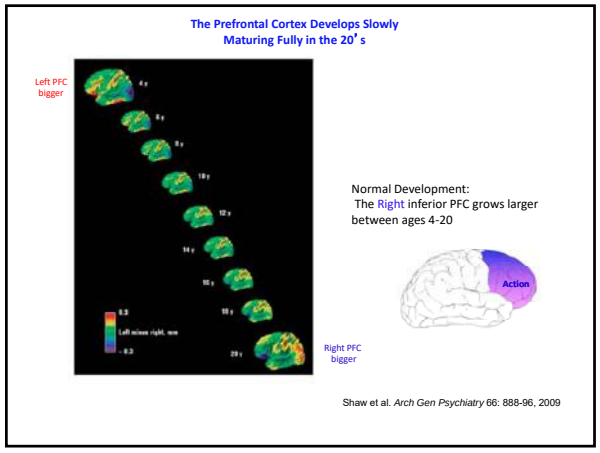
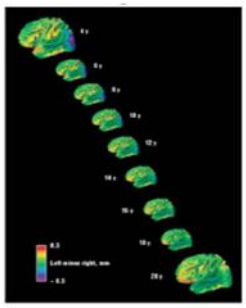


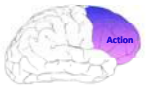
Shaw et al. *Arch Gen Psychiatry* 66: 888-96, 2009

24

Altered Maturation of PFC in ADHD



ADHD:
Laterality unchanged
(Right hemisphere does not enlarge)



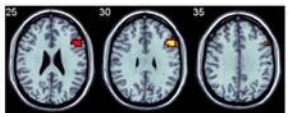
Left PFC bigger- right fails to grow

Shaw et al. *Arch Gen Psychiatry* 66: 888-96, 2009

25

Reduced Structure and Function of PFC in ADHD

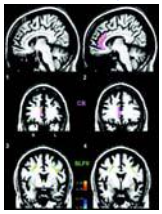
Reduced Right inferior dlPFC functional activity



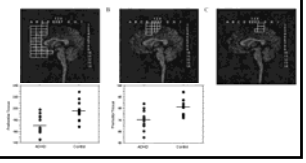
Motor inhibition
(similar results with impaired attention)

Rubia et al, (2009) Am J Psychiatry 166:83-94

Reduced PFC connectivity Mostofsky et al, (2002)



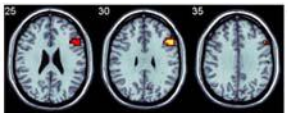
Reduced PFC volume Makris et al, (2007)



26

Disorder Specific Changes

Reduced Right inferior dlPFC functional activity



Motor inhibition
(similar results with impaired attention)

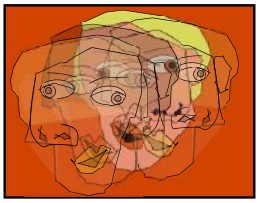
Rubia et al, (2009) Am J Psychiatry 166:83-94

Reduced Right Orbital PFC functional activity in Conduct Disorder

Impaired regulation of emotion

27

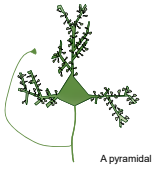
Prefrontal Cortex: Cellular Basis of Executive Function



28

The cellular basis of working memory and "top down" control

PFC neurons generate and maintain goals to guide attention and action, including representing goals used to inhibit inappropriate actions

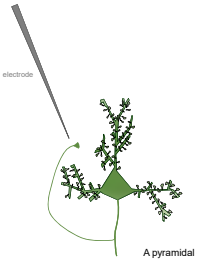


A pyramidal cell

29

The cellular basis of working memory and "top down" control

Much has been learned about the cellular basis of higher cognition from recordings of PFC neurons as animals perform working memory tasks



A pyramidal cell

30

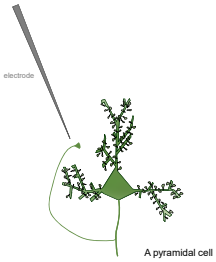
The cellular basis of working memory and "top down" control

Much has been learned about the cellular basis of higher cognition from recordings of PFC neurons as animals perform working memory tasks

A delayed response working memory task

Cue (flashes for 0.5 sec)

As the animal fixates on a central point on a computer screen, a cue is briefly flashed at 1 of 8 locations for just a half a second



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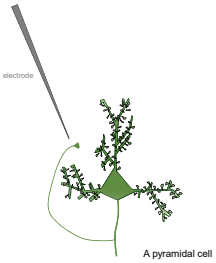
The cellular basis of working memory and "top down" control

Much has been learned about the cellular basis of higher cognition from recordings of PFC neurons as animals perform working memory tasks

A delayed response working memory task

Delay (remember for many seconds)

The cue disappears, and the subject must remember its location over a delay period e.g. for 5 seconds



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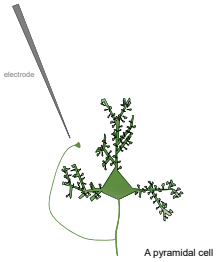
The cellular basis of working memory and "top down" control

Much has been learned about the cellular basis of higher cognition from recordings of PFC neurons as animals perform working memory tasks

A delayed response working memory task

Respond (look at remembered location)

When the fixation point goes off, the subject moves its eyes to look at the remembered location, and gets a reward if correct



33

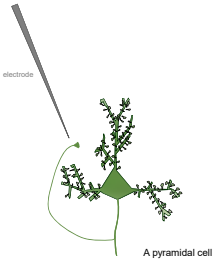
The cellular basis of working memory and "top down" control

Much has been learned about the cellular basis of higher cognition from recordings of PFC neurons as animals perform working memory tasks

A delayed response working memory task

Cue (flashes for 0.5 sec)

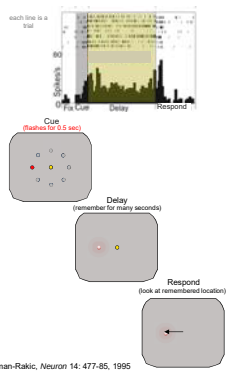
The next trial then begins, with the cue flashing in a new location, so that the contents of working memory must now be updated

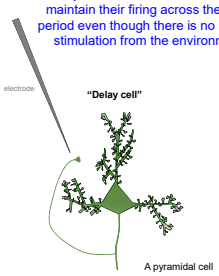


34

Neurons in dlPFC Excite Each Other to Keep Information "In Mind"

Recordings from the PFC have found "Delay cells", neurons that are able to maintain their firing across the delay period even though there is no sensory stimulation from the environment.



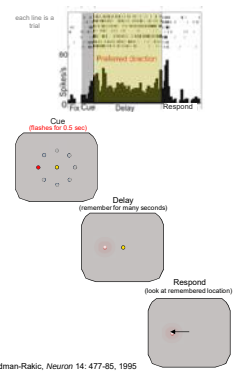


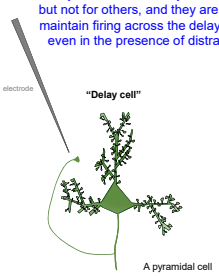
Goldman-Rakic, *Neuron* 14: 477-85, 1995

35

Neurons in dlPFC Excite Each Other to Keep Information "In Mind"

"Delay cells" have a preferred direction, i.e. they fire to the memory of one location but not for others, and they are able to maintain firing across the delay period even in the presence of distractors.

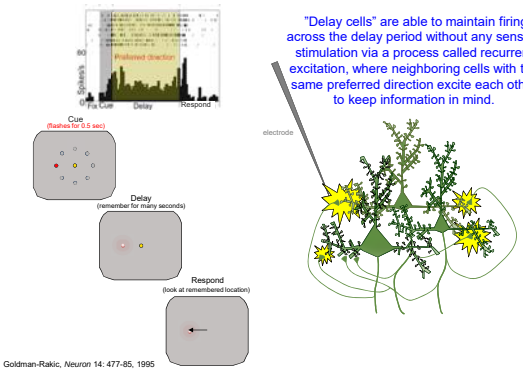




Goldman-Rakic, *Neuron* 14: 477-85, 1995

36

Neurons in dlPFC Excite Each Other to Keep Information "In Mind"

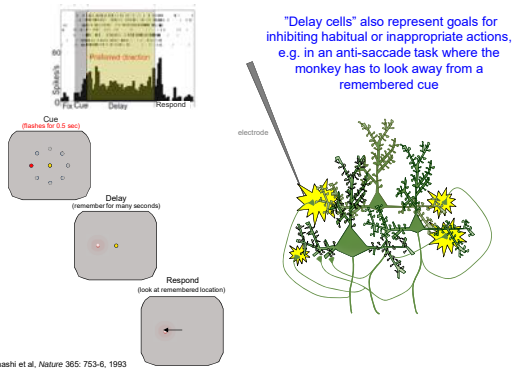


"Delay cells" are able to maintain firing across the delay period without any sensory stimulation via a process called recurrent excitation, where neighboring cells with the same preferred direction excite each other to keep information in mind.

Goldman-Rakic, *Neuron* 14: 477-85, 1995

37

Neurons in dlPFC Excite Each Other to Keep Information "In Mind"

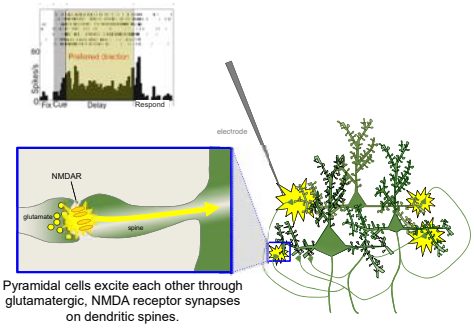


"Delay cells" also represent goals for inhibiting habitual or inappropriate actions, e.g. in an anti-saccade task where the monkey has to look away from a remembered cue

Funahashi et al, *Nature* 365: 753-6, 1993

38

Neurons in dlPFC Excite Each Other to Keep Information "In Mind"



Pyramidal cells excite each other through glutamatergic, NMDA receptor synapses on dendritic spines.

Wang et al, *Neuron* 77: 736-49, 2013

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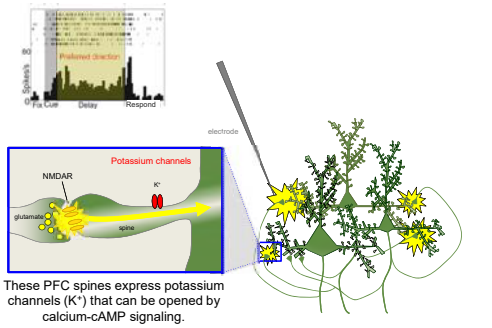
Neurons in dlPFC Excite Each Other to Keep Information "In Mind"

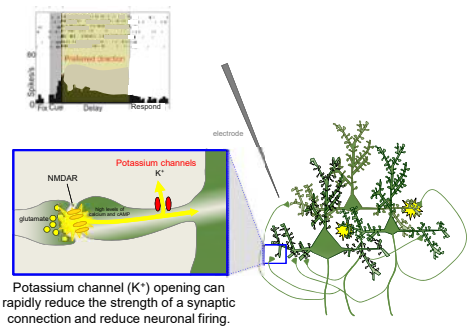


These PFC spines express potassium channels (K^+) that can be opened by calcium-cAMP signaling.

Arnsten et al, *Neuron* 76: 223-39, 2012

40

Potassium Channel Opening Rapidly Reduces Neuronal Firing

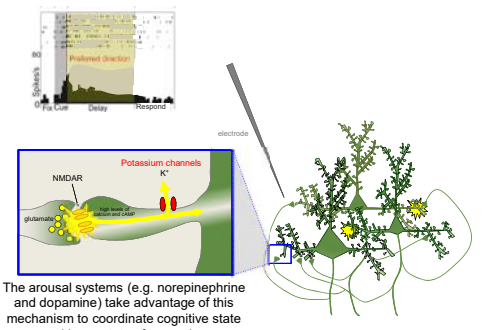


Potassium channel (K^+) opening can rapidly reduce the strength of a synaptic connection and reduce neuronal firing.

Arnsten et al, *Neuron* 76: 223-39, 2012

41

Potassium Channel Opening Rapidly Reduces Neuronal Firing

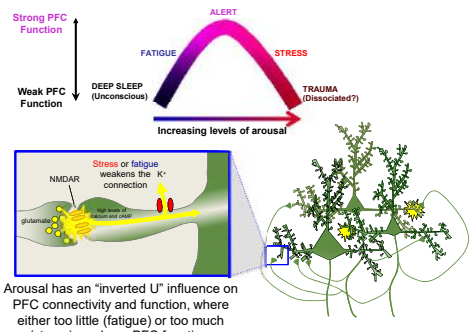


The arousal systems (e.g. norepinephrine and dopamine) take advantage of this mechanism to coordinate cognitive state with our state of arousal.

Arnsten et al, *Neuron* 76: 223-39, 2012

42

Prefrontal Connectivity and Function Depends on Arousal State



Arousal has an "inverted U" influence on PFC connectivity and function, where either too little (fatigue) or too much (stress) weakens PFC function.

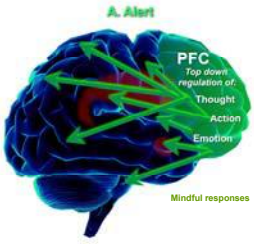
Arnsten et al, *Neuron* 76: 223-39, 2012
Arnsten et al, *Nat Neurosci* 18: 1376-85, 2015

43

Prefrontal Cortex: Powerful Roles of Catecholamines

44

Arousal Systems Orchestrate Brain State

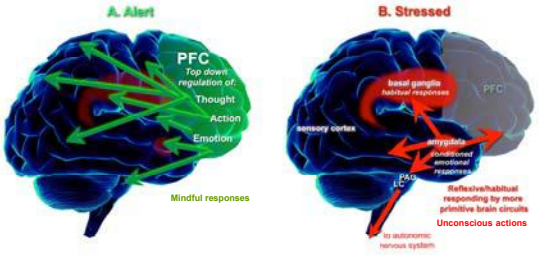


Optimal levels of catecholamines promote dlPFC function.

Arnsten, *Nature Rev. Neurosci* 10: 410-22, 2009

45

Arousal Systems Orchestrate Brain State



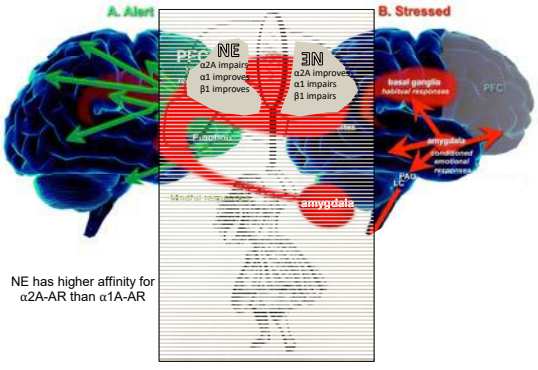
Optimal levels of catecholamines promote dlPFC function.

In contrast, high levels of catecholamines during stress impair dlPFC function, and strengthen more primitive circuits, switching the brain from a reflective to reflexive state

Arnsten, *Nature Rev. Neurosci* 10: 410-22, 2009

46

Arousal Systems Orchestrate Brain State

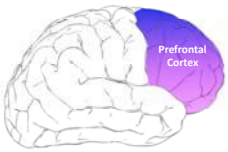


NE has higher affinity for α2A-AR than α1A-AR

Arnsten *Neural Plasticity* 7: 133-46, 2000

47

PFC Requires Catecholamines to Function



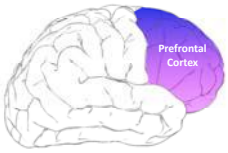
Catecholamine depletion from dlPFC markedly impairs working memory
Brozoski et al. *Science* 205: 929-31, 1979

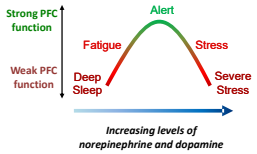
Dopamine D1R Blockade in dlPFC markedly impairs working memory
Sawaguchi & Goldman-Rakic, *J. Neurophys* 71:515-28, 1994

Norepinephrine α2A-AR Blockade in dlPFC markedly impairs working memory
Li & Mei, *Behav Neural Biol* 62: 134-9, 1994

48

Inverted U Dose Response





Arnsten et al., *Neuron* 76: 223-39, 2012

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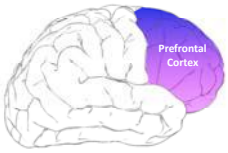
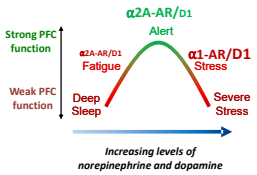
Inverted U Dose Response



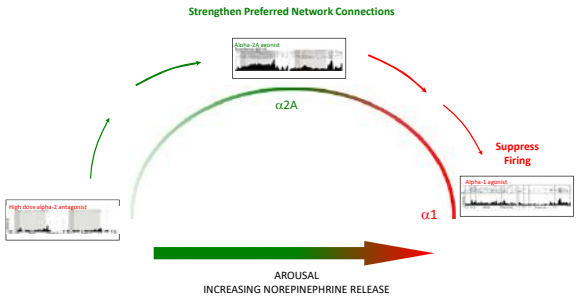


Note: NE has higher affinity for α2A-AR than α1A-AR

Arnsten *Neural Plasticity* 7: 133-46, 2000
Arnsten et al., *Neuron* 76: 223-39, 2012

50

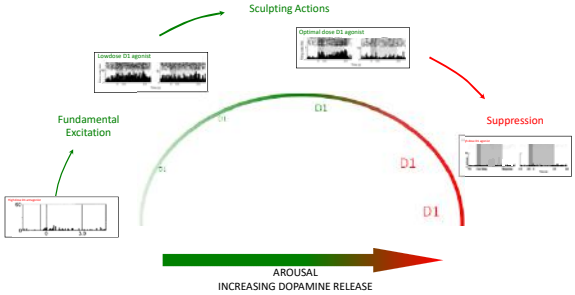
NE Effects on PFC Physiology: The Inverted U



Adapted from Arnsten Biol Psychiatry 69: e89-99, 2011

51

DA D1 Effects on PFC Physiology: The Inverted U

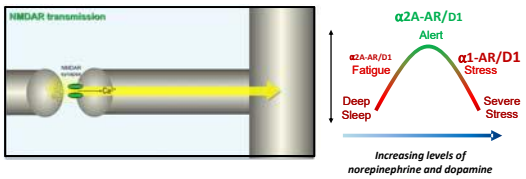


Vijayraghavan et al, Nature Neuroscience 10:376, 2007

Adapted from Arnsten et al. in the Dopamine Handbook, A Bjorklund, S Dunnett, L Iversen, & S Iversen Eds, Oxford Univ Press, pp 230-48, 2008.

52

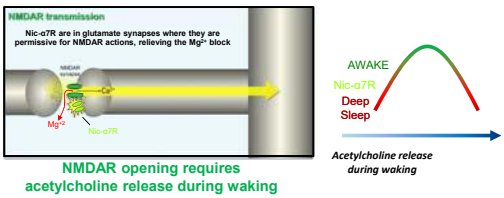
Cellular Basis of Inverted U



Wang et al. *Neuron* 77: 736-49, 2013

53

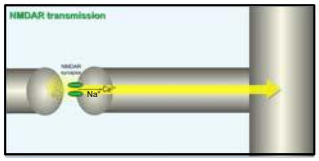
Cellular Basis of Inverted U



Wang et al. *Neuron* 77: 736-49, 2013

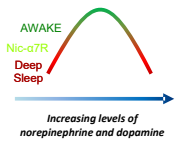
54

Cellular Basis of Inverted U



Glutamate stimulation of NMDAR fluxes calcium as well as sodium into the cell

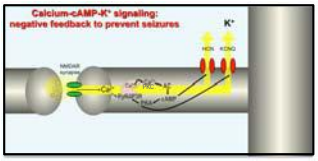
Inverted U Dose-Response Related to Arousal State



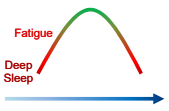
Wang et al. *Neuron* 77: 736-49, 2013

55

Cellular Basis of Inverted U



Inverted U Dose-Response Related to Arousal State



Negative feedback on cell firing:

1) Calcium from NMDA receptors drives further calcium release from the **smooth endoplasmic reticulum**;
2) Calcium activates PKC, which increases cAMP production;
3) High levels of cAMP-PKA open K^+ channels to reduce firing;
4) PKA can further increase calcium release, creating a vicious cycle that rapidly reduces cell firing

Arnsten *Nature Neuroscience* 18: 1376-85, 2015

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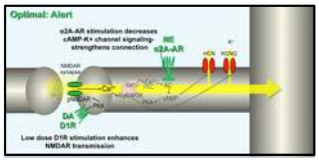
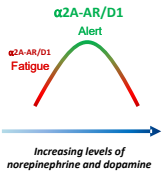
Optimal Levels of Catecholamines Strengthen PFC Function



Optimal catecholamine levels increase NMDAR and reduce cAMP-K^+ channel signaling

Inverted U Dose-Response Related to Arousal State



57

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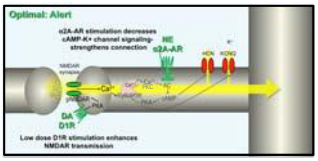
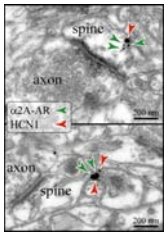


Optimal catecholamine levels increase NMDAR and reduce cAMP-K^+ channel signaling

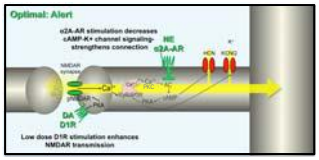
Wang et al (2007) Cell 129:397-410

α2A-AR on spines next to HCN channels



58

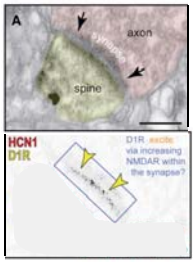
Optimal Levels of Catecholamines Strengthen PFC Function



Optimal catecholamine levels increase NMDAR and reduce cAMP-K^+ channel signaling

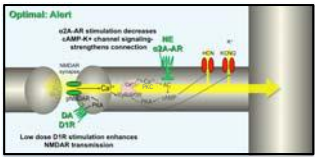
Arnsten et al (2015) Pharmacol Rev. 67: 681-96

D1R on spines within the glutamatergic PSD



59

Optimal Levels of Catecholamines Strengthen PFC Function



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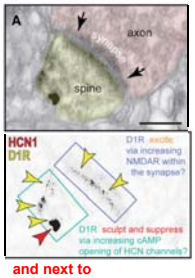
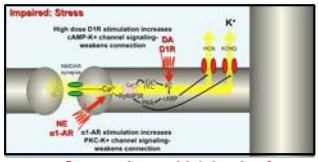


and next to HCN channels

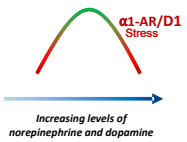
60

High Levels of Catecholamines (eg Stress) Impair PFC



Stress releases high levels of catecholamines in PFC. This rapidly weakens PFC connections by driving feedforward Ca^{2+}-PKC-cAMP-PKA-K^+ channel signaling

Inverted U Dose-Response Related to Arousal State



Arnsten *Nature Neuroscience* 18: 1376-85, 2015

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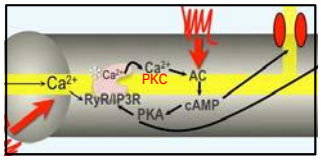
High Levels of Catecholamines (eg Stress) Impair PFC



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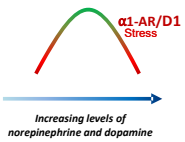
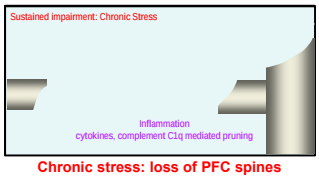


Arnsten *Nature Neuroscience* 18: 1376-85, 2015

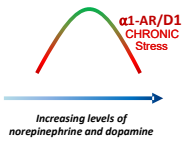
62

High Levels of Catecholamines (eg Stress) Impair PFC



Chronic stress: loss of PFC spines and dendrites- impaired function-

Inverted U Dose-Response Related to Arousal State



Arnsten *Nature Neuroscience* 18: 1376-85, 2015
Hains et al, *PNAS* 106: 17957-62, 2009
Hains et al, *Neurobio Stress* 2:1-9, 2015
Datta and Arnsten, unpublished

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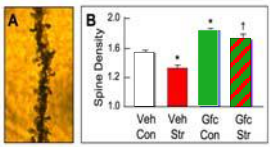
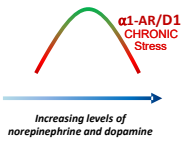
High Levels of Catecholamines (eg Stress) Impair PFC



Chronic stress: loss of PFC spines and dendrites- impaired function-

Blocked by inhibiting:
PKA activity with guanfacine, or
PKC activity with chelerythrine

Inverted U Dose-Response Related to Arousal State



Arnsten *Nature Neuroscience* 18: 1376-85, 2015
Hains et al, *PNAS* 106: 17957-62, 2009
Hains et al, *Neurobio Stress* 2:1-9, 2015
Datta and Arnsten, unpublished

64

Relevance to Diagnosis

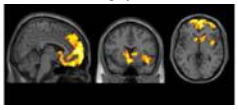
65

Uncontrollable Stress Causes PFC Dysfunction Which Can Mimic ADHD

Acute Stress- reduced activity of PFC

Qin et al., *Biol Psychiatry* 66: 25-32, 2009

Chronic Stress- gray matter in PFC



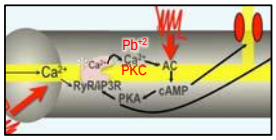
Ansell et al. *Biol Psychiatry* 72: 57–64, 2012

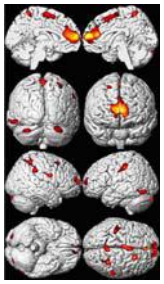
In both animals and humans, acute uncontrollable stress impairs dlPFC function; chronic stress induces PFC gray matter loss

Arnsten *Nature Reviews Neurosci* 6: 410-22, 2009

66

Lead Poisoning Causes PFC Dysfunction Which Can Mimic ADHD





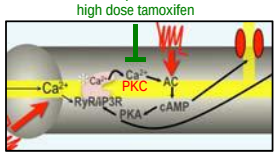
Cecil et al, PLoSMed 5: e112, 2008

Lead poisoning is associated with reduced PFC gray matter. Lead (Pb^{+2}) mimics calcium and thus may increase PKC intracellular stress signaling pathways in PFC neurons

67

Bipolar Mania Causes PFC Dysfunction Which Can Mimic ADHD

lithium
valproate
high dose tamoxifen



Excessive PKC signaling is also associated with mania,
e.g. anti-manic agents such as lithium and valproic acid reduce PKC activity

Manji et al., Biol Psychiatry 46: 1328-51, 1999
Arnsten and Manji, Future Neurology 3: 125-1, 2008

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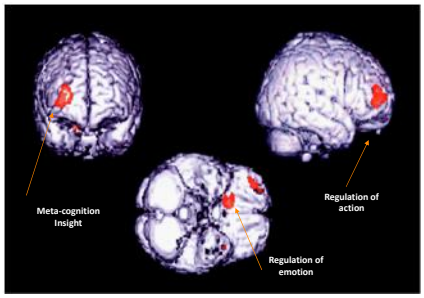
Bipolar Mania Causes PFC Dysfunction Which Can Mimic ADHD



The right PFC is underactive during mania

Blumberg et al., (1999) Arch Gen Psych 156:1986-8

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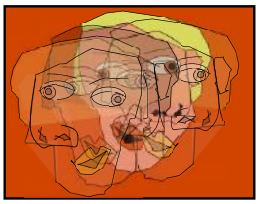
Relevance to Treatment



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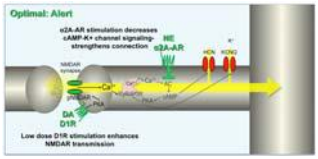
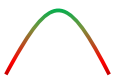
ADHD Treatments Optimize Catecholamine Actions in PFC



Optimal catecholamine levels increase NMDAR and reduce cAMP-K^+ channel signaling

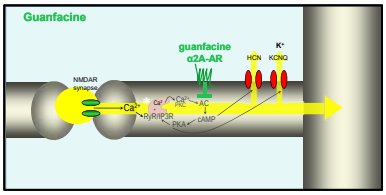
Guanfacine
Atomoxetine
Methylphenidate
Amphetamines

α2A-AR/D1



71

Guanfacine



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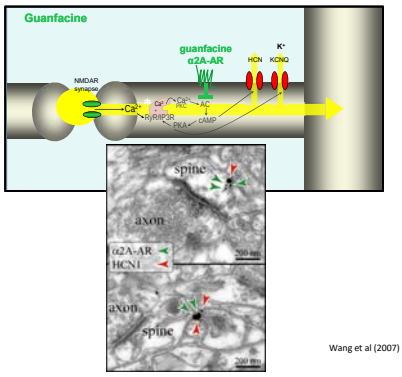
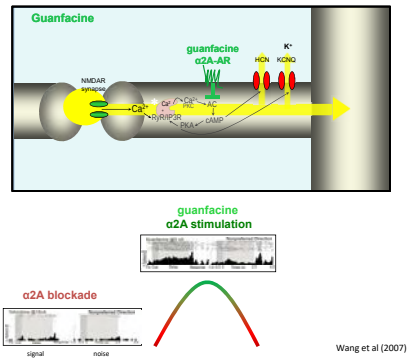
Guanfacine



Wang et al (2007) Cell 129:397-410

73

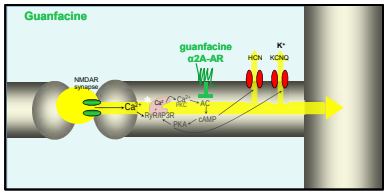
Guanfacine



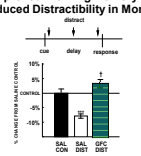
Wang et al (2007) Cell 129:397-410

74

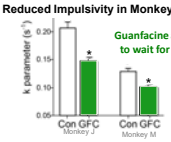
Guanfacine



Improved Working Memory and Reduced Distractibility in Monkeys



Reduced Impulsivity in Monkeys

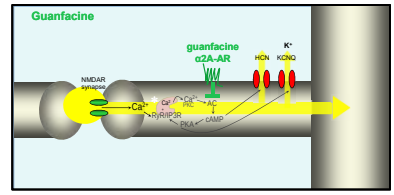


Guanfacine allows monkey to wait for larger reward

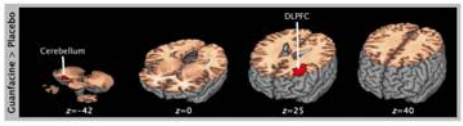
Arnsten & Contant (1992) *Psychopharm* 108:159-69.
Kim et al. (2012) *Psychopharm* 219:363-75

75

Guanfacine



Enhances fMRI BOLD to a warning signal in human dlPFC



Clerkin et al Biol Psychiatry 66: 307-12, 2009

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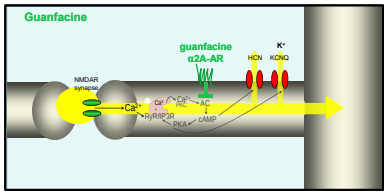
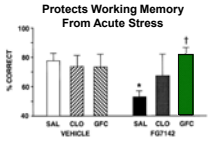
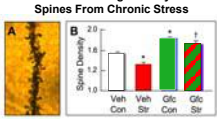
Guanfacine



Protects Working Memory From Acute Stress



Protects Working Memory and Spines From Chronic Stress



Birnbaum et al. *Pharm Biochem Beh.* 67:397-403, 2000
Arnsten et al. *Neurobiol. Stress* 1:89-99, 2015
Hains et al. *Neurobiol Stress* 2:1-9, 2015

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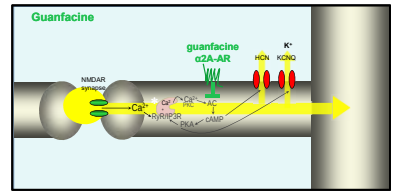
Guanfacine



Extended release guanfacine (Intuniv™- approved by FDA for use in ADHD in 2009 based on our work in monkeys

α2A-AR

Biederman et al. *Pediatrics* 121: 73-84, 2008
Sallee et al. *JAACAP* 48: 155-65, 2009

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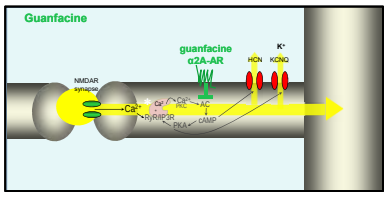
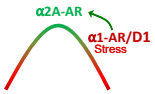
Guanfacine



Extended release guanfacine (Intuniv™- approved by FDA for use in ADHD in 2009 based on our work in monkeys

Also uniquely helpful in children who have been abused or traumatized



Connor et al. *CNS Drugs* 24: 755-68, 2010

Connor et al. *Journal of Child and Adolescent Psychopharmacology* 23: 244-51, 2013

Arnsten et al. *Neurobiol Stress* 1: 89-99, 2015

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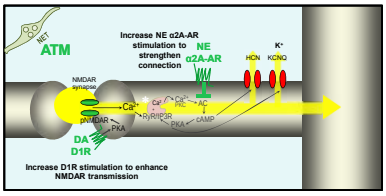
Atomoxetine

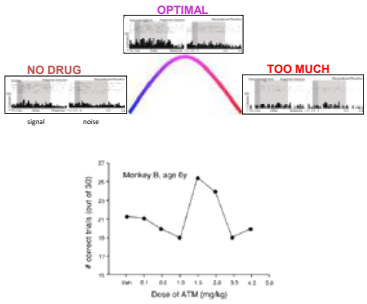


Blocks the NE transporter which takes up both NE and DA in rodent PFC

Bymaster et al. *Neuropsychopharm* 27: 699-711, 2002

80

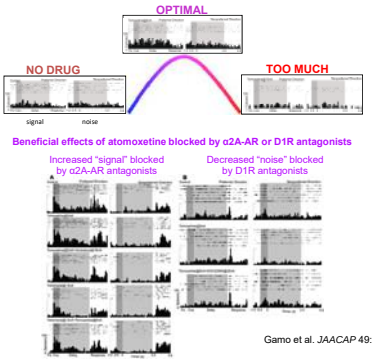
Atomoxetine



Gamo et al. *JAACAP* 49: 1011-23, 2010

81

Atomoxetine



Gamo et al. *JAACAP* 49: 1011-23, 2010

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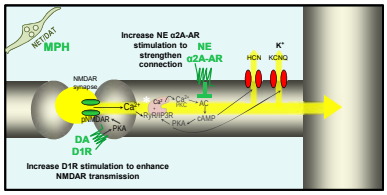
Stimulants

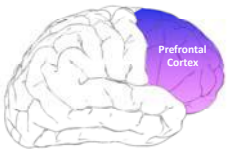
Methylphenidate/Amphetamines

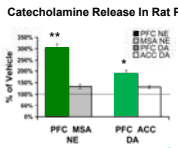


Block NE and DA transporters; amphetamine also increases release

83

Low Doses of Methylphenidate that Produce Therapeutic Blood Levels Increase Catecholamines Predominantly in PFC





mPFC > Nuc. Accumbens

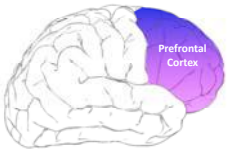
NE > DA

The work of Craig Berridge:

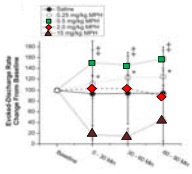
Berridge et al, (2006) *Biol Psychiat* 60: 1111-20.
Berridge et al, (2008) *Biol Psychiat* 64: 626-35.
Berridge (2011) *Biol Psychiat* 69:e101-11.
Spencer et al, (2015) *Biol Psychiat* 77: 940-50.

84

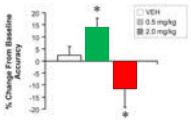
Low (but Not High) Doses of Methylphenidate that Produce Therapeutic Blood Levels Enhance PFC Neuronal Firing



PFC Neuronal Firing In Rats



Working Memory In Rats



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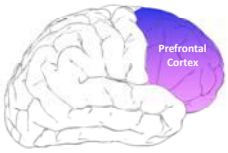
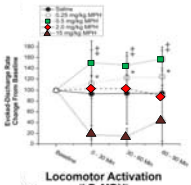
Berridge et al, (2006) *Biol Psychiat* 60: 1111-20.
Berridge et al, (2008) *Biol Psychiat* 64: 626-35.
Berridge (2011) *Biol Psychiat* 69:e101-11.
Spencer et al, (2015) *Biol Psychiat* 77: 940-50.

85

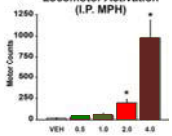
Low (but Not High) Doses of Methylphenidate that Produce Therapeutic Blood Levels Enhance PFC Neuronal Firing



PFC Neuronal Firing In Rats



Locomotor Activation (I.P. MPH)



The work of Craig Berridge:
Berridge et al, (2006) *Biol Psychiat* 60: 1111-20.
Berridge et al, (2008) *Biol Psychiat* 64: 626-35.
Berridge (2011) *Biol Psychiat* 69:e101-11.
Spencer et al, (2015) *Biol Psychiat* 77: 940-50.

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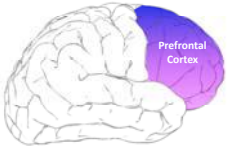
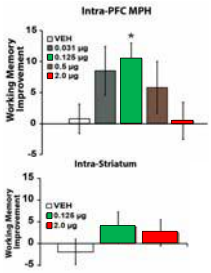
Low (but Not High) Doses of Methylphenidate Infused in PFC Improve Working Memory





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Berridge et al, (2008) *Biol Psychiat* 64: 626-35.
Berridge (2011) *Biol Psychiat* 69:e101-11.
Spencer et al, (2015) *Biol Psychiat* 77: 940-50.

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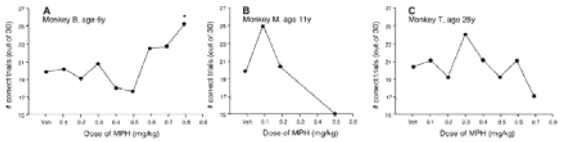
Low Dose Methylphenidate Improves Working Memory In Rhesus Monkeys

agespan: young adult to aged



Gamo et. al, *JAACAP* 49: 1011-23, 2010

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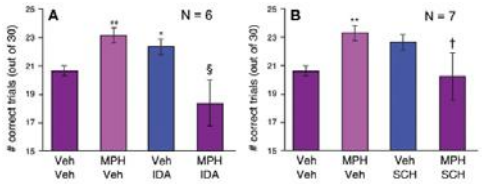
Low Dose Methylphenidate in Monkeys Improves Working Memory via NE α2A-AR and D1R Actions

Enhancement Reversed by NE α2A-AR Antagonist

Enhancement Reversed by DA D1R Antagonist



Gamo et. al, *JAACAP* 49: 1011-23, 2010

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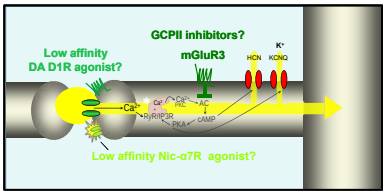
New Treatments?



Yang et al (2013) PNAS 29: 12078-83
Jin et al (2017) Cerebral Cortex 28: 974-87
Wang et al, in submission

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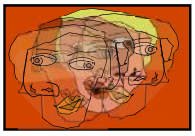
Acknowledgements



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Lu Jin
Avis Hains
Rebecca Shansky
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Shari Birnbaum
Beth Murphy

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Sheng-Tao Yang
James Mazer
Daeyeol Lee
Yang Yang
Nao Gamo
Lu Jin
Susheel Vijayraghavan
Marcus Altman
Veronic Galvin
Taber Lightbourne

Molecular Biology
Becky Carlyle
Shannon Leslie
Angus Nairn

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1RL1AA017536
Pioneer Award DP1AG047744
and
Kavli Center at Yale,
NARSAD Distinguished
Investigator Award

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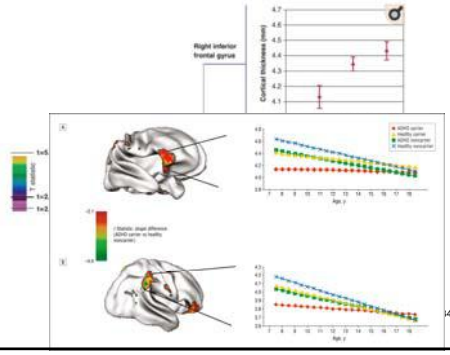
Typically developing children: Higher levels of catecholamines corresponds to greater PFC thickness



49, 2009

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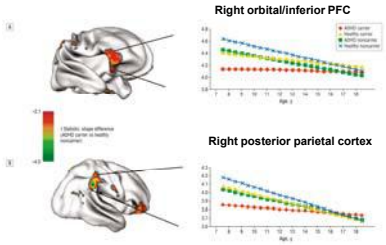
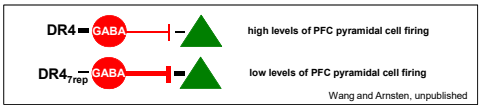
DR4- 7 repeat in ADHD: Thinner cortex

Shaw et al, *Arch Gen Psychiatr.* 64: 921-31 2007





Wang and Arnsten, unpublished

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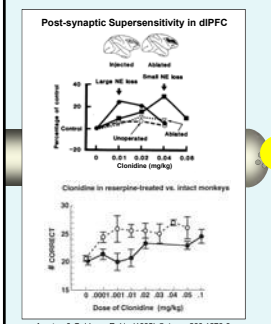
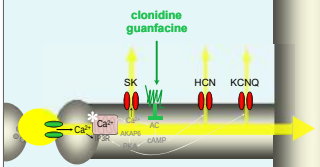
Inhibition of Ca^{2+}-cAMP-K^+ signaling with α2A-adrenoceptor stimulation strengthens PFC network connectivity and improves cognitive function



Arnsten & Goldman-Rakic (1985) *Science* 230:1273-6.
Cai et al. (1993) *Brain Res.* 614:191-6.
Franowicz & Arnsten (1999) *Neuropsychopharm* 21:611–621.



Evidence for post-synaptic actions:

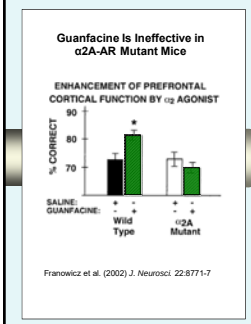
The beneficial effects of clonidine on working memory performance are potentiated, not diminished, when the presynaptic terminals are destroyed with 6-OHDA in the dlPFC, or depleted with systemic reserpine treatment.

Guanfacine is less potent than clonidine at reducing LC firing and NE release, but more potent in improving working memory.

Engberg & Eriksson (1991) *Naunyn-Schmiedebergs Arch. Pharmacol.* 242: 472-7

95

Inhibition of Ca^{2+}-cAMP-K^+ signaling with α2A-adrenoceptor stimulation strengthens PFC network connectivity and improves cognitive function



Franowicz et al. (2002) *J. Neurosci.* 22:8771-7

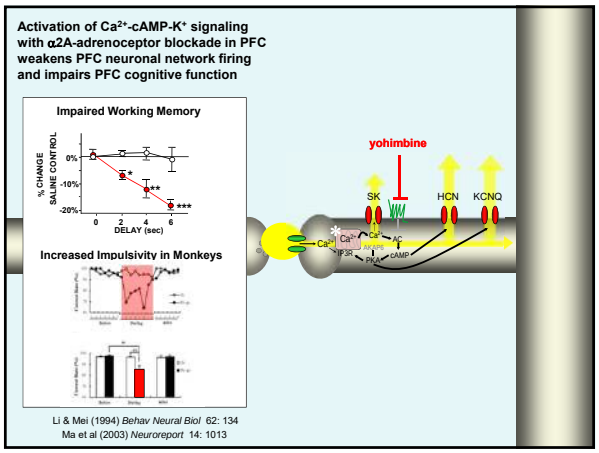
Evidence for actions at α2A-AR:

Improvement in working memory with fewer side effects correlates with selectivity for α2A-AR site: guanfacine>UK14,204=guanabenz>lofexidine >clonidine>BHT-920>dexmedetomidine

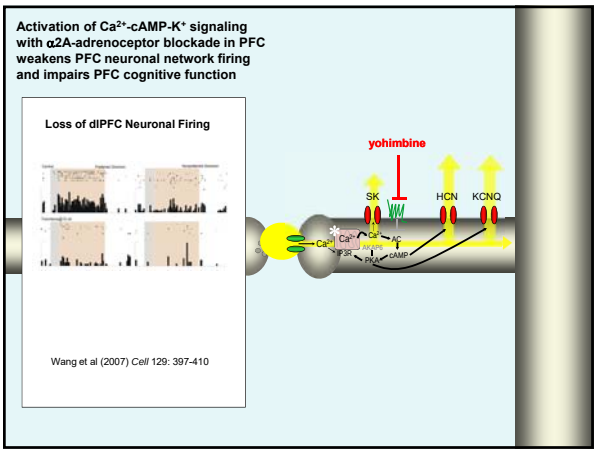
The enhancing effects of guanfacine on working memory are not evident in α2A-AR mutant mice

Arnsten et al (1988) *J Neurosci* 8:14287-98

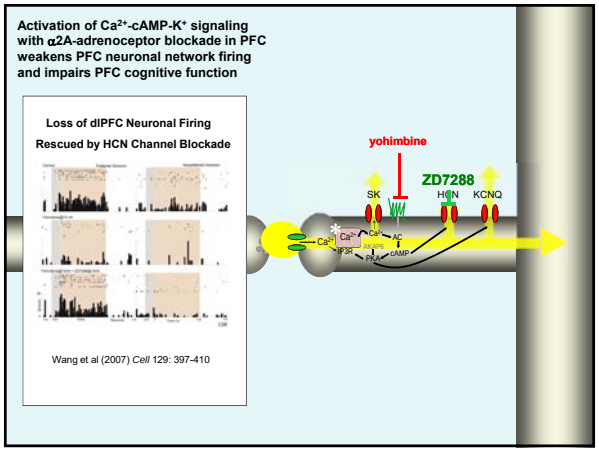
96


Activation of Ca2+-cAMP-K+ signaling with α2A-adrenoceptor blockade in PFC weakens PFC neuronal network firing and impairs PFC cognitive function
Impaired Working Memory
% CHANGE SALINE CONTROL
0%
-10%
-20%
0
2
4
6
DELAY (sec)
*
**
***
Increased Impulsivity in Monkeys
yohimbine
SK
HCN
KCNQ
Ca2+
IP3R
AC
cAMP
PKA
Li & Mei (1994) Behav Neural Biol 62: 134
Ma et al (2003) Neuroreport 14: 1013

97


Activation of Ca2+-cAMP-K+ signaling with α2A-adrenoceptor blockade in PFC weakens PFC neuronal network firing and impairs PFC cognitive function
Loss of dlPFC Neuronal Firing
yohimbine
SK
HCN
KCNQ
Ca2+
IP3R
AC
cAMP
PKA
Wang et al (2007) Cell 129: 397-410

98


Activation of Ca2+-cAMP-K+ signaling with α2A-adrenoceptor blockade in PFC weakens PFC neuronal network firing and impairs PFC cognitive function
Loss of dlPFC Neuronal Firing
Rescued by HCN Channel Blockade
yohimbine
ZD7288
SK
HCN
KCNQ
Ca2+
IP3R
AC
cAMP
PKA
Wang et al (2007) Cell 129: 397-410

99

Using genetics to evaluate environments and endophenotypes for ADHD

Joel Nigg, Ph.D.
Oregon Health & Science University

APSARD Plenary Session
Saturday January 19, 2019

1

Declaration of conflicts of interest

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
NIMH	X							
Abracadabra Foundation	X							
Guilford Press*					X			

*Royalties for Getting Ahead of ADHD (2017) Guilford Press.

2

I. CONCEPTUALIZING ADHD AND THE ENVIRONMENT: IS ADHD "GENETIC"?

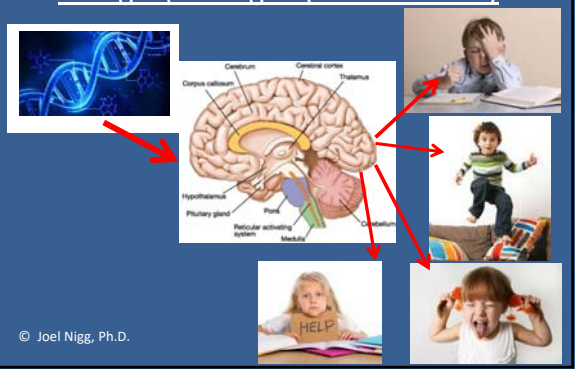
3

What is the paradigm?

- Paradigm=exemplar (Aristotle, Kuhn)
- Wrong paradigm 1: metabolic disease
  - "find the gene, solve the disease"
- Wrong paradigm 2: Linear causality
  - "like a machine; mass=force x acceleration. Find the causal chain, solve the disease"

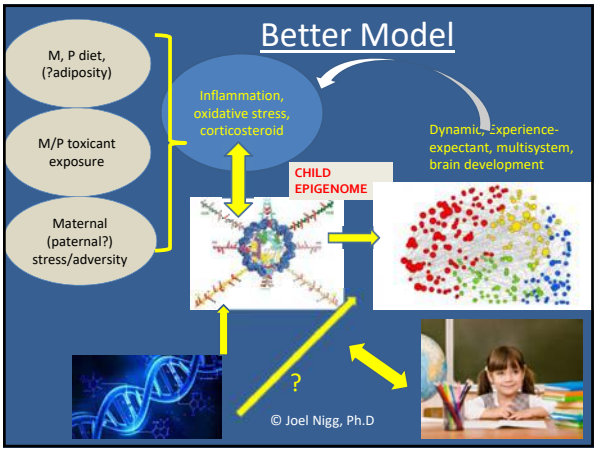
4

OLD VIEW combined those two ideas into a single paradigms(1980s-2000's)



5

Better Model



6

Why? Reasons to reconsider the environment and integrate it with our progress in genetics

- Complex disease model more appropriate
- GxE (heritability of liability) hidden in heritability
- Epigenetic insight— GxE determines phenotype biologically (if not always statistically)

© Joel Nigg, Ph.D.

7

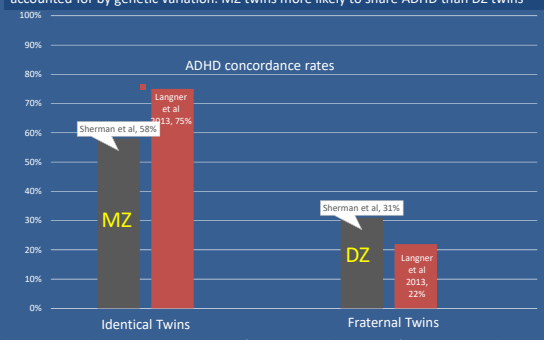
Simple versus complex disease: Is it "genetic"? What does that mean?

• Single gene disorder	• Complex disease
• Deterministic	• Probabilistic
• Rare (< 1/10,000)	• Common (> 1/500)
• Large risk increase in relatives	• Small risk increase in relatives
• PKU, Huntingtons'	• Hypertension

© Joel Nigg, Ph.D.; Data from R. Depue & S. Monroe, 1986

8

"Heritability" of ADHD is about 70%, suggesting that ~ ¾ of variation in the trait is accounted for by genetic variation. MZ twins more likely to share ADHD than DZ twins



- Sherman et al 1997, *Am J Psychiatry* (parent+teacher ratings); Langner et al 2013 *PLoS-One (male-female average)*

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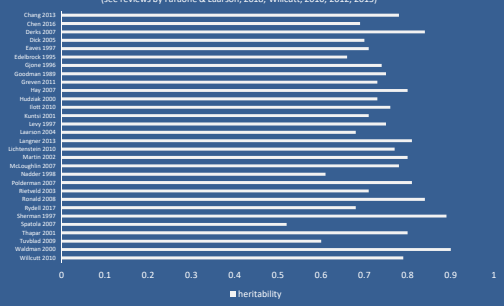
9

Strong evidence of genetic influences on ADHD symptoms based on twin studies

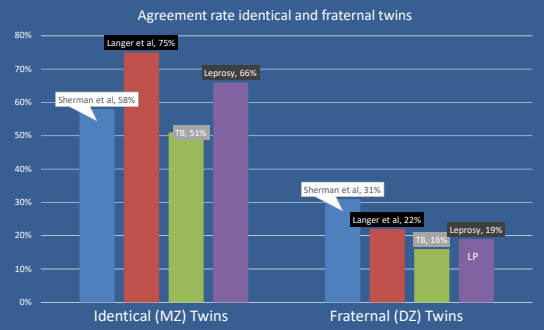
(see reviews by Faraone & Laarson, 2018; Willcutt, 2010, 2012, 2015)



Slide Courtesy of Eric Willcutt and Steve Faraone. © Eric Willcutt

10

With complex disease and polygenic liability, heritable ≠ inherited



© Joel T Nigg, 2017. Data from TB and Leprosy estimated from studies cited in Hill, AVS, 1998; *Ann Rev Immu.; and in* Fine PE,1981, *Int J Lepr Other Mycobact Dis, 49*, 437-454

11

Proposed view of ADHD as involving genetic liability interacting with activating environment (possibly via epigenetic alterations)

- Does NOT mean "all environmental" and not "2 types"
- ADHD heterogeneous
  - but many routes are potentially GxE or epigenetic.
  - Likely very little "all or none"
- Thus: susceptibility (substantially genetic) + experience (epigenetically mediated effects) = complex syndrome
- With
  - varying manifestations
  - temporal variations,
  - multiple routes to emergence and recovery

12

WHEN ARE ENVIRONMENTAL CORRELATES OF ADHD CAUSAL?

13

If we accept this susceptibility model of ADHD: Which Environments do we study and are they causal?

- Sociological Effects
  - Impending collapse of civilization?
  - Too much pharma marketing?
  - Performance pressures on children, starting school too young?
- Caregiver Problems
  - Over-indulgent or else hostile/intrusive parenting
  - Under-trained or inexperienced teachers
- Developmental and Biological Context
  - Rare events
    - Perinatal problems, teratogens (alcohol, drugs); micro-ischemias
    - Extreme toxicant exposures, extreme neglect (Romanian orphans)
  - *** Common but harmful environmental and biological contexts
    - Screen Media
    - Moderate psychosocial stress/distress (esp. prenatal)
    - Poor diet
    - Low grade Toxicant/pollutant exposures (pre-natal, post-natal)

14

Substantial literature links ADHD (non-specifically) to environmental risk factors

- Toxicants
  - Lead; PCB's; BPA; Pesticides
- Dietary insults
  - Western high-fat diet during gestation
  - Western diet (additives) in development
- Gestational and perinatal risks
  - Parental stress, BMI, smoking, other exposures
  - Infant distress, birthweight, delivery complications

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But are these causal?

- Plausibility (can "low amounts" do harm?)
- rGE and unexamined genetic effects
- Unmeasured confounders

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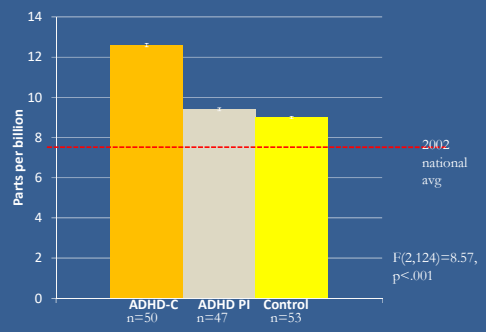
Example: Blood Lead and ADHD 2005-2007



Data from Nigg et al (2008) *Bio Psych, 63, 325-31; © Elsevier Inc., and Society of Biological Psychiatry*

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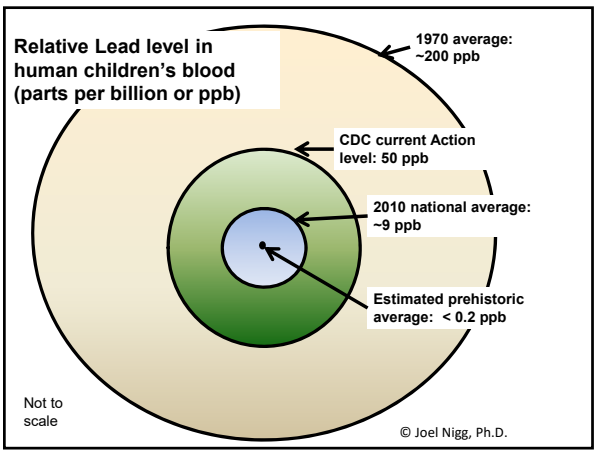


18

How can we evaluate causality of environmental influences on ADHD in humans when experimental tests are not possible?

- Surrogate pregnancy—(e.g., smoking, Thapar et al)
- Sibling, twin, adoption designs
- Natural stratifications (e.g., Dutch famine; or one city stops vaccinations)
- Mendelian randomization** (focus today)

19

Toddler attention altered by prenatal DHA supplementation (single object free-play session; increasing look time predicts stronger cognitive development later; i.e., high IQ=growing ability to sustain focus) from Columbo et al 2004, Child Development 75, 1254 © John Wiley&Sons, Inc.

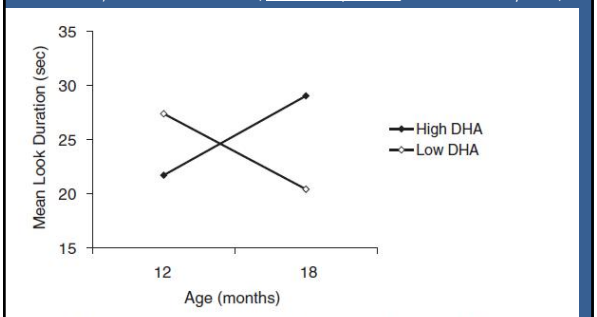
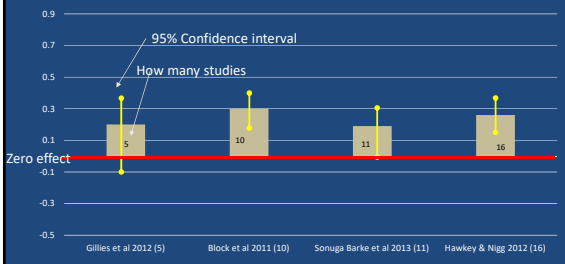


Figure 3. Developmental course of look duration during single-object, free-play sessions at 12 and 18 months as a function of high and low maternal docosahexaenoic acid (DHA) at delivery.

20

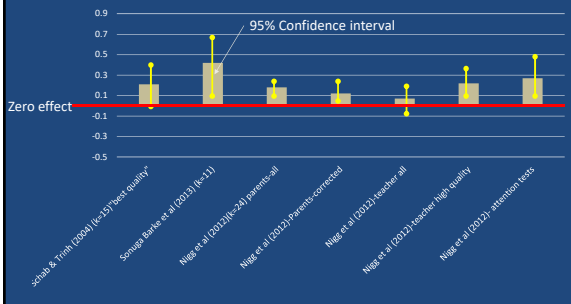
Fatty acid supplementation results: real but small effects



Data from Stevenson et al (2014)

21

Artificial food colors results



Data from Stevenson et al (2014)

22

How we proceeded on lead+ADHD

- Replicated the ADHD-low-lead correlationi(n=213)
- Then combined both samples, (Total N=363; ADHD+control)
- Mendelian randomization design
- HFE gene (6p22.2)
  - iron uptake in gut, lead x iron interplay)
- Weakness: Lacked an independent replication
- Strengths of our study
  - ADHD very well characterized
  - Genotype frequencies matched the regional population
  - Control group blood lead levels matched the population
  - No high blood levels (max=3ug/dL)
  - rGE controlled
  - Race/ethnicity, SES controlled

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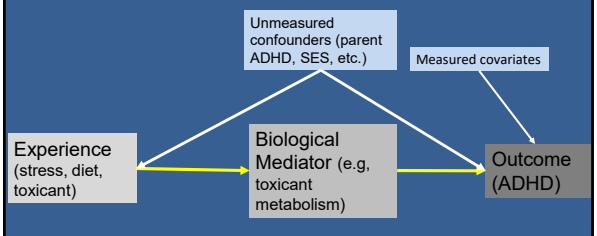
MENDELIAN RANDOMIZATION LOGIC



Source: Adapted from Lewis et al., 2013, Journal of Child Psychology and Psychiatry, 54, pages 1095-08; © ACAH, JCPP, Slide © Joel Nigg, Ph.D.

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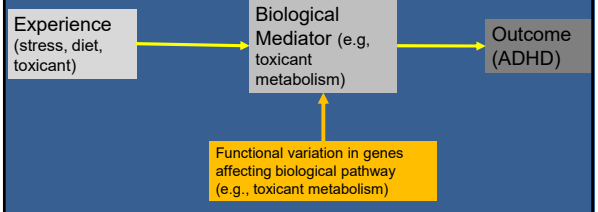
MENDELIAN RANDOMIZATION LOGIC



Source: Adapted from Lewis et al., 2013, Journal of Child Psychology and Psychiatry, 54, pages 1095-08; © ACAH, JCPP. Slide © Joel Nigg, Ph.D.

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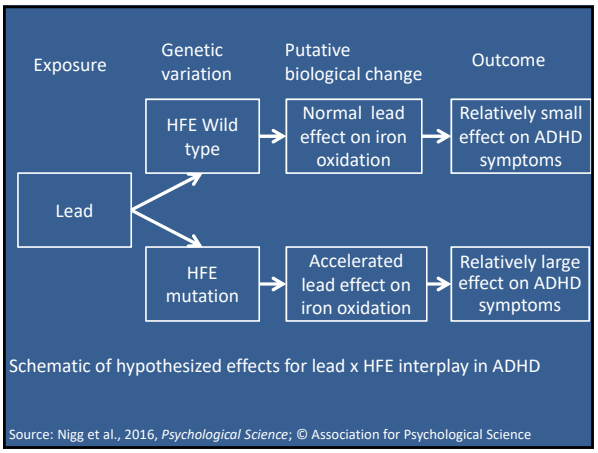

Schematic of hypothesized effects for lead x HFE interplay in ADHD

Source: Nigg et al., 2016, *Psychological Science*; © Association for Psychological Science

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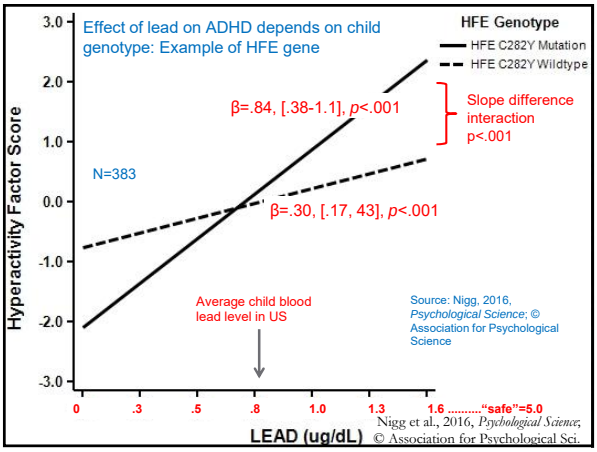

Nigg et al., 2016, *Psychological Science*; © Association for Psychological Sci.

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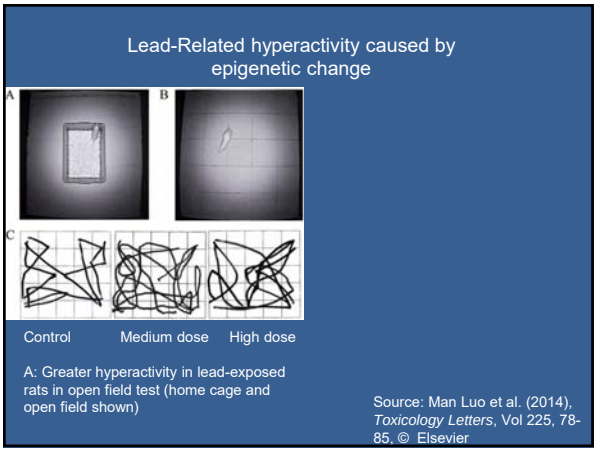

A: Greater hyperactivity in lead-exposed rats in open field test (home cage and open field shown)

Source: Man Luo et al. (2014), *Toxicology Letters*, Vol 225, 78-85. © Elsevier

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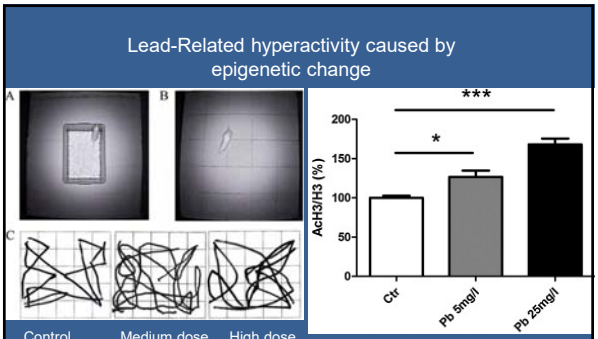

A: Greater hyperactivity in lead-exposed rats in open field test (home cage and open field shown)

B: Relative expression of histone H3 acetylation to β-actin in hippocampus

Source: Man Luo et al. (2014), *Toxicology Letters*, Vol 225, 78-85 © Elsevier

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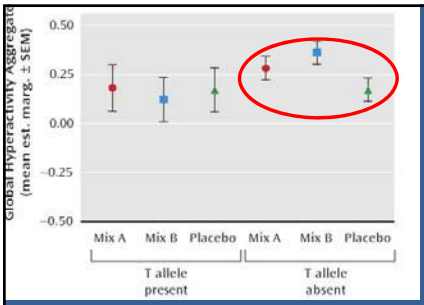


Evidence of causality for Food additives

Potential to identify responders genetically

Effect of food additives on hyperactivity in 8 yr olds is moderated by histamine degradation gene (*HNMT* Thr105Ile and *HNMT* T939C). On the left (Thr105ile), note that when the T allele is present, the food additive challenge has no effect. When the T allele is absent, the food additives cause more hyperactivity than the placebo. ((H3 receptors in the brain may be the mechanism.)) Source: Stevenson et al., 2010, Am J Psychiatry, 167, 1108-1115, © American Psychiatric Associatio

30

Mendelian Randomization: G x E liability effects on organic pollutants and cognitive outcome

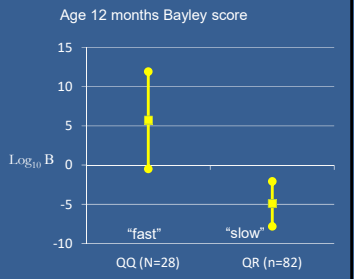
- PON1 gene (7q21.3) effect (slow vs fast metabolizing)

*NYC Mt Sinai cohort

*1998 ~ maternal urinary organophosphate metabolism DAP metabolite

*12 month G x E

Paraoxynase 1 enzyme



Source: Engel et al 2011, Env Health Per. 119, 1182, Published NIEHS, data in public domain; Figure © Nigg

PON1 genotype
Maternal metabolism

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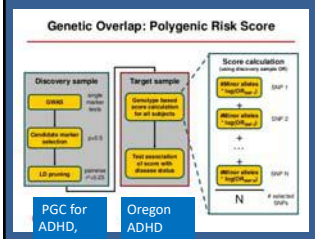
Use of polygenic score to begin to evaluate influences separate from genetic liability

Logic of Polygenic Score creation



PGC for ADHD, MDD, bipolar, other

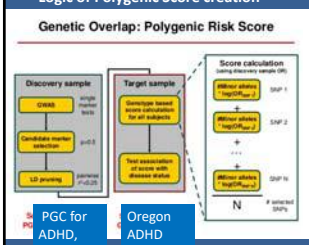
Oregon ADHD Cohort as test cohort

Image © S. DeWitt presented at ISBD 2015

32

Use of polygenic score to begin to evaluate influences separate from genetic liability

Logic of Polygenic Score creation



PGC for ADHD, MDD, bipolar, other

Oregon ADHD Cohort as test cohort

Image © S. DeWitt presented at ISBD 2015

Illustrative differentiation of ADHD components by genetic effect

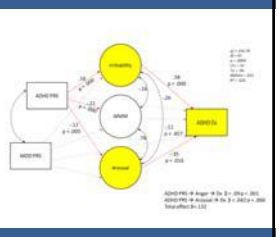


Image © Joel Nigg, 2018.

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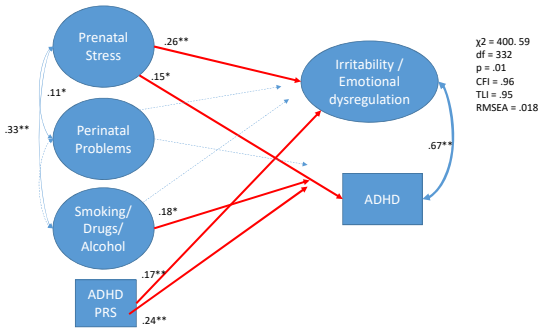
Additive effect or prenatal risks and common genetic liability in ADHD



Gustafsson et al,, in preparation

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Cautions and caveats

- More to go to properly map interplay of genetic liability (specifically), rGE, and exposures (specifically) along with causality
- Heterogeneity within ADHD (executive functioning/ cognitive control, attention-arousal, affect regulation and irritability)
- Overlap and intersection of disorders (non-specificity effects under the existing nosology)

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Conclusions

- Emerging evidence of causal role for at least some environmental risk factors for ADHD
- Effect size of GxE/epigenetic/environmental effects still unclear
- Balance openness and caution here—take these possibilities seriously while continuing to investigate
- Important due to potential to eventually identify reversible causal inputs and prevent/cure/ameliorate in new ways for some percentage of cases

36

- THANK YOU TO
- Collaborators (Partial List; Random Order)
  - Cynthia Huang Pollock, Ph.D.
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  - Karen Friderici, Ph.D.
  - Marsha Rappley, M.D.
  - Beth Wilmot, Ph.D.
  - Hannah Gustafson Ph.D.
  - Mike Mooney, Ph.D.
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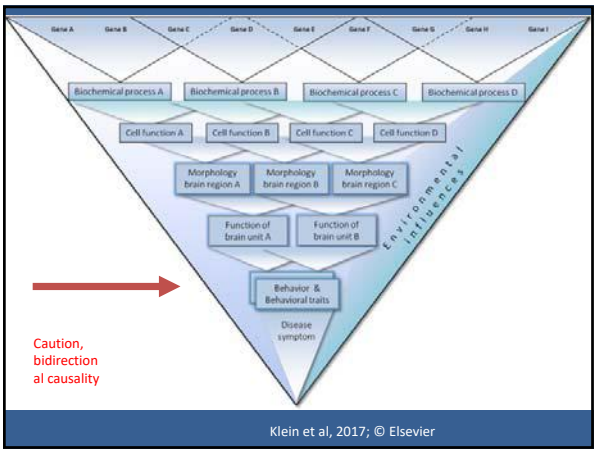

Klein et al, 2017; © Elsevier

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Examples Linking findings in ND: causally informative designs

- Lead → ADHD (Nigg et al, 2016)
- Lead → epigenetic change-> RNA brain-> hyperactivity (Luo et al. 2014)
- Prenatal chemical toxicant→ ADHD, IQ, autism (e.g., Engle et al 2011)
- Prenatal omega-3 intake → infant IQ (e.g., Columbo et al 2004)
- Food additives-> ADHD (Stevenson et al 2010)
- Epigenetic mediation (e.g. Skinner et al 2014)
- We should not be uncritical but should consider these linkages carefully

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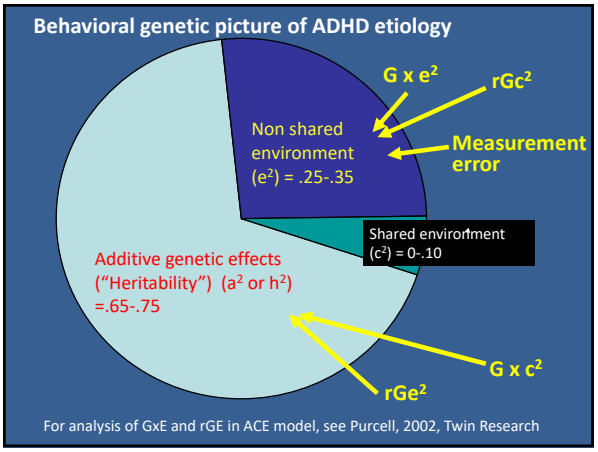

For analysis of GxE and rGE in ACE model, see Purcell, 2002, Twin Research

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APSARD

ADHD Comorbidity: Implications for etiology and treatment

Kathleen Ries Merikangas, Ph.D.

Chief, Genetic Epidemiology Research Branch
National Institute of Mental Health
Intramural Research Program

1

Disclosure

- This work was supported by the National Institute of Mental Health Intramural Research Program.
- The views and opinions expressed in this article are those of the authors and should not be construed to represent the views of any of the U.S. Government.

2

Outline

- **Background**
- **Evidence from community surveys**
- **Explanations**
- **Implications for research, treatment and services**

3

Background

4

THE PRE-THERAPEUTIC CLASSIFICATION OF CO-MORBIDITY IN CHRONIC DISEASE*

ALVAN R. FEINSTEIN, M.D.†

J Chron Dis 1970, Vol. 23, pp. 455-468. Pergamon Press. Printed in Great Britain

- ….Co-morbidity refers any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study….

5

Robert Wood Johnson Foundation

THE SYNTHESIS PROJECT

NEW INSIGHTS FROM RESEARCH RESULTS

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RESEARCH SYNTHESIS REPORT NO. 21

FEBRUARY 2011

Mental disorders and medical comorbidity

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Robert Wood Johnson Foundation THE SYNTHESIS PROJECT

- ….”the mismatch between clinical reality of medical-mental comorbidity and a medical care system that separates these critical domains is a major future challenge in American health care”

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Impact of Comorbid Mental & Medical Conditions

- Increased mortality
- Greater health care costs
- Poorer treatment response
- More functional impairment

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Methodological Challenges

- Sampling variability
- Parent and/or child reported diagnoses
- Diagnosis solely based on ICD or DSM codes
- Non-comparable information on mental and physical disorders
- Limited range of mental and physical conditions
- Cross-sectional assessment
- Small numbers of cases of some conditions

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Evidence from Community Samples

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Specialty mental health samples are becoming more divergent from primary care and population samples

Spectrum of illness:

Most diseases demonstrate a range of manifestations and severity

Gerstman Chapter 2 11

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National Comorbidity Survey – Adolescent Supplement (NCS-A)

- Cross-sectional survey of a representative sample of 13-18 year-olds in the continental U.S.
- 2001-2004
- N=10,123 adolescents, Parent reports on 6,148
- Sample of households (9%); Schools (91%)
- Fully-structured interview assessing mental health, physical health conditions, demographics, individual and family characteristics

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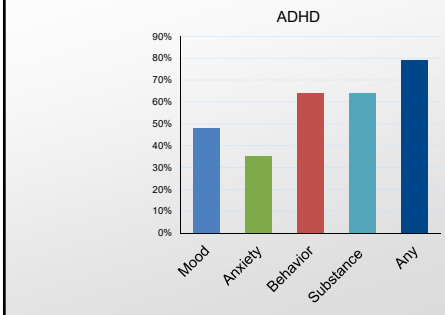
Lifetime rates of comorbid mental disorders among those with ADHD: NCS A



Kessler et al,2013

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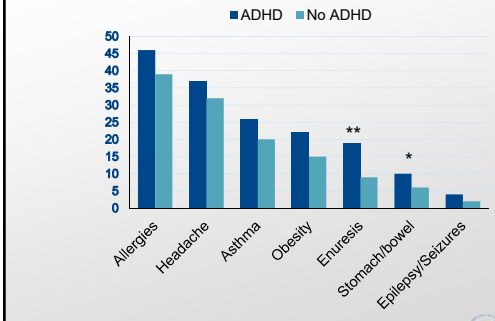
Lifetime rates of comorbid physical disorders among those with ADHD: NCS A



Jameson et al,2016

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Medical Mental Comorbidity: NCS-A (n=6,483)

Disorder	ADHD	ANXIETY	BEHAVIOR	MOOD
Allergies/Immune	---	---	---	1.3*
Cardiovascular	---	1.8*	---	---
Developmental	4.4**	---	---	---
Enuresis	1.6*	---	---	---
Gastrointestinal	---	---	---	---
Headaches/Migraine	---	1.8*	1.6*	1.8*
Learning Disabilities	5.1**	---	1.9*	1.6*
Skin/Acne	---	1.4*	---	---

Jameson et al, 2016

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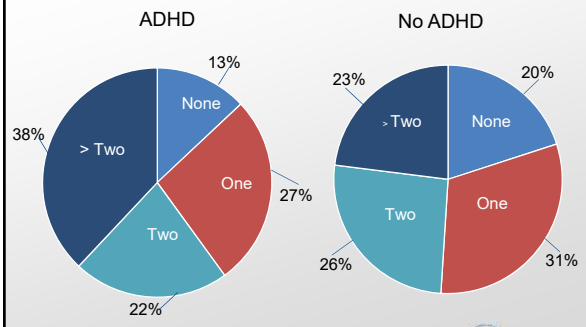
ADHD: Number of Comorbid Medical Conditions in NCS-A



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Philadelphia Neurodevelopmental Cohort

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Philadelphia Neurodevelopmental Cohort Study (PNC)

Sample

- N=9,700 youth ages 8-21
- Visits to the Children's Hospital of Philadelphia

Measures

- Comprehensive screening interview for mental disorders
- Chronic physical conditions reported by parent and/or youth
- Electronic medical record review

Investigators

- Raquel E. Gur, M.D., Ph.D.
- Hakon Hakonarson, M.D., Ph.D.

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Medical-Mental Comorbidity: PNC (n=9,014)

Medical Disorder	ADHD	BEHAVIOR	MOOD	Psychosis Sx
Autoimmune/ Inflammatory	---	---	2.2*	---
Developmental	3.1**	1.5*	0.9*	1.7**
Neurologic/CNS	1.3*	---	1.3*	---

Merikangas et al, 2013

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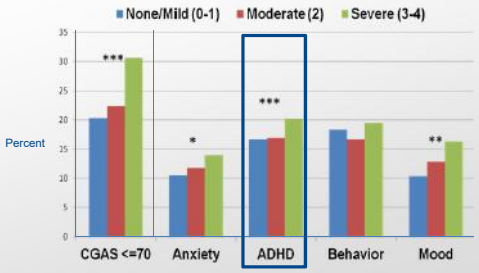
Mental Disorders by Severity of Medical Conditions:PNC (n=9014)



Merikangas et al, 2013

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Aggregate Patterns of Comorbidity

- ADHD is strongly associated with developmental disorders and other neurologic conditions (i.e., enuresis, seizures, learning disabilities, developmental disorders, stuttering)
- Mood disorders are associated with inflammatory and autoimmune disorders

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Comorbidity by ADHD Subgroups (N =1131, ages 5-21)

Child Mind Institute
healthy brain network

Subtype	Combined	Inattentive	Hyperactivity
Autism Spectrum	+	+	+
Communication	++	++	+
Elimination	+	+	++
Learning	++	++	+
Motor	+	+	+

Milham, Alexander, Escalera et al, unpublished

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Explanations

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Sources of Comorbidity

Causal

ADHD ⟷ Physical Dx

Common Etiology

Risk Factors → ADHD
Risk Factors → Physical Dx

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Potential Mechanisms: ADHD and Neurologic Disorders

Causal:

- ✓ Seizures/epilepsy lead to impairment in executive and motor functioning
- ✓ Learning disability inhibits development of attention and/or motor control

Common Risk Factors:

- ✓ Pre- or peri-natal factors, e.g., maternal tobacco
- ✓ Early environmental exposures, i.e., lead, nutritional deficiencies, head injures, neglect/abuse
- ✓ Common genetic factors
- ✓ Risky health behaviors

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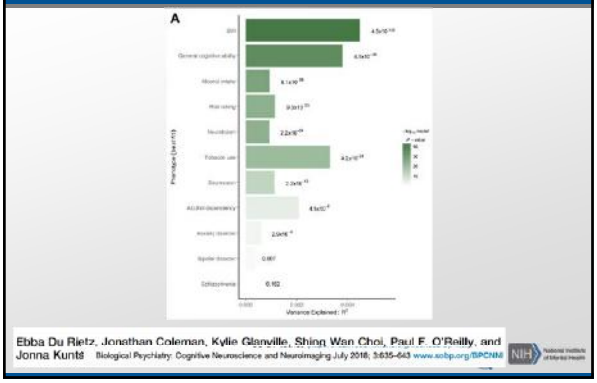
Polygenic Risk for ADHD with Co-Occurring Traits/Disorders in the UK Biobank



Ebba Du Rietz, Jonathan Coleman, Kylie Glanville, Shing Wan Choi, Paul F. O'Reilly, and Jonna Kuntsi Biological Psychiatry: Cognitive Neuroscience and Neuroimaging July 2018; 3:635-643 www.sobp.org/BPCNNI

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Implications

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THE PRE-THERAPEUTIC CLASSIFICATION OF CO-MORBIDITY IN CHRONIC DISEASE*

ALVAN R. FEINSTEIN, M.D.†

J Chron Dis 1970, Vol. 23, pp. 455-468. Pergamon Press. Printed in Great Britain

- Neglect of co-morbidity can lead to:
  - ✓ Inaccurate estimates of morbidity and mortality in populations
  - ✓ Misleading fatality rates for individual diseases
  - ✓ Spurious results of clinical trials

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VIEWPOINT

Future Surveillance of Mental Disorders in the United States
Count People, Not Disorders

Kathleen R. Merikangas, PhD
Evelyn J. Bromet, PhD
Ben G. Druss, MD, MPH

JAMA Psychiatry May 2017 Volume 74, Number 5

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Incorporation of Comorbidity in Research

- Prospective collaborative international studies of pathways to and consequences of comorbidity in both clinical, household and registry data
- Research on the genetic, biologic and environmental determinants of comorbidity
- Investigate comorbidity as a source of heterogeneity or confounder of studies of ADHD and other mental disorders
- Expand the knowledge base on effective treatments for mental disorders (ADHD) comorbid with physical disorders

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Broader Health Sector Implications

- Shift from diagnostic-based single care approach to collaborative care model

  (RWJ, 2011; Lannon, Peterson, 2013)
- Broader coordination of the medical sector with other systems including education, and social services to identify points of prevention and intervention
- Systematic evaluation of outcome to inform evidence base

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Comprehensive Community Behavioral Health Clinics

Shift in community mental health care from disorders to "patient/person-centered" care to:

- Provide community-based mental/substance use disorder services
- Advance integration of behavioral with physical health care
- Utilize evidence-based practices
- Promote improved access to high quality care for individuals with SMI, SUD, youth with SED, and *those with co-occurring physical health disorders*

Protecting Access to Medicare Act of 2014

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Comorbidity and Professional Societies!

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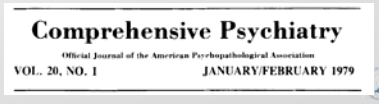
Interfaces between Medicine and Psychiatry
Leon Eisenberg, 1979

….we must move toward the provision of the full range of mental health services in the context of medical are rather than in the isolated mental hospitals and psychiatric clinics; primary care physicians working side by side with mental health personnel are more likely to refer patients for consultation ---and those patients are more likely to accept referral---than when medical and psychiatric services are geographically separated."


Comprehensive Psychiatry
Official Journal of the American Psychopathological Association
VOL. 20, NO. 1 JANUARY/FEBRUARY 1979

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Links between physical & mental disorders

"A full understanding of the human brain requires an integrated perspective, where mind and body fully interact with physical and social environment
…
… Brain and body are absolutely integrated by neural and biochemical circuits, going from one to the other, and the opposite"

Antonio R. Damasio, *Descartes' Error*, 1995

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Thank you!

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A 50 YEAR JOURNEY FROM LD TO ADHD

A RETROSPECTIVE FOR APSARD 2019

MARTHA BRIDGE DENCKLA, M.D.

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DYSLEXIA: MY ENTRY POINT INTO NEUROLOGY

- NORMAN GESCHWIND LECTURE, "PURE ALEXIA WITHOUT AGRAPHIA"
- CONNECTIONISM AND COGNITIVE BEHAVIORAL NEUROLOGY
- A TEN WEEK ROTATION WITH GESCHWIND AT START OF INTERNAL MEDICINE RESIDENCY!
- DECISION (MET WITH DIFFICULTIES) TO GO INTO NEUROLOGY WITH GESCHWIND

2

EDITH KAPLAN AND NORMAN GESCHWIND

3

DEVELOPMENTAL DYSLEXIA:ENTRY TO CHILD NEUROLOGY

- SID CARTER'S SURPRISING WELCOME TO COLUMBIA'S NEUROLOGICAL INSTITUTE
- WEEKLY CHILD NEUROLOGY CLINIC: EVERY CHILD LATE TOTALK OR TO READ
- GRADUAL TRANSITION TO MORE DEVELOPMENTAL ,LESS AQUIRED ADULT, CLINIC
- RESEARCH APPLICATIONS FOLLOW "SUTTON'S LAW;" SUCCESSFUL FUNDING FOR DYSLEXIA

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NEUROPSYCHOLOGY: MY RESEARCH DISCIPLINE THANKS TO RITA RUDEL

- TEAMED UP WITH RITA RUDEL, WHO REALLY TRAINED ME IN RESEARCH METHODS
- EXPANDED BRAIN LOCALIZATION PERSPECTIVE INTO "4TH DIMENSION" OF DEVELOPMENT
- RITA BROUGHT EXPERIENCE WORKING WITH "BRAIN DAMAGED" ADOLESCENTS AND CHILDREN
- RITA WAS A TOUGH CRITICAL THINKER AND WRITER

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MBD(MY INITIALS) AND MBD(THE OLD DIAGNOSIS)

- LUCKY TO BE LIVING IN NEW JERSEY: THERE, CLASSES FOR "NEUROLOGICALLY IMPAIRED"
- REQUIRED NORMAL RANGE IQ AND NEUROLOGIST STATING "BRAIN DYSFUNCTION" FOUND
- "BRAIN" TERM IN MBD DIAGNOSIS; MOST RELIABLE SIGNS ARE MOTOR SYSTEM ABNORMALITIES
- WITH DATA, DEVELOPMENTALLY IMMATURE MOTOR SIGNS SERVE AS ANOMALIES

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NEUROMOTOR SYSTEMS: THE "OLD RELIABLES"

- PRAGMATIC PURPOSE IN NEW JERSEY: PLACE IN CLASS FOR "NEUROLOGICALLY IMPAIRED"/MBD
- "HAD THE CHILD BEEN YOUNGER, THE FINDING WOULD HAVE BEEN NORMAL," e.g. OVERFLOW
- REFERRING TO THE ADULT BRAIN MAP, PARALLEL CIRCUITS WITH FRONTAL LOBES AT TOP
- MOTOR CONTROL BEFORE COGNITIVE CONTROL AND LAST COMES EMOTIONAL CONTROL

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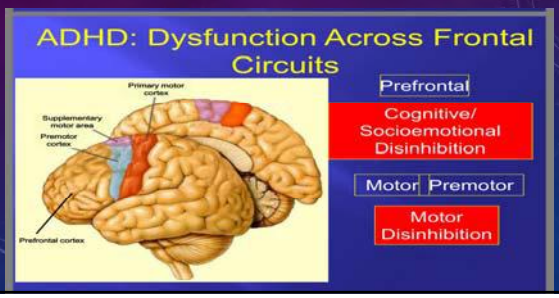
THE 3 CONTROL CIRCUITS



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NEUROMOTOR SYSTEMS GUIDE MAGNETIC RESONANCE IMAGING AND TMS RESEARCH

- FIRST LOOK AT MOTOR CONTROL AT LEVEL OF BASAL GANGLIA IN THE CIRCUIT;LATER, FRONTAL
- SEQUENCE OF RESEARCH: ANATOMIC MRI, FUNCTIONAL MRI, DIFFUSION WEIGHTED (PATHWAY) MRI,NON TASK ELICITED (SO-CALLED RESTING STATE) MRI
- TO STUDY DEVELOPMENT OF AUTOMATIC MOTOR INHIBITION,

  TRANSCRANIAL MAGNETIC STIMULATION STUDY OF MIRROR OVERFLOW

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APPLICATION OF NEUROMOTOR SIGNS TO PRECURSOR OF ADHD

- 1978 PUBLICATION,"ANOMALIES OF MOTOR DEVELOPMENT IN HYPERACTIVE BOYS FREE OF LD" (DENCKLA AND RUDEL, ANNALS OF NEUROLOGY) AFTER SOME CORRESPONDENCE WITH EDITOR
- MANY PUBLICATIONS DOCUMENTING INDIRECT SIGNIFICANCE OF MOTOR SIGNS TO ADHD
- 2011 PUBLICATION ON TMS/MIRROR MOVEMENTS IN ADHD (MY JUNIOR COLLEAGUES ,IN *NEUROLOGY,* ACCOMPANIED BY EDITORIAL "FAULTY BRAKES?" BY JONATHAN MINK, M.D.,PH.D)
- RECENTLY IN PSYCHIATRY WRITING, "MOTOR ENDOPHENOTYPE" OF ADHD

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CHILD PSYCHIATRY RELATIONSHIPS: A TALE OF TWO CITIES

- JOINT APPOINTMENT AND WARM COLLABORATIONS IN NEW YORK CITY, COLUMBIA'S 2 INSTITUTES
- RETURN TO BOSTON, NEUROLOGY ONLY, BUT "OASIS" OF WELCOME BY PETER WOLFF,M.D.
- CONVERGENT VALIDATION OF MOTOR WORK BY WOLFF AND WABER; CHOREIFORM MOVEMENTS AND ATTENTION RATINGS IN SCHOOL
- MULTIDISCIPLINARY LD CLINIC INCLUDED CHILD PSYCHIATRY FELLOWS

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NONVERBAL LD, ITS RISE AND FALL AND WHAT IT NEGLECTED

- NEUROPSYCHOLOGIST BYRON ROURKE,PH.D, HIGHLIGHTED A " RIGHT HEMISPHERE SYNDROME" POPULAR BECAUSE OF THE SOCIAL COGNITION COMPONENT(MORE THAN THE MATH LD)
- NEUROLOGIST KYTJA VOELLER, INTERESTED IN SOCIAL PERCEPTION,REPORTED ON CASES OF LEFT HEMIPLEGIC CP, FOUND MOST HAD ADHD
- IMPORTANT CONNECTION OF ADHD WITH SOCIAL ATTENTION/PERCEPTION/COGNITION
- NONVERBAL LD APPLIED TO SEVERAL GENETIC DISORDERS, NOT CONFIRMED, *e.g.*
- WABER FINDS VERBAL FLUENCY DEFICIT IN GIRLS WITH TURNER SYNDROME

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NIH YEARS: EXILE FROM ACADEMIA:PROGRAM PORTFOLIO ON AUTISM, TOURETTE, ADHD

- RESEARCH OPPORTUNITY PROVIDED BY BENEVOLENT BOSS, SAM DRAGE,M.D., AND JUDITH RAPOPORT, M.D., AT INTRAMURAL NIMH, WITH JUDITH RUMSEY,PH.D
- RESEARCH ON DYSLEXIA, MOTOR SIGNS IN UNTREATED CHILDREN WITH OCD
- MET NIH GENETICS CLINIC, STARTED RESEARCH ON NEUROFIBROMATOSIS-1
- MET THROUGH PROGRAM DUTIES MOST OF AUTISM RESEARCH COMMUNITY
- TOURETTE SYNDROME ASSOCIATION BECAME MY FAVORITE NGO

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30 YEARS AT KENNEDY KRIEGER INSTITUTE/JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

- BACK TO JOINT APPOINTMENT, THIS TIME ADDING PEDIATRICS AND EDUCATION
- CENTER GRANT FUNDING,"GENE TO BRAIN TO SYNDROME OF LD" INCLUDED NF-1, TOURETTE PROJECTS
- *BOTH* FOUND TO BE ASSOCIATED WITH ADHD, NO SURPRISE WITH TOURETTE
- ADHD CONNECTED TO LD THROUGH *EXECUTIVE DYSFUNCTION*

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TWO INTERESTING BUT UNDERAPPRECIATED FINDINGS FROM NEUROGENETIC RESEARCH

- TOURETTE, IF FREE OF COMORBID ADHD, ASSOCIATED WITH HIGHER IQ THAN MIDPARENTAL, IQ THAT DOES NOT REGRESS TO THE MEAN
- LONGITUDINAL STUDY OF NF-1 PROBAND/SIBLING NEUROPSYCHOLOGICAL TESTS: LANGUAGE RESCUED BY FAMILY ENVIRONMENT, OTHER IMPAIRMENTS REMAIN

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IMPACT OF EXECUTIVE FUNCTION/DYSFUNCTION ON EMERGING LD WITH ADHD

- EARLY ENROLLEES WITH ADHD TEST WELL ACADEMICALLY
- FOLLOWED 2 YEARS, THOSE WITH ADHD FALL BEHIND, FIRST IN WRITING*
- NEXT, READING COMPREHENSION FALTERS BY THIRD GRADE
- LONG DIVISION PROVES A STUMBLING BLOCK IN MATH
- PERSISTENTLY, LONG FORM WRITTEN EXPRESSION DISORDER

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GROWING CONCEPT OF EXECUTIVE FACTOR (EF)AS MEDIATOR OF COGNITIVE AND SOCIAL ADAPTATION

- RESEARCH FINDINGS OF NEUROPSYCHOLOGICAL TESTS INCONSISTENT
- RATINGS, LIKE *BRIEF,* POORLY CORRELATED WITH TESTS,LIKE *DK-EFS*
- DISTINCTION BETWEEN "COLD" AND "HOT" EXECUTIVE FUNCTION
- "HOT" MEANS SOCIAL-EMOTIONAL, EVEN MORE DIFFICULT TO MEASURE

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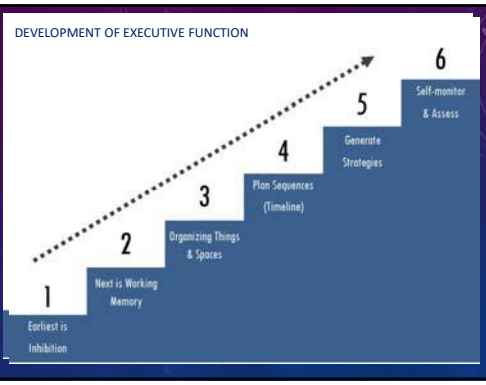

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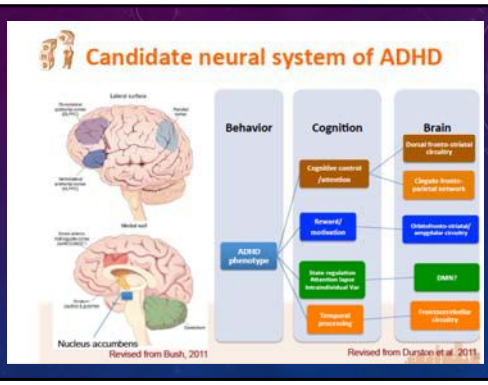

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TEACHING NEUROLOGISTS AND EDUCATORS

- ANNUAL LECTURES AT AMERICAN ACADEMY OF NEUROLOGY CME COURSE
- LECTURES AND SEMINARS WHEN TEACHING IN MASTER'S PROGRAM AT SCHOOL OF ED AND LATER AT KENNEDY KRIEGER CENTER FOR LEADERSHIP IN SPECIAL EDUCATION
- EMPHASIS ON *NON PHARMACOLOGICAL TREATMENT OF ADHD IN MULTIMODAL PROGRAM*
- BEHAVIOR MODIFICATION,"A-B-C" REMARKABLY UNDERUTILIZED
- EXECUTIVE COACHING CAN BE ALONG WITH OR WITHIN COGNITIVE/BEHAVIORAL RX

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CURRENT CONCEPT OF "PRIMARY" ADHD

- A TRUE EXAMPLE OF *DEVELOPMENTAL DELAY?* IF SO, NOT TRIVIAL
- CONSEQUENCES OF 3 YEAR "LAG" CAN BE CRIPPLING
- EVIDENCE FOR ADHD DIFFERS FROM DYSLEXIA'S DIFFERENT ARCHITECTURE
- ADHD AND DYSLEXIA EXEMPLIFY TWO TYPES OF *INCONVENIENT BRAINS*

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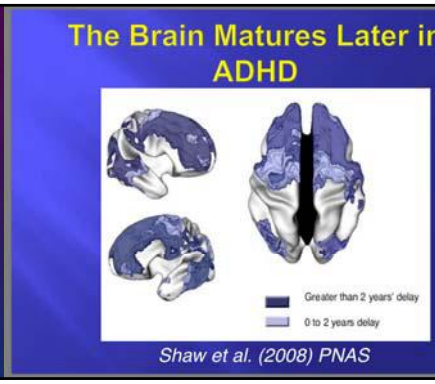

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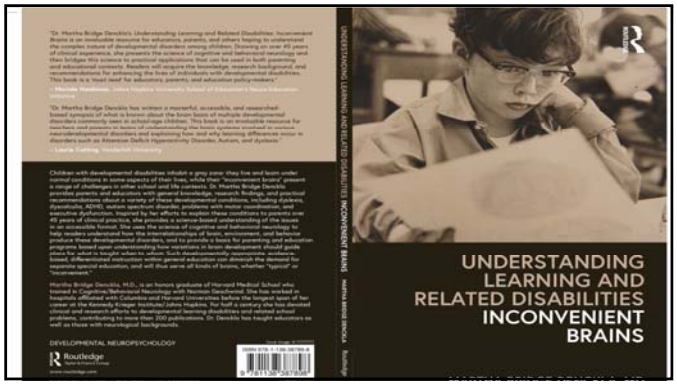

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COLLEAGUES, MENTORS,MENTEES,1971-2018

RITA G RUDEL.
JANE HOLMES BERNSTEIN
DEBORAH WABER
PETER WOLFF
JUDITH RAPOPORT
JUDITH RUMSEY
LAURIE CUTTING
HARVEY SINGER
CAROL GROSS
CHRISTIANE COX
FRANK VELLUTINO
ALLAN REISS
STEWART MOSTOFSKY
DONALD GILBERT
E.MARK MAHONE
NANCY GRASMICK
MARY ELLEN LEWIS

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THE 3 RUSSELLS OF ADHD

1

PROMISE AND PERILS OF EVIDENCE –BASED PSYCHOSOCIAL TREATMENTS FOR ADHD

Are There Adverse Events? If So, What Are They? And How Common Are They?

Russell A. Barkley, Ph.D., Linda Pfiffner, Ph.D., and Laura Knouse, Ph.D.

2

Presenter Disclosure – Prior 12 Months

Speaker (Honoraria):

- Yachad, Union of Orthodox Jewish Associations, Brooklyn, NY
- Archimede – ADHD Association, Padua, Italy
- Chesapeake Academy, Virginia Beach, VA
- Kansas City Children's Mercy Hospital & Midwest ADHD Conference, Kansas City, MO
- Lines & Thoughts, ADHD Association of Israel, Tel Aviv
- US Navy Hospital, Portsmouth, VA
- Medical College of Wisconsin – Dept. of Psychiatry
- Forman School, Litchfield, CT
- Delaware Valley Friends School, Palais, PA
- Regents University, Virginia Beach, VA
- Florida Association of School Psychologists, Orlando, FL
- Children and Adults with ADHD, annual meeting, St. Louis, MO
- Seminarer Denmark, Copenhagen

Royalties:

- Guilford Publications (books, videos, newsletter);
- Premier Educational Seminars Inc. (PESI) (webCE courses and books);
- ContinuingEdCourses.net (web CE courses),
- Aptus Health (CE course for physicians)

Industry Speaker/Consultant:

- Team Esteem – ADHD Website – Consultant
- Shire Pharmaceutical Development Co. - Consultant

3

SOURCES: *THE ADHD REPORT*

February and March 2018 Issues:

Behavioral Parent Training – Carla Allan & Anil Chacko

Social Skills Training – Amori Mikami

Behavioral Family Training of Teens – Russell Barkley

Classroom Behavior Management – Linda Pfiffner & George DuPaul

Teen (Parent) Organizational Training – Joshua Langberg

Cognitive Behavioral Therapy for Adults – Laura Knouse & J. Russell Ramsay

Adult ADHD Coaching (college students) – David Parker, Shlomo Sawilowski, and colleagues

Mindfulness Meditation for ADHD – John Mitchell & Lydia Zylowska

4

EVIDENCE-BASED PSYCHOSOCIAL TREATMENTS FOR ADHD

- Among nonmedication therapies, the top three evidence-based practices for ADHD management:
- **Parent counseling and behavioral parent (BPT)/family training (BFT) (Behavior Management Skills, Problem-Solving and Communication Training, or PSCT)**
  - Largest effects are for improved parenting skills and sense of competence, and to some extent parent-child relationship. Somewhat smaller effects on childhood conduct problems and oppositional defiant behavior with weaker and inconsistent effects on ADHD symptom dimensions
- **Classroom behavior modification methods** (often coupled with academic accommodations and formal special educational services)
- **Cognitive behavioral therapy for adult ADHD**
- **No Question of Efficacy/Effectiveness**

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HISTORY OF RECOGNIZING ADVERSE EVENTS IN PSYCHOSOCIAL TREATMENTS

- Adverse events (AEs) have been documented for more than 50 years for psychotherapy (Strupp et al., 1977; Stuart, 1970). Other reports of AEs followed suit:
  - Hazards of encounter groups
  - Deterioration during inpatient hospitalization
  - Adverse reactions (anxiety) to relaxation training
  - Adverse events linked to hypnosis
  - Deviancy training in peer therapy groups (e.g. social skills training, group homes)
  - Adverse events in crime prevention programs
  - Increases in suicidality from suicide prevention efforts
  - Deterioration in and iatrogenic effects of drug treatment programs

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MORE HISTORY

- Increased disruptive behavior following behavioral parent training (BPT)(Herbert, 1973)
- **5-10% of adults** in RCTs deteriorate and **14% do so in routine care** (Lambert & Ogles, 2004; Hansen et al., 2002)
- **14-24% of children** in managed or community care deteriorate during treatment (Warren et al., 2010) – Children seem more likely than adults to deteriorate during psychosocial treatments

- **So why have they not been studied very much and systematically?**
  - Initial perceptions psychosocial **therapies were ineffective**. (Duggan and colleagues, 2014); **clinician belief that identifying AE was bad practice**
  - With growing evidence that some therapies were effective, interest in AEs has increased.
  - **Clinicians are grossly inaccurate** in identifying when patients are getting worse (40 or 7% of patients worsened in therapy but only 3 (<1%) as reported by clinicians)(Hannon et al.,)
  - **Lack of training and confirmation bias** made clinicians ill-equipped to judge when treatment is going badly; they could not adapt therapy to avoid doing more harm (Allan & Chacko, 2018) .

7

MORE BACKGROUND

- 2010 -- Barlow argues that we **cannot begin to understand how to manage** the side effects of psychotherapies if we don't study them.
- 2012 – Linden develops the Unwanted Events/Adverse Treatment Reactions Checklist for use by psychotherapists. **Identifying AEs is not bad clinical care but of good clinical practice.**
- **In ADHD**, AE recognition in BPT is very recent and grossly neglected:
  - 2001 by Barkley & colleagues in teen therapy
  - 2008 by Evans et al., among others, but nothing changes regarding ignoring AEs in therapies.
- **This creates a glaring hypocrisy** -- side effects of ADHD medications are routinely studied but not for psychosocial treatments yet authors cite drugside effects as justification for their own research. Also for developing alternative nonmedical therapies. BUT, the psychosocial studies don't assess or report their own AEs
- History suggests there is **every reason for adverse events in psychosocial treatments for ADHD** even if grossly under-studied and under-reported

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WHY SIDE EFFECTS? BECAUSE OF THE SUBSTANTIAL VARIATION IN

- **Client variables:** demographics (age, sex, etc.), severity of disorder, comorbidity, personality, intelligence, etc. For children, this domain extends to parent variables as well, such as parental demographics, ADHD, other disorders, intelligence, marital status, social isolation/insularity, etc.
- **Therapy variables (inappropriate treatment):** nature and complexity of the techniques, fidelity to expert manuals, intended cognitive-behavioral targets, method of delivery (in-person, Internet automated, Internet telepsychiatry, video recordings, print medium, audio, etc.), likely acceptability to client and parents, etc.
- **Therapist variables (inappropriate application of appropriate treatment):** variation in training in the methods, competence in learning and implementing them, therapist drift and therapeutic integrity relative to manualized treatment, therapist disorders, personality, and interpersonal and therapeutic style. [e.g. therapist assertiveness; burnout]
- **Conflict with Cultural and Historical Context:** the complementarity and acceptability of the methods and their rationale within the cultural context of the client (and parents). [e.g. spanking, time out, material rewards, etc.]

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NATURE OF ADVERSE EVENTS (WITH A FOCUS ON BPT AND FAMILY TRAINING)

- The **few existing reports of AEs** are often qualitative, usually based on therapist observation and opinion, and rarely formally evaluated using standardized methods and statistical analyses:
  - **Need for more systematic assessment tools, such as rating scales** of AEs, standardized direct observations, possible lab measures, etc.
  - Need to report **statistics evaluating reliable change** at the individual level, such as that promoted by Jacobson and Truax (1991), *J. Cons. Clin. Psychol.*, 59, 12-19.
- **Two Types of Adverse Events**:
  - Deterioration in primary or secondary endpoints
  - Onset of new harms – unwanted or detrimental events

10

MORE ON ADVERSE EVENTS

- (1) Deterioration in treatment:
  - Percent of families reliably worsening on the endpoint measures/constructs based on reliable change statistics
    - BPT reliable improvement = 64-75%, age dependent (23-30% teens)
    - BPT reliable deterioration = 7-15% in children
    - BFT is 20-30% reliable improvement but reliable deterioration is 6-22% fathers and 4-23% mothers depending on which measure of conflict was used and which therapy (BMT vs. PSCT)

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MORE ADVERSE EVENTS

- (2) Occurrence of new unwanted detrimental or harmful events
  - Types of AEs reported for BPT and BFT (especially during PSCT):
    - Decreased self-worth, greater demoralization in child or parent
    - Reduce sense of parenting competence (if not an endpoint)
    - Increased defiance, arguing, refusal to obey
    - Especially increased parent-teen conflict during problem discussions in PSCT forms of BFT
    - Increased irritability anger, frustration, and aggression by child or parent
    - Increased self-injurious behavior and breath-holding by child
    - Spitting, vomiting, urination by child especially while in time out
    - Threats by child to contact police or child protective services
    - Teen refusal to participate in sessions, refusal to attend therapy, and increased family drop out risk (more in PSCT than in BPT

12

A TYPOLOGY OF AE

Duggan et al. (2014) developed a typology for AEs that Allan & Chacko (2018) applied to BPT and that I believe extend to BFT.

Harm can arise from:

- Inappropriate choice of treatment
- Inappropriate application of treatment
- Underlying patient characteristics that interact with treatment

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HARM DUE TO INAPPROPRIATE TREATMENT

I. When BPT or BFT treatment is **not aligned** with presenting problems or when **access** to more effective treatment is postponed due to choice of a less effective or ineffective one. Can lead to:

- **Harm to the child or teen** due to prolonged impairment
- **Harm to the parent-child (teen) relationship** due to prolonged conflict and parental frustration with therapy ineffectiveness
- **Harm to the family** due to disillusionment with psychosocial approaches to therapy

Problems posed here are **not hypothetical** – in 2016 the CDC stated that BPT should always be implemented before using medication with preschoolers with ADHD, that it was as effective as medication, and that it produced no side effects. Clinicians following this guideline are actually doing harm to ADHD children for 3 reasons.

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INAPPROPRIATE APPLICATION OF A TREATMENT

- Alan & Chacko (2018) believe this is likely the greatest source of adverse events. Clinicians may lack skills in:
  - Applying the therapy or doing so with complex cases on which the therapy was not tested
  - Effective and reflective listening
  - Monitoring progress and potential side effects; adjusting therapy as needed
  - Recognizing and resolving barriers to treatment implementation
- These problems can lead to **inappropriate parental application** of the methods and **parental negativity and antagonism** toward BPT
  - The issue becomes even more complicated in BFT where the teen is an active participant in and applier of the therapy
- **Excess intervening** with rewards or punishments can result in parent and child demoralization and loss of compliance with program
- **Failure to warn of post-extinction bursts** when attention is withdrawn from and discipline applied to negative behavior causes increase parent-child conflict, potential aggression, and loss of parental motivation to continue the program

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PARENT CHARACTERISTICS BY TREATMENT INTERACTIONS

- Increased **parental frustration** when treatment initially focuses on building positive relationships while parent wants help with child negative behaviors
- Parents with **adult ADHD** inappropriately or inconsistently apply treatment methods
- Parents with **depression** routinely drift toward exclusive use of punishment due to intolerance of and irritability with even typical child misbehavior; parental depression may worsen
- Parents with **serious marital conflict** may find therapy worsens their marital interactions (parents differ markedly in use)
- Parents prone to **alcohol/drug use** may increase use in response to confrontations with child over discipline or increased child disruptive behavior generally (Pelham & colleagues)

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CHILD BY TREATMENT ADVERSE EVENTS

- **Highly aggressive and violent children** may increase such reactive behavior during limit setting and disciplinary sessions of therapy
- **Highly emotionally dysregulated** children manifest explosive anger, hostility, destruction, and physical aggression
- **Intellectually disabled** children or those on the moderate to extreme end of ASD may manifest self-injurious behavior or elimination behaviors during limit setting and disciplinary sessions
- **Highly predatory** children with psychopathy may plan and initiate vindictive actions toward parents

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THERAPIST ADVERSE EVENTS (TEEN THERAPIES)

- Decreased morale and risk of burnout – quitting therapy
- Theft of clinician and clinic property
- Increased arguing and fighting in clinic waiting room and parking lot
- Destruction of clinic property

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FURTHER AE ISSUES

- Significant imbalance in **reliable improvement vs. worsening**
  - Does therapy have to improve the majority of patients? **No**
  - Or must therapy just be significantly better than alternatives (either at the group or individual level of analysis)? **Yes**
  - **But if AE rate exceeds reliable improvement – reconsider Tx**
  - For Instance, Behavioral Family Training using both PSCT or BMT with PSCT was significantly better than traditional family therapy (5-10%) or wait-list control groups yet only 17-35% showed reliable improvement. 4-23% showed reliable worsening in PSCT on measures of greater conflict and greater anger intensity, especially on father ratings, compared to BMT/PSCT.
- Significant imbalance **cost/benefit ratio**

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CONCLUSIONS-1

- Evidence-based behavioral parent and family training **are effective** for a significant percentage of families having children and teens with ADHD – but therapy focuses primarily on parent-child conflict and less so on ADHD.
- These therapies **can result in deterioration** in treatment endpoints, adverse events, or other harms in a significant minority of families
- Clinical researchers need to **develop standardized methods** such as rating scales to implement in RCTs of psychosocial treatments
- **Require monitoring** in grant funded trials **and reporting** of AEs in all journal publications

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CONCLUSIONS - 2

- **Clinicians** must recognize that they are **inaccurate judges** of patient deterioration and related adverse events from their treatments.
- **Researchers can assist clinicians** with systematically monitoring of adverse events by disseminating such standardized methods to practitioners
- **Adverse events can be reduced** through improved training of clinicians in the appropriate selection and application of BPT and BFT and in assessing treatment x parent-child characteristic interactions that may heighten the probability of such adverse events – adjust therapies accordingly

21

Adolescent Developmental Trajectories of Impulse Control, Sensation-seeking, and Risk Factors Related to Substance Use

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Department of Psychiatry
UT Health San Antonio

UT Health San Antonio

1

Design Overview and Characteristics of the Cohort

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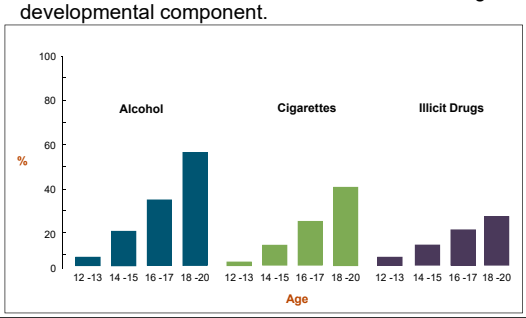
2

Substance Use Involvement among Youth

The course of substance use initiation has a strong developmental component.



3

Study Design Overview

Screening Procedures at Study Entry	Existing Cohort	Longitudinal Assessment Battery
Psychiatric Evaluation	FH+ (n = 272) Minimum criteria is having a biological father with a Substance Use Disorder	Health History and Medical Exam Psychiatric Assessment Externalizing and Internalizing Symptoms Physical Maturation Alcohol and Substance Use Assessment • Age of onset, frequency, duration, quantity of use, and symptoms of SUD Environmental Risk and Resiliency Assessment • Stressors, peer delinquency, and family environment • Individual, caregiver, and contextual strengths Sensation Seeking and Risk-Taking Assessments • Self-reported willingness to task risks • Risk-taking behavior Impulse Control Assessment • Response Initiation • Response Inhibition • Delay Discounting • Self-reported Trait Impulsivity
Family History of Substance Use Assessment		
Health, Developmental History, and Medical Exam		
Intelligence Testing and Mental Age	FH– (n = 75) No first-degree relatives with past or present Substance Use Disorders	
Alcohol and Other Substance Use Screening		
Socioeconomic Assessment for Group Matching		Repeated at 6-month Intervals

4

Cohort Demographics at Study Entry

	FH- (81)	FH+ (305)
Demographics (M, SD)		
Age	11.6 (.9)	11.5 (.9)
Intelligence Score	102.3 (12.2)	94.9 (11.2)
Socioeconomic Class	43.4 (10.8)	32.7 (11.4)
ADHD Diagnosis (N, %)	0 (0)	90 (29.4)
Race: White/Black/Other (%)	91.4/6.2/2.5	85.3/12.4/2.3
Ethnicity: Latino/Non-Latino (%)	70.4/29.6	80.7/19.3
Father's Substance Use Disorder – Lifetime (N, SD)*		
Alcohol Use Disorder	-	208 (75.6)
Amphetamine Use Disorder	-	44 (16.0)
Cannabis Use Disorder	-	154 (56.0)
Cocaine Use Disorder	-	159 (57.8)
Opioid Use Disorder	-	61 (22.2)

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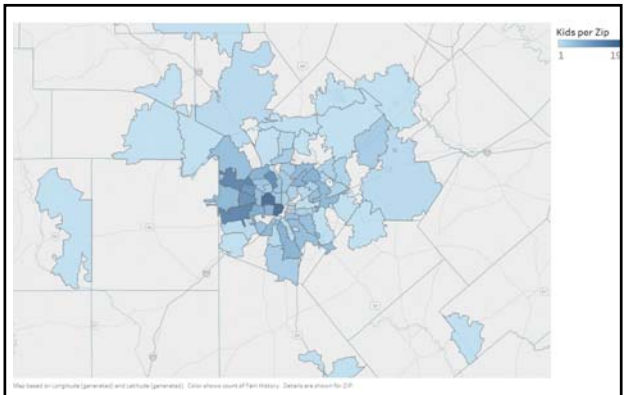

Youth recruited across the San Antonio area

6

Prevalence of Psychiatric Disorders Among FH+ Parents

	FH+ Father (n=275)	FH+ Mother (n= 275)
% Alcohol Use Disorder Only	17.8	9.5
% Other Mental Health Diagnoses Only	-	18.90%
% Substance Use *and* Other Psychiatric Diagnoses	36.70%	13.80%
# of SUDs (Mdn; Range)	2;8	0;7
Other Psychiatric Diagnoses (Lifetime)	**N (%)**	**N (%)**
Adjustment Disorder	1 (.4)	1 (.4)
Antisocial Personality Disorder	78 (28.4)	8 (2.9)
Bipolar I or II	7 (2.5)	11 (4.0)
Conduct Disorder	2 (.7)	3 (1.1)
Delusional Disorder	0 (0)	1 (.4)
Dysthymia Disorder	1 (.4)	2 (.7)
Major Depressive Disorder	31 (11.3)	71 (25.8)
Schizoaffective Disorder	1 (.4)	0 (0)

Ryan et al., 2016. Clinical and social/environmental characteristics in a community sample of child with and without family histories of substance use disorder in the San Antonio area: A descriptive study. *J Child Adolesc Subst Abuse, 25*, 327-339

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Prevalence of Psychiatric Disorders Among FH+ Youth

	FH+ Boys (n=152) Median; Range	FH+ Girls (n=153) Median; Range
# of Diagnoses		
Lifetime	1.0; 7	1.0; 6
Current	1.0; 5	1.0; 5
Current Diagnoses	**%**	**%**
ADHD	39.5	19.6
Disruptive Behavior Disorder	13.2	7.2
Oppositional Defiant Disorder	12.5	6.5
Conduct Disorder	0.7	0.7
Dysthymia Disorder	0.0	0.7
Any Anxiety	13.2	24.2
Generalized Anxiety Disorder	4.6	5.9
Separation Anxiety Disorder	3.3	6.5
Specific/Simple Phobia	5.3	3.3
Social Phobia	1.3	4.6
PTSD	2.0	8.5
Panic + Agoraphobia	0.0	0.7
Elimination Disorder	7.9	5.2
Adjustement Disorder	0.7	0.7
Any Tic Disorder	3.9	0.7

Ryan et al., 2016. Clinical and social/environmental characteristics in a community sample of child with and without family histories of substance use disorder in the San Antonio area: A descriptive study. *J Child Adolesc Subst Abuse, 25*, 327-339

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8

Two Primary Purposes of the Study

1. Examine how traits like impulse control differ prior to drug use initiation and are in turn affected by subsequent drug use
2. Examination of the Dual Systems Model

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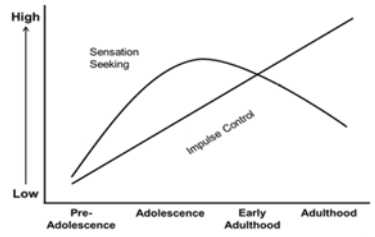
Dual Systems Model

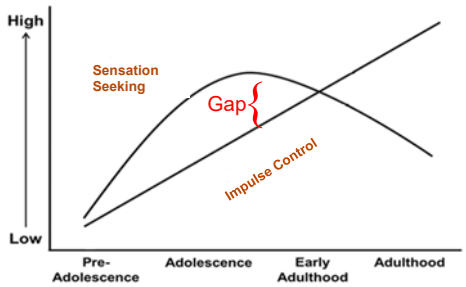
If "typical" adolescent behavior is thought to be accounted for by developmental mismatch in sensation seeking and impulse control development



Steinberg 2008. A social neuroscience perspective on adolescent risk taking. *Developmental Review, 28*, 78-106.

10

Finding a "Gap" with the Dual Systems Model



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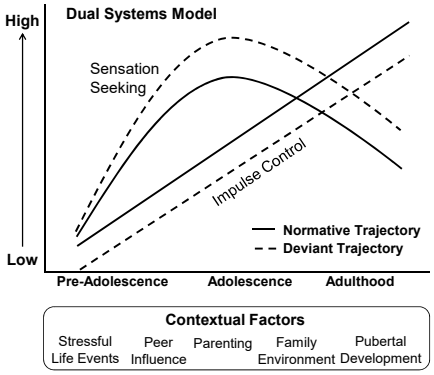
Does the "Gap" Explain Deviant Behaviors?



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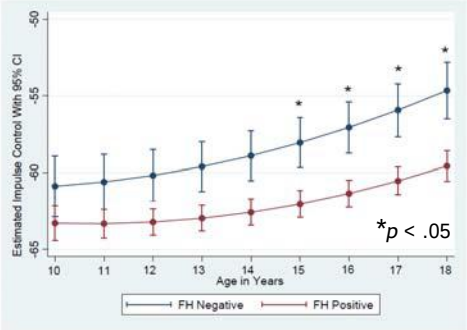
Impulse Control Across Adolescence



Developmental Trajectories of Impulse Control and Sensation-seeking Across Adolescence among an At-Risk Sample of Youth with Family History of Substance Use. *Manuscript in preparation*

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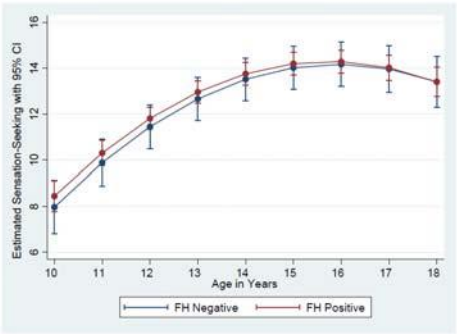
Sensation Seeking Across Adolescence



Developmental Trajectories of Impulse Control and Sensation-seeking Across Adolescence among an At-Risk Sample of Youth with Family History of Substance Use. *Manuscript in preparation*

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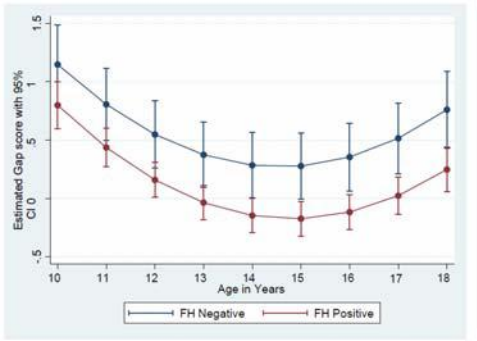
Gap Scores Across Adolescence



Developmental Trajectories of Impulse Control and Sensation-seeking Across Adolescence among an At-Risk Sample of Youth with Family History of Substance Use. *Manuscript in preparation*

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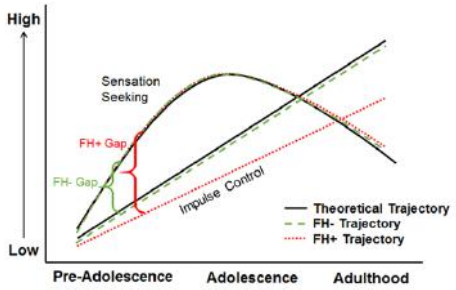
In other words…



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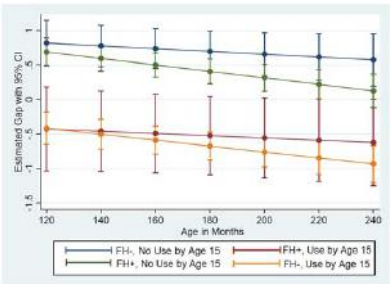
Substance use initiation and the gap

Once more, drug use in and of itself appears to influence the gap

- Substance use initiation by age 15, *but not FH*, was associated with a larger, more negatively-valenced gap between ages 13 and 18



Dougherty et al., Quantifying an Impulse Control and Sensation-Seeking Gap among a Longitudinal Sample of Adolescents at Risk for Substance Use. *Manuscript in submission*

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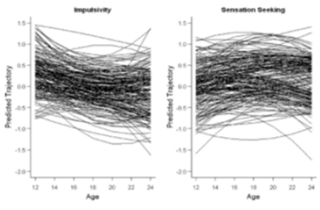
The Development of Impulsivity and Sensation Seeking

- Substantial individual differences in stability and developmental change in impulsivity and sensation seeking
- Do these individual differences predict substance use?
- Moreover, does aberrant development of impulsivity (both stability and change over time) alter the development of sensation seeking?



Harden & Tucker-Drob, 2011

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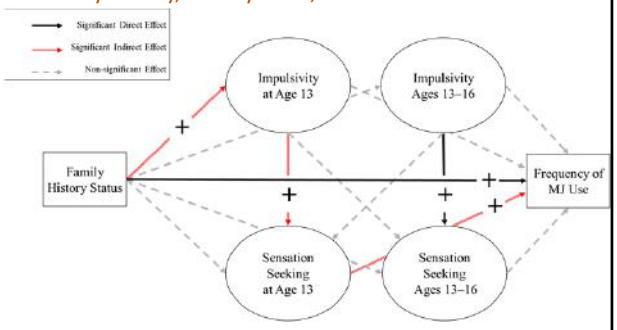
Family History, Dual Systems, and Substance Use



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Family History, Dual Systems, and Substance Use

1. Higher levels of impulsivity at age 13 predicted higher levels of sensation seeking at age 13
2. A slower rates of impulsive control development predicted a faster rates of sensation seeking development (i.e., positive association)
   - Impulsivity and sensation seeking may not be developmentally independent, as previously thought
3. FH status indirectly predicted substance use through higher levels of impulsivity to higher levels of sensation seeking

In Conclusion: the higher levels of impulsivity among FH+ youth resulted in heightened levels of sensation seeking, which in turn predicted marijuana use

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Thank you!

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21

Associated Risk Factors: Parenting and Family Environment

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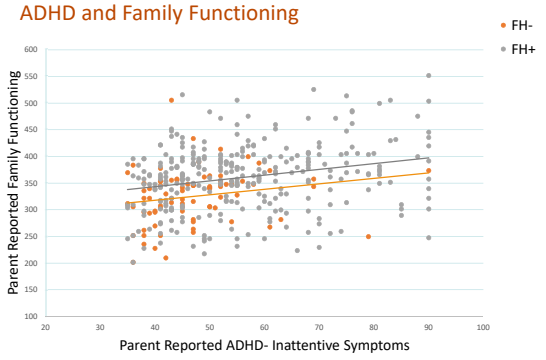
ADHD and Family Functioning



Mendoza et al., ADHD Symptoms and intrafamilial relationship quality. *Poster presented at Texas Research Society on Alcoholism, Feb. 2018*

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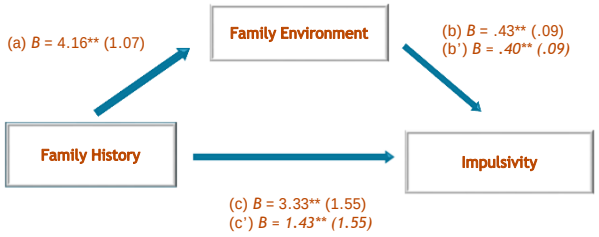
23

Mediational Role of Family Environment



Ryan et al., 2016. Family functioning as a mediator of relations between family history of substance use disorder and impulsivity. *Addict Disord Their Treat, 15,* 17-24.

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Associated Risk Factors: Stress

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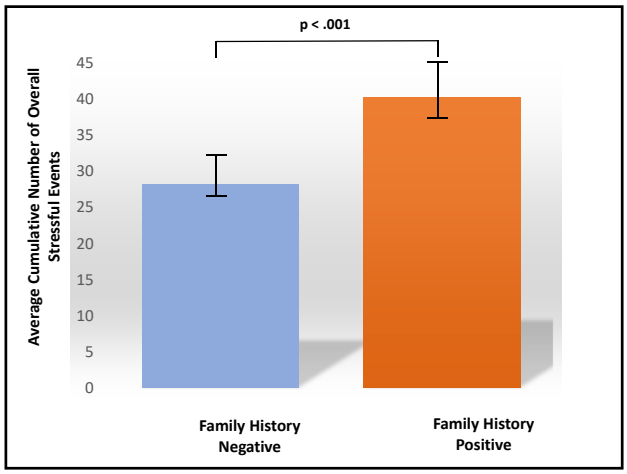

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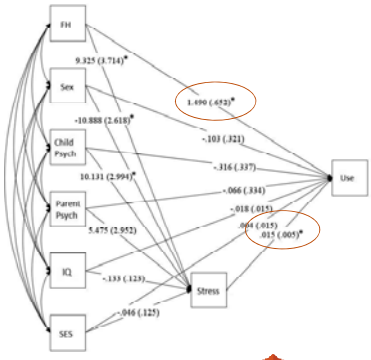
Stress puts youth at risk for substance use initiation

Risk for substance use initiation during adolescence was influenced directly by:

- Family History of Substance Use Disorders
- Increased exposure to stress



Charles, et al., 2015. Childhood stress exposure among preadolescents with and without family histories of substance use disorders. *Psychol Addict Behav, 29,* 192-200.

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Other risk factors

We can add a slide each for:
Aggression (Mathias, 2015)
Psychopathic traits (Charles, 2012)

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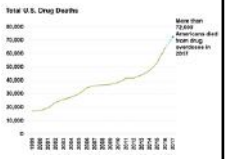
ADHD and Opioid Use Disorders: How to Best Intervene

Amy Yule M.D.
Psychiatrist, Massachusetts General Hospital
Assistant Professor, Harvard Medical School
ayule@partners.org



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Disclosures

- I have no financial relationships with an ACCME defined commercial interest
- Current research funding: 5K12DA000357-17
- Consultant to the Phoenix House & Gavin Foundation (clinical services)
- AACAP representative to the PCSS steering committee

2

Outline

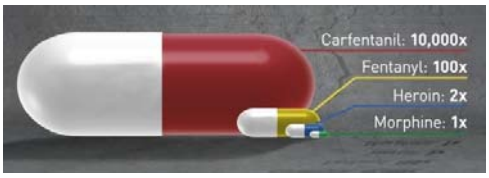
- Provide background on the opioid epidemic and opioid use disorders (OUD)
- Discuss research on OUD/ADHD co-morbidity
- Discuss clinical challenges in the management of OUD/ADHD in the substance use disorder treatment setting

3

The Opioid Epidemic and Opioid Use Disorders (OUD)

4

Opioids vary considerably in potency



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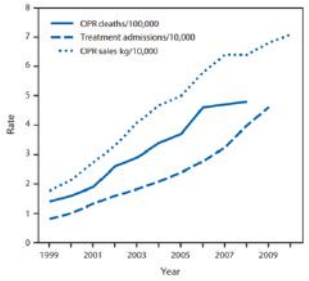
In the 2000's as prescriptions for opioids increased so did overdose deaths



↑ emphasis on pain management

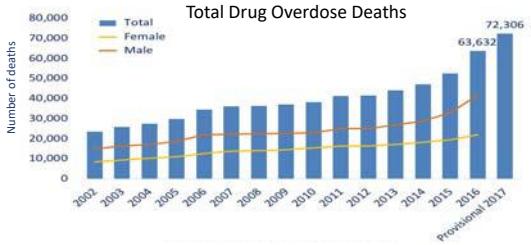
↑ in prescription opioids for chronic pain

↑ overdose deaths

Paulozzi 2011

6

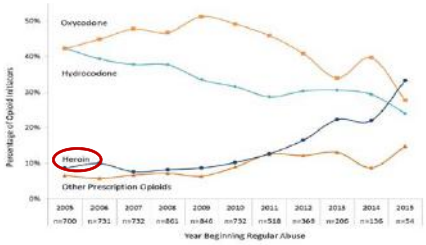
Overdose deaths continue to increase despite increased awareness & resources



National Center for Health Statistics, CDC Wonder

7

The opioid epidemic has been evolving



1st opioid used among individuals entering treatment for an OUD

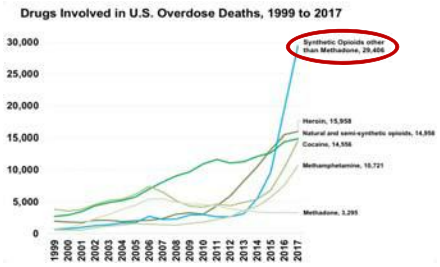
↓ availability of prescription opioids

↑ individuals initiating opioid use with heroin

Cicero 2017

8

The opioid epidemic has been evolving



OD deaths are currently being driven by very potent synthetic opioids such as fentanyl and carfentanil

National Center for Health Statistics, CDC Wonder

9

Risk factors for overdose

- High impulsivity has been identified as a risk factor associated with non-fatal overdose in one study (Maloney 2009)
  - Individuals with an opioid use disorder were recruited from opioid maintenance treatment clinics in Australia from 2004 to 2008.
  - Impulsivity assessed with the Barratt Impulsiveness Scale (BIS-11)
  - Individuals with a history of non-fatal overdose were 1.4 times more likely to have high impulsivity (OR 1.43, 1.03-1.98)
- No association between lifetime history of ADHD and OD in treatment seeking young people with substance use disorders (Yule 2018)

10

Positive news—medication for OUD decreases risk for drug overdose death

Buprenorphine	Methadone	Naltrexone ER
↓ rate of OD death by 70% when stabilized	↓ rate of OD death by 80% when stabilized	↓OD in individuals treated with naltrexone vs control

Sordo 2017, Lee 2018

11

Impact of OUD medication on attention

- Limited research to date—no RCT comparing individuals with an OUD on medication versus no medication (Maglione 2018)
- Relative to healthy controls individuals with OUD have deficits in attention and cognition
  - Polysubstance use is a contributing factor
  - Toxic brain injury—hypoxic and anoxic brain injuries related to drug overdose

12

Impact of OUD medication on attention

- RCT Buprenorphine versus methadone versus controls (Soyka 2011)
  - Evaluated *selective attention, verbal memory, motor/cognitive speed, and cognitive flexibility* after 8 to 10 weeks of treatment with either buprenorphine or methadone
  - At the time of testing ~50% of OUD patients were actively using substances (cannabis, benzodiazepines, or opioids)
  - Results:
    - Buprenorphine and methadone groups showed improved concentration skills and executive functioning between baseline and 8/10 weeks
    - **No difference between buprenorphine and methadone groups on all tests**
    - Buprenophine and Methadone groups versus Controls—subjects with OUD on medication had impaired psychomotor speed, semantic word fluency, and verbal learning

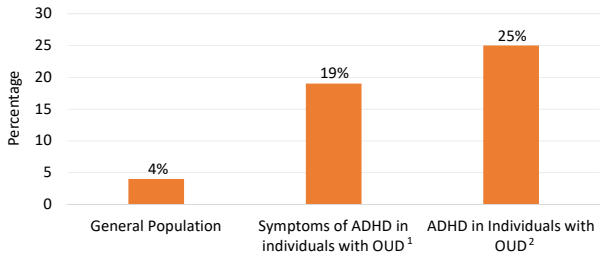
Soyka 2011

13

OUD/ADHD co-morbidity

14

Prevalence of ADHD



[1]Lugoboni 2017, [2]Carpentier 2011

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ADHD in individuals with OUD is associated with:

- Greater addiction severity
- More comorbid psychopathology
- Poor functioning

Lugoboni 2017, Carpentier 2011

16

Treatment of Co-occurring ADHD and OUD

- RCT comparing **methylphenidate (MPH) SR** or **Bupropion (BPR) SR** to placebo in adults with ADHD and OUD on methadone maintenance treatment
  - 2 week placebo lead in, 2 week dose titration, 8 weeks maintenance
  - **Medication:**
    - MPH 40 mg to 80 per day
    - BPR 200 mg to 400 mg per day
  - **Therapy:** Methadone maintenance treatment as usual **plus** weekly CBT for SUD
  - Sample characteristics: 98 patients; 57% male; 40% caucasian, 40% Hispanic; 53% cocaine use disorder

Levin 2005

17

Treatment of Co-occurring ADHD and OUD

- RCT comparing **methylphenidate (MPH) SR** or **Bupropion (BPR) SR** to placebo in adults with ADHD and OUD on methadone maintenance treatment

dence of prescription stimulant misuse, no serious adverse events

05

18

Clinical management

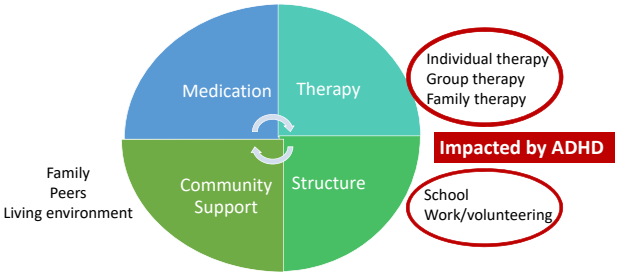
1. Assess co-morbidity—1st priority is to make sure co-occurring disorders, including SUD, are stabilizing
2. Therapy for SUD is important
3. Medications for ADHD
   a. Consider non-stimulant medications—atomoxetine, bupropion
   b. If using a stimulant medication:
      i. Use long acting stimulants
      ii. Involve a support person if possible
      iii. Medication guidance: safe medication storage, take medication as prescribed
      iv. Initial medication management: Frequent follow up, short prescriptions

19

Clinical challenges in the management of OUD/ADHD in the substance use disorder treatment setting

20

Key components of a Treatment Plan for an individual with OUD



21

Challenges—Community Supports

- Medications with potential for misuse (buprenorphine, stimulants) are often not allowed/encouraged by community supports
- Mutual help groups
  - Types—12-step (Alcoholics Anonymous, Narcotics Anonymous), Secular (SMART recovery)
  - Pro: FREE!, easy to access, access to peers who have a goal of recovery
  - Con: Not always supportive of buprenorphine and/or stimulant medication, 60 to 90 min in duration—many are not very interactive
- Most residential programs and recovery houses in the country are 12-step oriented

22

Summary

- Medication for OUD is very important to decrease overdose risk
- No major differences between agonist medications (buprenorphine and methadone) have been identified to date in attention or cognition
- Individuals with OUD and co-occurring ADHD are sicker than individuals with OUD without co-occurring AHD
- Co-occurring ADHD needs to be identified and addressed as part of the treatment plan for individuals with OUD

23

Resources

- SAMHSA funded projects:

PCSS Providers Clinical Support System www.pcssnow.org

STR-TA Consortium State Targeted Response Technical Assistance www.getstr-ta.org

Questions?

24

Nonmedical Use of Prescription Stimulants

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Massachusetts General Hospital
Harvard Medical School

1

Faculty Disclosure

. Timothy Wilens, M.D. has served as a consultant, or has received grant support from the following

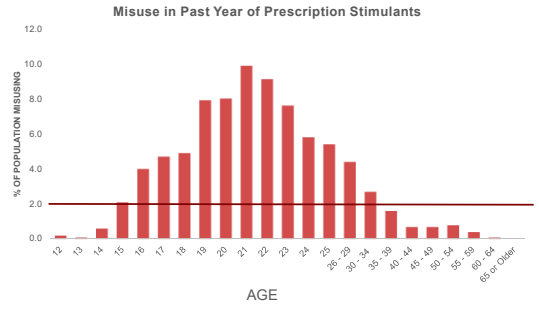
- Alcobra, KemPharm, Neurovance/Otsuka, NIH (NIDA), Ironshore
- Licensing agreement with Ironshore (Before School Functioning Questionnaire)
- Clinical care: MGH, Bay Cove Human Services, Gavin/Phoenix, National Football League (ERM Associates), Major/Minor League Baseball
- (Co)Edited Straight Talk About Psychiatric Medications for Kids (Guilford); ADHD Across the Lifespan (Cambridge) , MGH Comprehensive Clinical Psychiatry (Elsevier), MGH Psychopharmacology and Neurotherapeutics (Elsevier)
- Some of the medications discussed may not be FDA approved in the manner in which they are discussed including diagnosis(es), combinations, age groups, dosing, or in context to other disorders (eg, substance use disorders)

2

How frequent is diversion/misuse of prescription stimulants?

3

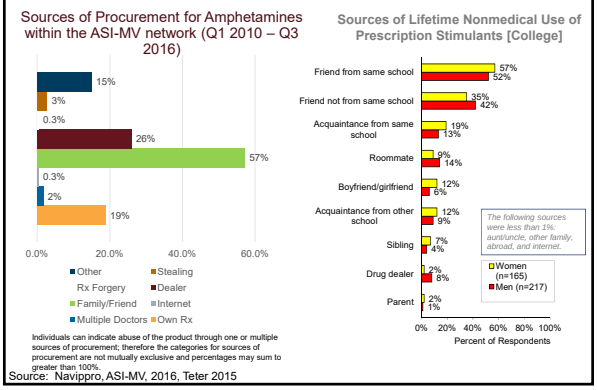
Misuse Peaks at Age 21, with 10% of the Population Reporting Lifetime Misuse of Stimulants



Source: SAMHSA, Center for Behavioral Health Statistics & Quality, National Survey on Drug Use and Health, 2015

4

Stimulants are Frequently Diverted

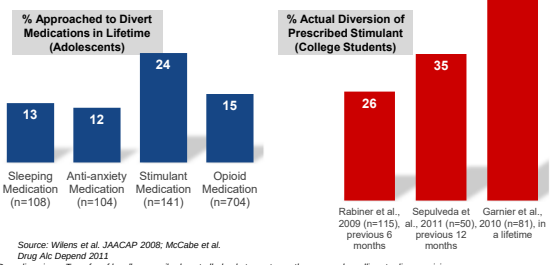


Source: Navippro, ASI-MV, 2016, Teter 2015

5

Stimulants are Frequently Diverted

- 65-85% of stimulants are diverted[1] from "friends"
  - Majority *not* "scamming" local docs
  - Not seen as potentially dangerous
- May occur in substance (ab)users during academic decline

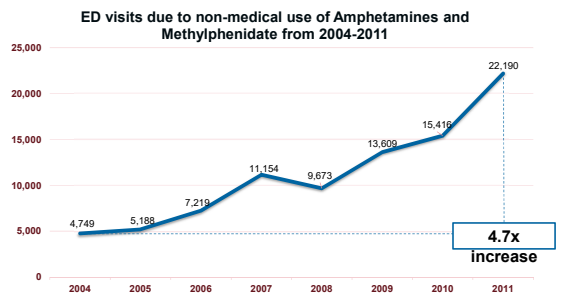


Source: Wilens et al. JAACAP 2008; McCabe et al. Drug Alc Depend 2011

[1] *Drug diversion = Transfer of legally prescribed controlled substance to another person by selling, trading, or giving away*

6

Emergency Department visits due to non-medical use of stimulants more than quadrupled (2004-11)



Drug Abuse Warning Network Report, 2011, pg 21, table 5.2, Central Nervous System Stimulants, amphetamine/dextro-amphetamine and methylphenidate only (excluded caffeine)

7

What are the characteristics of those who misuse prescription stimulants?

8

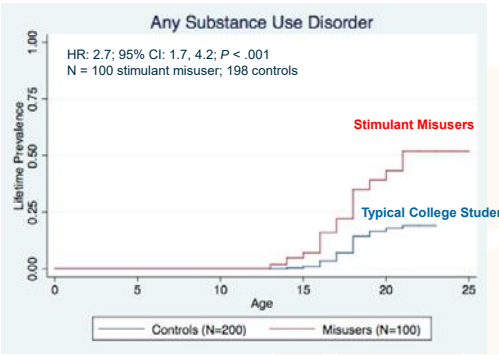
Reasons for Misusing Stimulants (N=100)

- To help me concentrate or to focus better (79%)
- To stay awake (62%)
- To reduce distraction (56%)
- To get more energy (48%)
- To experiment - to see what it's like (42%)
- To have a good time with my friends (22%)
- To feel good or get high (21%)
- To get through the day (12%)

(Wilens et al. AACAP Seattle, 2018)

9

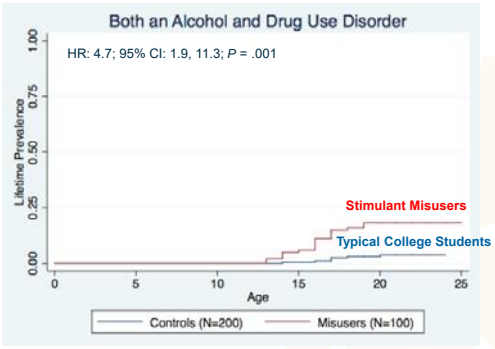
College Stimulant Misusers Have High Rates of SUD



Wilens TE, et al. *J Clin Psychiatry*. 2016;77(7):940-947.

10

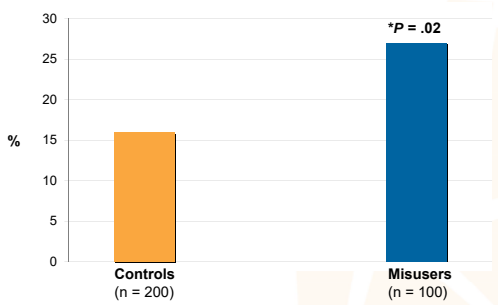
College Stimulant Misusers Have High Rates of Polysubstance Use Disorders



Wilens TE, et al. *J Clin Psychiatry*. 2016;77(7):940-947.

11

Rates of ADHD are Higher in College Students Who Misuse Stimulants Compared to Controls

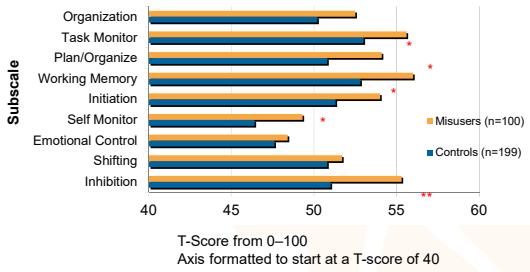


N = 300. Subthreshold + full diagnosis of ADHD.
Wilens TE, et al. *J Clin Psychiatry*. 2016;77(7):940-947.

12

More Executive Dysfunction in Stimulant Misusers

Subscales of the Self-Report Behavior Rating Inventory of Executive Functioning (BRIEF)

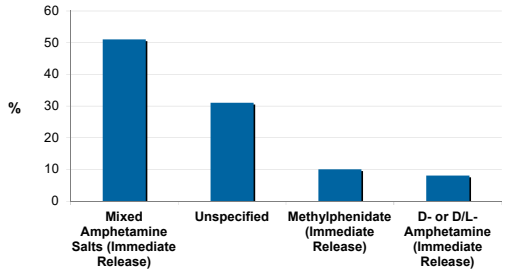


N = 299. *P < .05
Wilens TE, et al. *Am J Addict*. 2017;26(4):379-387.

13

Immediate-Release Stimulants are Misused by College Students with a Stimulant Use Disorder

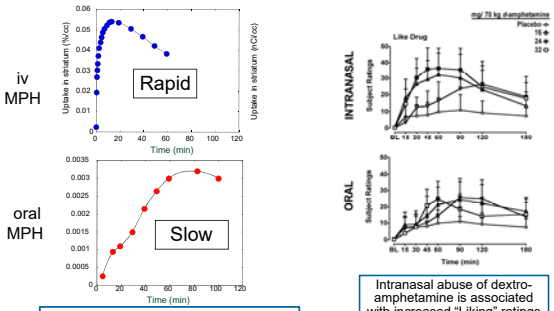
(N=100)



Wilens TE, et al. *J Clin Psychiatry*. 2016;77(7):940-947.

14

Rapidity of Brain Dopaminergic Uptake Drives Euphoric Effects of Stimulants



Intravenous (IV) methylphenidate leads to stronger rewarding effects (euphoria) than oral methylphenidate

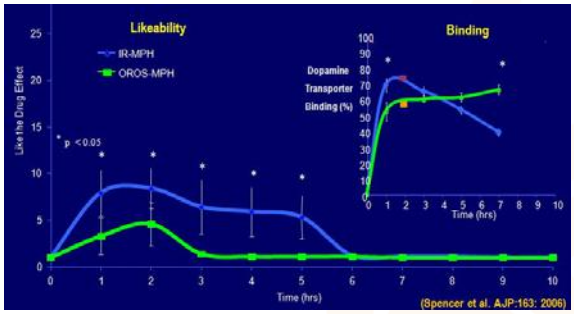
Intranasal abuse of dextro-amphetamine is associated with increased "Liking" ratings over oral abuse

Volkow et al., Arch Gen Psych 52:1995, J Neurosci 2001 Lile JA et al, J Clin Pharmacol 2011; 51(6):888-

15

Stimulant Preparation Linked to Dopamine Transporter Binding and Likeability

40 mg IR-MPH vs 90 mg OROS MPH



Spencer TJ, et al. *Am J Psychiatry*. 2006;163(3):387-395.

16

Illicit Use Survey from ADHD Clinic

- **Of 335 survey responses – 73 (14%) reported stimulant misuse**

Type of Stimulant Abused

Bright GM. *Medscape J Med*. 2008;10(5):111.

17

Immediate- vs Extended-Release Stimulant Preparations are More Frequently Misused

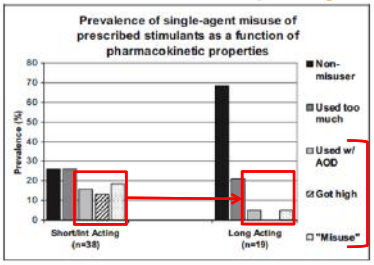


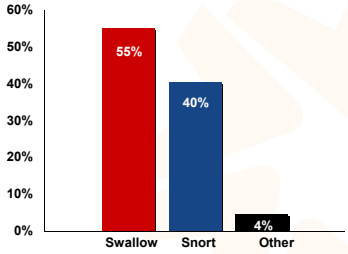
Figure 1. Prevalence of single-agent misuse of prescribed stimulants as a function of pharmacokinetic properties. Short-/intermediate-acting (3-8 hours); long-acting (8-12 hours) pharmacokinetic properties of each formulation.[35]

Sepúlveda DR, et al. *J Pharm Pract*. 2011;24(6):551-560.

18

Misuse by Alternative Routes is Common: Snorting is Frequently Reported

Method of Stimulant Misuse by College Students (n = 1025)



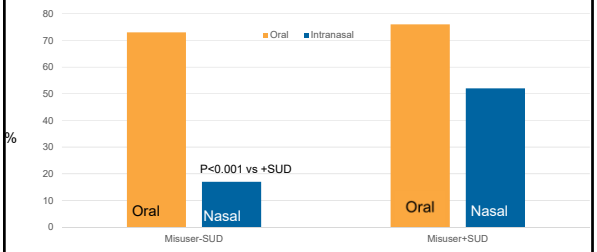
Random sample: Anonymous surveys at the University of New Hampshire administered via e-mail and paper, 1025 received out of 5000 distributed, 6.6% diagnosed with ADHD, over 16% of students abuse stimulants.

White BP, et al. *J Am Coll Health*. 2006;54(5):261-268.

19

Rates of Oral and Intranasal Misuse of Stimulants in College Students (N=100)

(Wilens et al. AACAP, 2018)



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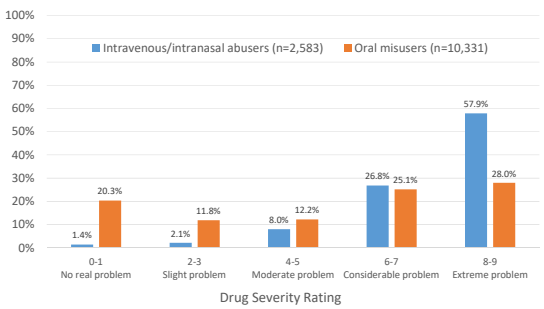
More Severe Problems Linked to Substance Use are Found with Intranasal/Intravenous vs. Oral Misuse



Source: Navippro, ASI-MV, 2016

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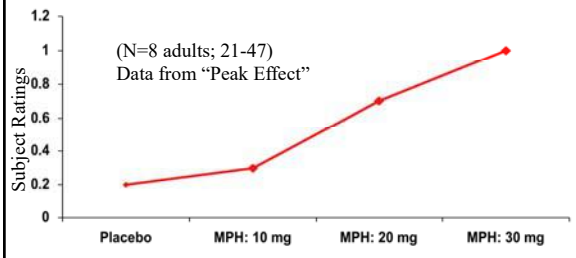
TW5

Effects of Intranasal MPH on Subjective Ratings: Any effects

(Stoops et al., Drug Alc Depend 2003:71:179-186)



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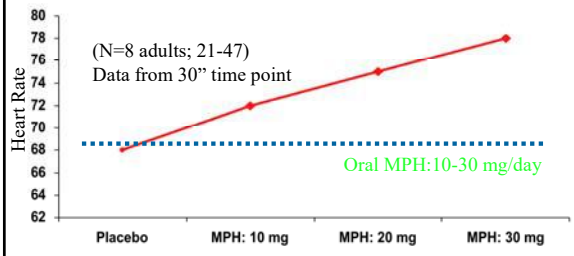
Effects of Intranasal Methylphenidate on Pulse

(Stoops et al., Drug Alc Depend 2003:71:179-186)



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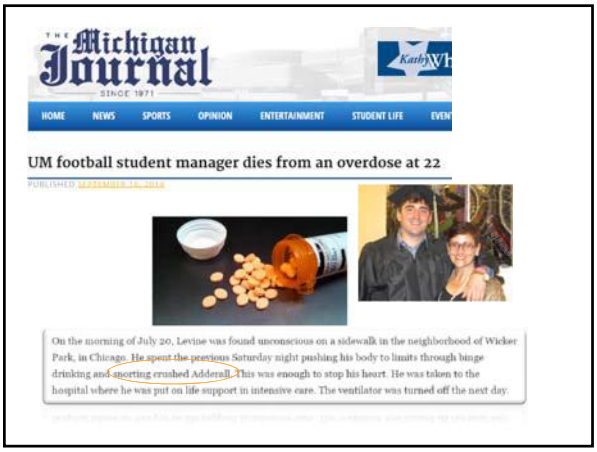


24

Adolescents' Prescription Stimulant Use and Adult Functional Outcomes: A National Prospective Study

Sean Esteban McCabe, PhD, Philip Veliz, PhD, Timothy E. Wilens, MD, John E. Schulenberg, PhD

Objective: To assess the prospective 17-year relationship between the medical and nonmedical use of prescription stimulants during adolescence (age 18 years) and educational attainment and substance use disorder (SUD) symptoms in adulthood (age 35 years).

Method: A survey was self-administered by nationally representative probability samples of US high school seniors from the Monitoring the Future study; 8,362 of these individuals were followed longitudinally from adolescence (age 18, high school senior years 1976–1996) to adulthood (age 35, 1993–2013).

Results: An estimated 8.1% reported medical use of prescription stimulants, and 16.7% reported nonmedical use of prescription stimulants by age 18 years. Approximately 43% of adolescent medical users of prescription stimulants had also engaged in nonmedical use of prescription stimulants during adolescence. Among past-year adolescent nonmedical users of prescription stimulants, 97.3% had used at least one other substance during the past year. Medical users of prescription stimulants without any history of nonmedical use during adolescence did not differ significantly from population controls (i.e., non–attention-deficit/hyperactivity disorder [ADHD] and non–stimulant-medicated ADHD during adolescence) in educational attainment and SUD symptoms in adulthood. In contrast, adolescent nonmedical users of prescription stimulants (with or without medical use) had lower educational attainment and more SUD symptoms in adulthood, compared to population controls and medical users of prescription stimulants without nonmedical use during adolescence.

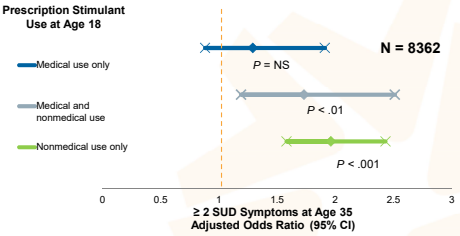
Conclusion: Nonmedical use of prescription stimulants is common among adolescents prescribed these medications. The findings indicate youth should be carefully monitored for nonmedical use because this behavior is associated with lower educational attainment and more SUD symptoms in adulthood.

Key words: stimulants, adolescent, prescription drug misuse, substance-related disorders, adult

J Am Acad Child Adolesc Psychiatry 2017;56(3):226–233.

25

SUD Symptoms at Age 35 Years as a Function of Medical and Nonmedical Use of Prescription Stimulants at Age 18 Years

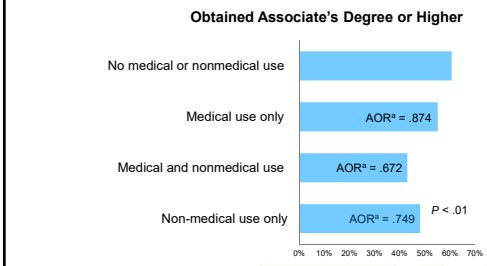


All analyses control for race/ethnicity, sex, truancy, average grade during high school, parental education, geographical region, metropolitan statistical area, cohort year at baseline, annual alcohol use at baseline, annual cannabis use at baseline, and annual other drug use at baseline.

McCabe SE, et al. *J Am Acad Child Adolesc Psychiatry*. 2017;56(3):226-233.e4

26

Educational Attainment at Age 35 Years as a Function of Medical and Nonmedical Use of Prescription Stimulants at Age 18 Years



All analyses control for race/ethnicity, sex, truancy, average grade during high school, parental education, geographical region, metropolitan statistical area, cohort year at baseline, annual alcohol use at baseline, annual cannabis use at baseline, and annual other drug use at baseline.

N = 7813.

AOR = adjusted odds ratio.

McCabe SE, et al. *J Am Acad Child Adolesc Psychiatry*. 2017;56(3):226-233.e4

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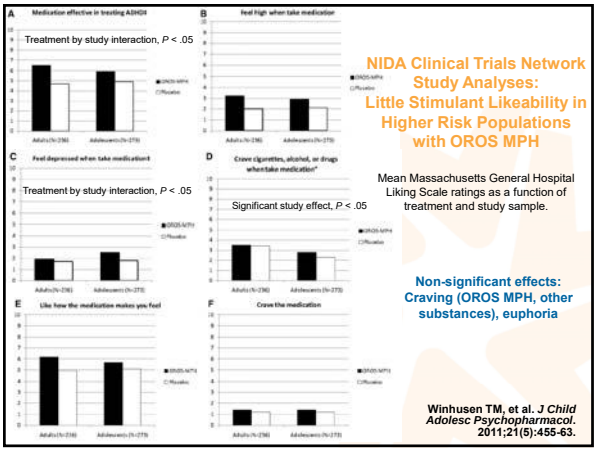


NIDA Clinical Trials Network Study Analyses: Little Stimulant Likeability in Higher Risk Populations with OROS MPH

Mean Massachusetts General Hospital Liking Scale ratings as a function of treatment and study sample.

Non-significant effects: Craving (OROS MPH, other substances), euphoria

Winhusen TM, et al. *J Child Adolesc Psychopharmacol*. 2011;21(5):455-63.

28

Summary

- **Stimulants are frequently misused**
- **Stimulant misuse is more common with immediate vs extended-release preparations**
- **Snorting and intravenous use is common in stimulant misusers: some develop a stimulant use disorder as a result.**
- **Myths: " It is benign" and "it is really just kids taking it orally to study for exams…"**
- **There are short- and long-term adverse medical/psychological risks associated with stimulant misuse**
- **More practitioner & patient education, and abuse-deterrent stimulants are necessary**

29

ADHD AND CANNABIS USE DISORDERS
ADDRESSING THE COMORBIDITY

Kevin M. Gray, M.D.
Professor and Director of Child and Adolescent Psychiatry
Medical University of South Carolina

1

Disclosures

Source	Research Funding	Advisor/ Consultant
NIH (NIDA, NIAAA)	×	
Pfizer, Inc.		×

2

Educational Objective

- To become knowledgeable about the recent advances in behavioral and pharmacological treatments for CUD in youth and the clinical consideration for individuals presenting with co-occurring CUD and ADHD.

3

Overview

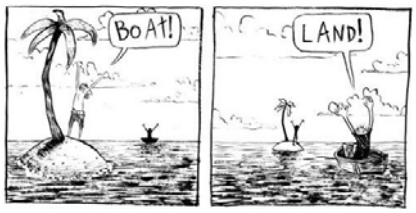
- Navigating the cannabis information landscape
- What do we know about cannabis-associated risks?
- How do we address cannabis use problems?
- Are there recent advances in addressing cannabis use disorder (CUD) in young people?
- Is any of this work specifically focused on youth with ADHD?

4

Polarization

5

Perspective(s)



6

Duality

- "*It seems as though we must use sometimes the one theory and sometimes the other, while at times we may use either. We are faced with a new kind of difficulty. We have two contradictory pictures of reality; separately neither of them fully explains the phenomena of light, but together they do.*" – Albert Einstein

7

Embrace complexity!

- Cannabis can
  - Be potentially safe and benign
  - Contain potentially medicinal components
  - Be potentially risky and harmful
- These can all be simultaneously true
- And we can manage nuanced messaging during clinical encounters
- It is particularly important to personalize the message based on individual/family characteristics that may impact potential risk/benefit

8

What do we know about cannabis-associated benefits?

- Many people have occasional, benign, and pleasant experiences with recreational cannabis use
- There is evidence of therapeutic roles of specific, reliably-dosed, orally-administered, pharmaceutical-grade cannabinoids for specific conditions
- However, there may be times when benefits are outweighed by risks and/or alternatives
- The balance between risk and benefit may depend upon a number of factors, both at the human level (age, genetic and environmental factors) and at the cannabis/cannabinoid level (strain, constituency, route of administration)

9

What do we know about cannabis-associated risks?

- Acute/intoxication
  - Driving performance and decision-making
- Chronic/repeated use
  - Cannabis use disorder (CUD)
    - More prevalent than previously thought
      - 1/5 lifetime users, of whom 23% are symptomatically severe, of whom 48% are not functioning in any role (e.g., work)
    - Treatment outcomes are limited – room for improvement!
  - Use during pregnancy – effects on neonate/child
  - **Exposure/use during childhood/adolescence**
    - **Higher (~2×) rate of CUD than in adult cannabis users**
    - **Adverse effects on cognition, emotion, and development**

(for review, Hasin 2018)

10

Should we be particularly worried about youth with ADHD?

- Childhood ADHD predicts earlier cannabis use onset and escalation to frequent/heavy use (Elkins et al., 2018)
  - Population-based twin samples (*N*=3762)
  - Even when considering co-occurring CD/ODD and use of other substances, hyperactivity-impulsivity and inattention symptoms were significantly associated with cannabis use
  - Females with hyperactivity-impulsivity symptoms were at particular risk for frequent/heavy cannabis use
- Young adults with ADHD who use cannabis are more likely (compared to non-ADHD young adults) to sustain heavy use (Vogel et al., 2016)

11

Evidence-based treatments for CUD in youth

- Psychosocial approaches supported by evidence in youth (largely paralleling the evidence in adults)
  - Motivational Interviewing / Motivational Enhancement Therapy (Walker et al., 2011)
  - Cognitive Behavioral Therapy (Hendriks et al., 2011)
  - Family Therapy (a variety of modalities) (Rigter et al., 2012)
- While these treatments are effective for cannabis reduction, long-term abstinence outcomes are generally poor (Compton & Pringle, 2004; Dennis et al., 2004; Waldron & Turner, 2008; Hogue et al., 2014)
- Contingency Management can be used to reinforce abstinence and improve outcomes (Stanger et al., 2009; Stanger et al., 2015)

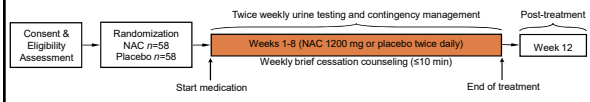
12

Medication to complement psychosocial treatment?

- The over-the-counter supplement *N*-acetylcysteine (NAC) has been studied as a candidate treatment for CUD
- Glutamate dysregulation in the nucleus accumbens underlies drug seeking (LaLumiere & Kalivas, 2008; McFarland et al., 2003, 2004)
- NAC administration activates the cystine/glutamate exchanger and upregulates the GLT-1 receptor, leading to reduction in reinstatement of drug seeking in animal models (Baker et al., 2003; Madayag et al., 2007; Moran et al., 2005; Reissner et al., 2015)
- Our open-label pilot study in young cannabis users supported feasibility and tolerability for further study (Gray et al., 2010)

13

Adolescent NAC trial (Gray et al., 2012)



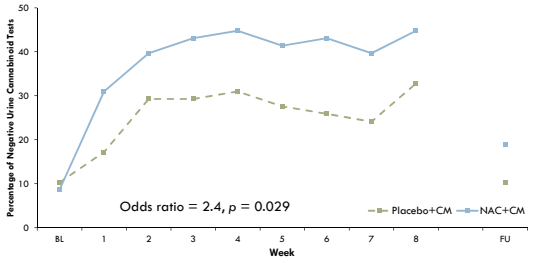
- DSM-IV cannabis-dependent adolescents (*n*=116; ages 15-21)
- Eight weeks of active treatment
  - Double-blind placebo-controlled NAC 1200 mg BID
- All participants received weekly brief cessation counseling and twice-weekly contingency management (CM)
  - Two-tiered escalating reinforcement schedule with resets, rewarding both study retention and cannabis abstinence (Carroll et al., 2006)

14

Adolescent NAC trial

Primary outcome

- Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit



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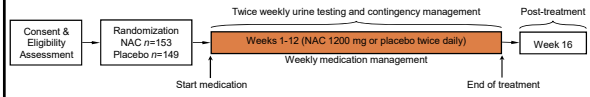
Adolescent NAC trial

Secondary outcomes

- *Cognitive task performance improved with cannabis abstinence* (Roten et al., 2015)
- Low impulsivity and high medication adherence predicted abstinence; *adherence optimization is particularly critical in high-impulsivity individuals* (Bentzley et al., 2016)
- NAC was more effective in adolescents with elevated depressive symptoms (Tomko et al., under review)
- Tobacco use and alcohol use did not increase with cannabis use reduction (McClure et al., 2014; Squeglia et al., 2016)
- In the NAC group, but not the placebo group, reductions in cannabis use were associated with reductions in alcohol use (Squeglia et al., 2016)

16

Does it work in adults, too?



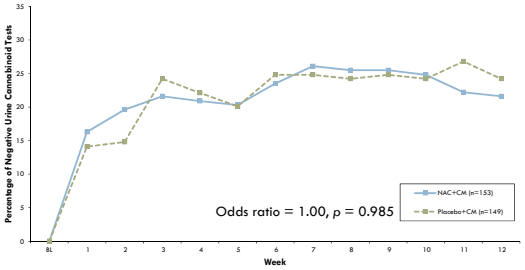
- National Drug Abuse Treatment Clinical Trials Network (CTN) effort to see if positive adolescent findings extend to adults (CTN-0053) (Gray et al., 2017)
- DSM-IV cannabis-dependent adults (*N*=302; ages 18-50; recruited across six CTN sites)
- Twelve weeks of active treatment
  - Double-blind placebo-controlled NAC 1200 mg BID
- All participants received weekly medication management and twice-weekly contingency management
  - Two-tiered escalating reinforcement schedule with resets, rewarding both study retention and cannabis abstinence

17

Adult Trial

Primary Outcome

- Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit

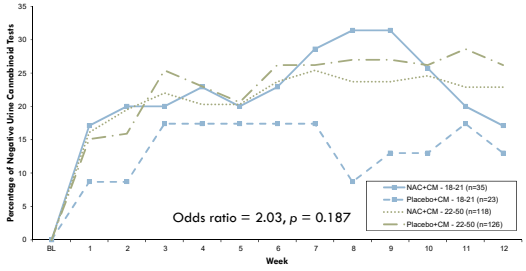


18

Adult Trial

Ages 18-21 versus 22-50 (under-powered *post-hoc* comparison)

- Intent-to-treat (all randomized participants) with participants assumed to be non-abstinent at any missed visit



19

Trials of medication for ADHD + CUD?

- RCT of OROS methylphenidate in youth with ADHD + substance use disorder (*N*=303, ages 13-18, most had CUD; all received motivational interviewing and CBT) (Riggs et al., 2011)
  - Self-rated ADHD-RS and days of substance use (primary outcomes) did not differ between groups
  - OROS methylphenidate group had lower parent-rated ADHD-RS and more negative urine drug tests (secondary outcomes) than the placebo group
  - Similarly designed study (*N*=70) with atomoxetine yielded null findings (Thurstone et al., 2010)

20

Summary

- This topic is complex, and we're still learning about it, and that's OK
- Avoid polarization, and embrace nuance and multiple viewpoints
  - Cannabis & cannabinoids are neither all good nor all bad
  - We can be both excited and cautious
- Let's frankly advise patients and families in this context
- **We must clearly convey why we are concerned about youth cannabis use, *particularly among youth with ADHD*, while allowing for open dialogue and discussion**

21

Summary

- The mainstays of CUD treatment for youth include motivational interviewing, cognitive-behavioral therapy, and family therapy, and outcomes can be enhanced by adding contingency management
- NAC appears to improve outcomes for youth, but not adult, CUD
- In treating co-occurring ADHD+CUD, OROS methylphenidate appears well-tolerated with some secondary indications of benefit for both conditions

22

Questions?

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23

The Boundaries of ADHD: A Genomic Perspective

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SUNY Upstate Medical University
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1

Financial Disclosures (Past 2 Years)

Source	Research or CME Funding	Consult Fees	Speakers Bureau	Royalties or IP	In Kind Services	Stock / Equity	Honorarium or expenses for this meeting
NHE Inhibitor Patent				X			
Shire/Takeda	X				X		
Guilford Press				X			
Akili		X				X	
VAYA		X					
Vallon		X					
Tris		X					
Otsuka	X						
IronShore		X			X	X	
Supernus		X					
Sunovion	X	X					
Genomind		X			X		
Arbor	X				X		
Oxford Univ. Press				X			

2

Background:

Most Common Forms of Psychopathology are Polygenic

3

Psychiatric Disorders are Highly Polygenic

(Smoller et al., Molecular Psychiatry, 2018)

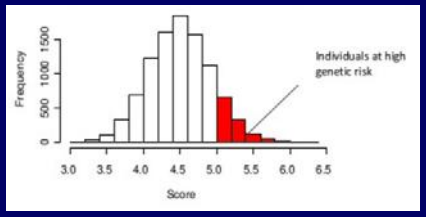
- Genomewide association studies of common DNA variants suggest that the most common forms of psychiatric disorders are caused by the accumulation of many genetic risk variants. This is seen in very large studies of:
  - Schizophrenia
  - Bipolar Disorder
  - ADHD
  - Major Depression
  - Autism Spectrum Disorders
  - Anorexia Nervosa

4

Understanding Molecular Polygenic Risk Scores

(Faraone, Biol Psychiat, 2014)

- A polygenic risk score indexes the number of ADHD risk alleles carried by an individual.



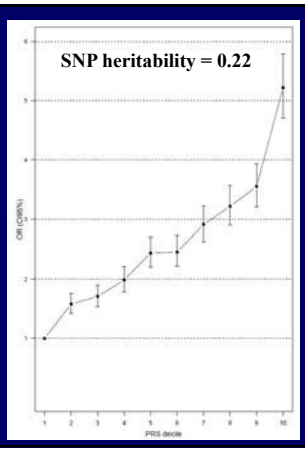
Calculated as $S = \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k$,
$X_2, \ldots, X_k$ - allele dosages for k independent markers (SNP-s)

5

ADHD Risk Increases with the Polygenic Risk Score

Those in the highest 10% of polygenic risk have five-fold increased risk for ADHD….

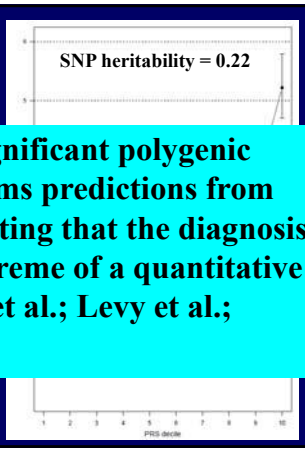
…But the PRS is a very weak predictor of who does and does not have ADHD



Demontis et al. Nat Gen, 2018

6

ADHD Risk Increases with the Polygenic



The finding of a significant polygenic background confirms predictions from twin studies suggesting that the diagnosis of ADHD is the extreme of a quantitative trait (e.g, Larsson et al.; Levy et al.; Gjone et al.)

have ADHD

Demontis et al. Nat Gen, 2018

7

Polygenicity and Genetic Correlations

(Smoller et al., Molecular Psychiatry, 2018)

- Given GWAS data from an individual, we can compute their polygenic risk score for many psychiatric and non-psychiatric disorders.
- These scores can be correlated with one another to compute a genetic correlation.
- The genetic correlation tells us the degree to which two disorders share common DNA variants

8

Genetic Correlation with ADHD Symptoms in the Population

(Demontis et al., Nature Genetics, 2018)

- The EAGLE/QIMR data comprises ADHD parental rating scale scores from 20,464 children and adolescents
- Correlation of ADHD GWAS and EAGLE/QIMR: $r_g = 0.97$, SE = 0.2

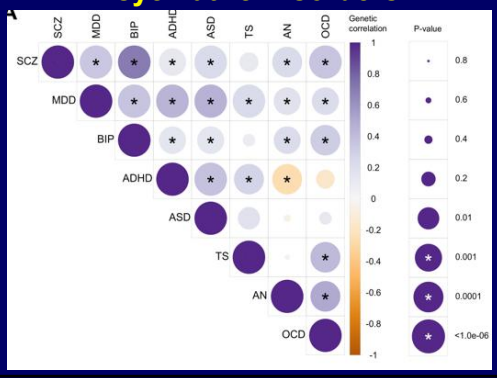
9

Is There a Genetic Boundary Between ADHD and other Psychopathology?

(PGC Cross Disorder Group, submitted)

10

Genetic Correlations among Psychiatric Disorders



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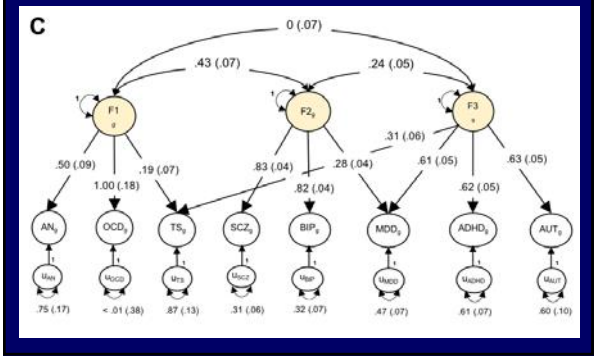
The Genetic Architecture of Psychopathology: Three Latent Traits



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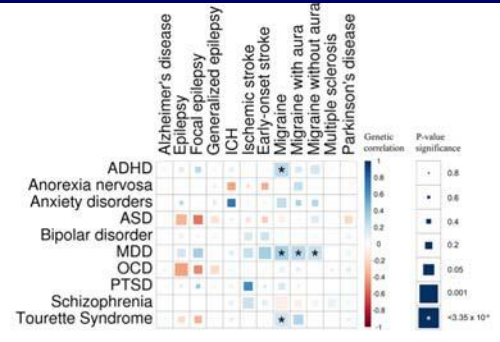
Genetic Correlations Between Psychiatric & Neurological Disorders

(Verneri et al., Science, 2018)



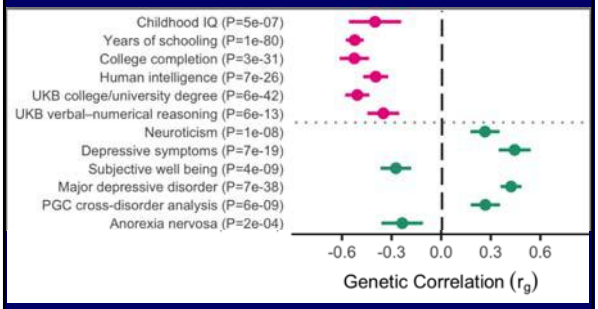
13

Is There a Genetic Boundary between ADHD and Associated Psychological Traits and Medical Conditions?

14

Genetic Correlations: Cognitive and Psychiatric Traits

(Demontis et al., Nature Genetics, 2018)



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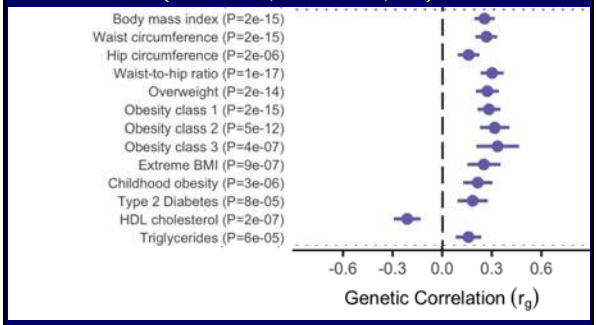
Genetic Correlations: Obesity and Lipid Levels

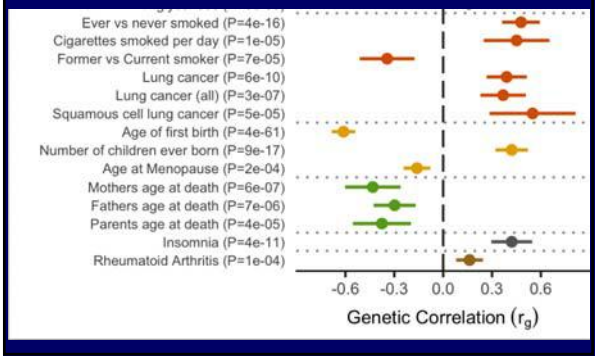
(Demontis et al., Nature Genetics, 2018)



16

Genetic Correlations: Other Traits

(Demontis et al., Nature Genetics, 2018)

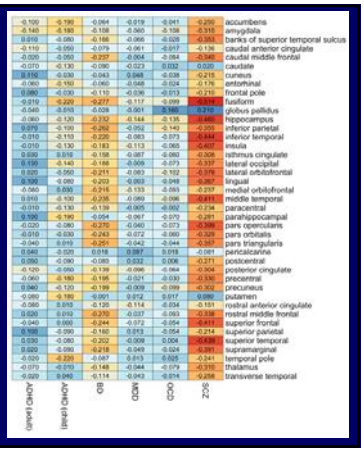


17

Does the Genetics of Brain Structure Inform us About Genetic Boundaries of ADHD with Other Disorders?

18

Structural Brain Changes (SBCs) in ADHD, Bipolar, MDD, OCD and Schizophrenia Data from ENIGMA



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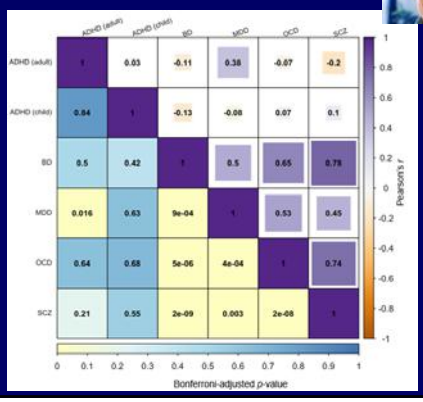
SBCs: Cross Disorder Correlations



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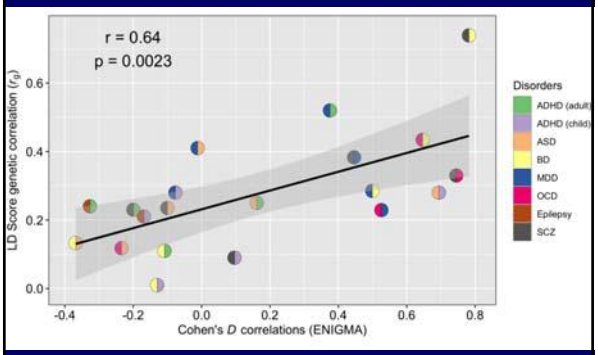
Cross Disorder Genetic Correlations are Similar to Cross Disorder SBC Correlations



21

Is There a Genetic Boundary Between Childhood and Adult ADHD?

22

Common Genetic Variants Mostly the Same for Childhood and Adult ADHD

(Rovira et al., Submitted)

PGC Psychiatric Genomics Consortium

h^2_{SNP} = 0.20 (SE = 0.023)

IMAGEN

h^2_{SNP} = 0.21 (SE = 0.025)

Genetic Correlation

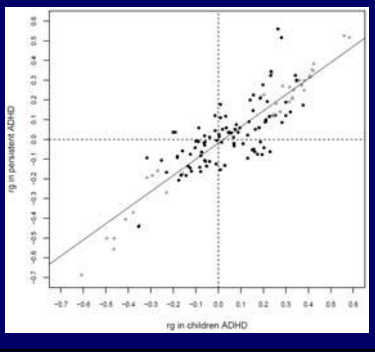
R_g = 0.81 (0.08)

P-Value= 5.1235e-21

23

Genetic Correlations with Other Traits the Same for Childhood and Adult ADHD

(Rovira et al. submitted)



24

Clinical Implications of the New Genetic Architecture of Psychopathology

25

Can We Use DNA to Make Psychiatric Diagnoses?

- **No**
- **Current polygenic risk scores are not sufficiently accurate for use in the clinic**
- **Accuracy may improve as samples get larger, more sophisticated algorithms are applied and other data sources (transcriptome, epigenome imaging) are combined**

26

How Should we Think about Psychiatric Comorbidity in ADHD?

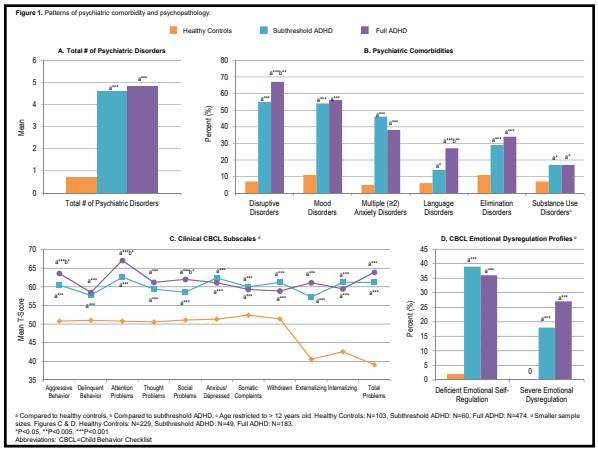
- The new molecular genetic data will, hopefully, put an end to debates about psychiatric comorbidity.
- We now know that most psychiatric disorders are correlated with one another at the level of DNA.
- Diagnosticians should expect "pervasive comorbidity"
  - ADHD can co-occur with many disorders
  - Multiple comorbidities are to be expected in some patients

27

Viewing ADHD as a Dimension Changes How we View Diagnostic Controversies

- DSM-IV subtypes
  - Appropriately retired
- Adult Onset ADHD as a distinct disorder
  - On its way to retirement (hopefully)
- Subthreshold ADHD
  - Why does a child with 5 impairing inattentive symptoms and 5 impairing hyperactive-impulsive symptoms not have ADHD?

28



29

The Overdiagnosis Controversy

- Categorical model implies that overdiagnosis is a huge error
  - Child has ADHD vs. Child is neurotypical
- Dimensional model implies degrees of error
  - Child has DSM ADHD vs. degrees of subthreshold ADHD

30

ADHD is a Fluctuating Dimension

- DSM emphasizes ADHD as chronic and cross-situational
- But conceiving of ADHD as a dimension makes one wonder how (and why) it fluctuates?
  - Due to fluctuating demands on self-regulation?
  - Due to fluctuations in the internal and external "scaffolding" that supports self-regulation
  - Due to developmental recovery of ADHD impaired brain functions with some data suggesting that recovery is augmented by treatment

31

Summary: Genetics & the Boundaries of ADHD

- Genetic studies indicate weak or non-existant boundaries between
  - The diagnosis of ADHD and symptoms in the population
  - ADHD and other psychiatric disorders
  - ADHD and many psychological & medical features
  - Childhood ADHD and adult ADHD
- The diagnostic manual should define the dimension and how to choose the threshold for diagnosis

32

Thanks for Listening!

Free CME: www.adhdinadults.com

MyADHD Blogs: www.linkedin.com/in/stephenfaraone

Tweets: @StephenFaraone

33

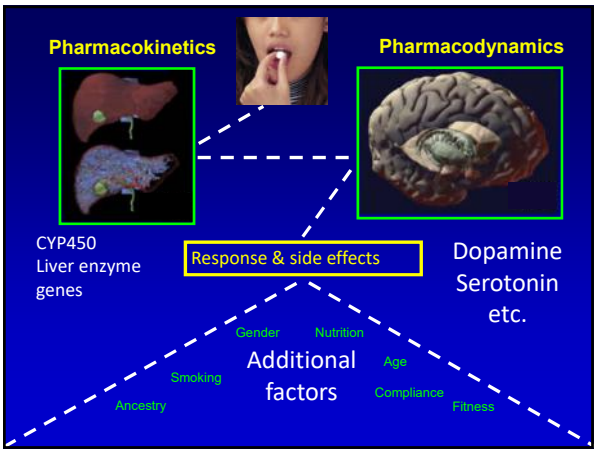
Pharmacogenomic Marker Discovery & Delivery of Optimized Medication Treatment

James L. Kennedy MD FRCPC FRSC

Head, Tanenbaum Pharmacogenetics Centre,
Director, Molecular Brain Science Dept
Centre for Addiction and Mental Health;
Professor, Brain & Therapeutics,
Depts of Psychiatry and Medical Science,
University of Toronto

Amer Professional Soc for ADHD & Related Dis, Jan 19, 2018
Disclosures:
-member of Assurex Health Inc. scientific advisory board (unpaid)
- Pharmacogenetic test patent applications

1

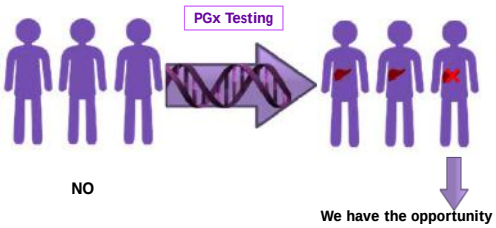


2

WHY IS PHARMACOGENETICS BETTER?

Can the doctor determine which patient will not respond?

With genetics...

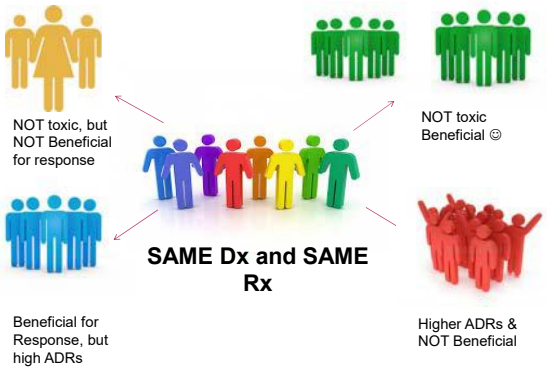


NO

We have the opportunity to see abnormal responders

3

Smarter Prescribing



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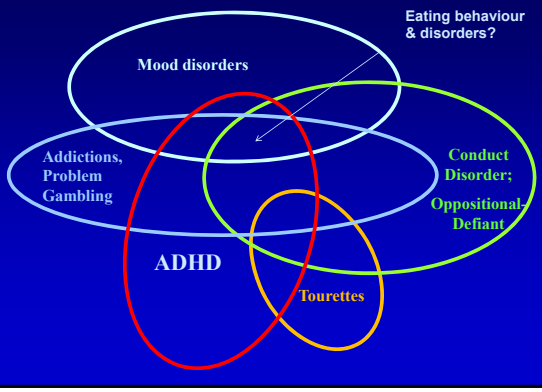
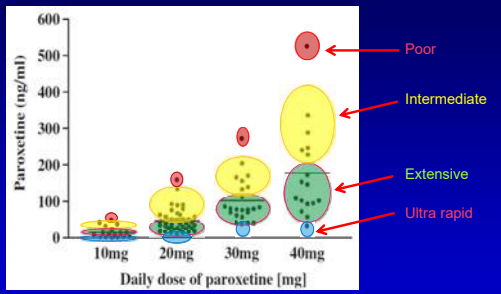
PHENOTYPE COMPLEXITY



5

CYP2D6 Genotype alters paroxetine levels (Japan sample)



Ueda M, et al. The impact of CYP2D6 genotypes on the plasma concentration of paroxetine in Japanese psychiatric patients. *Progress in Neuro-Psychopharmacology & Biological Psychiatry.* 2006; 30:486-491.

6

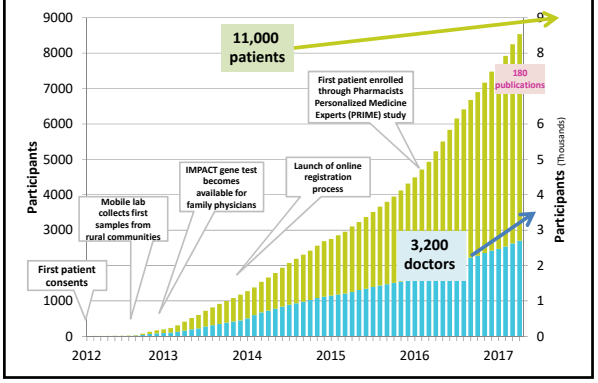
The CAMH Pharmacogenetics Research Project IMPACT STUDY

- 2012 - began with in-house gene panel - Kennedy Lab
- Assessment of important drug metabolism genes (CYP2D6, -2C19, -2C9, -1A2, -3A4, -2B6)
- e-Report of genetic interpretation to Dr in 48h
- Testing feasibility and acceptance of genetic report by physician and patient
- Patient follow-up & Physician Survey
- Over 11,400 pts tested as of Jan 1, 2019

www.IMPACTSTUDY.ca

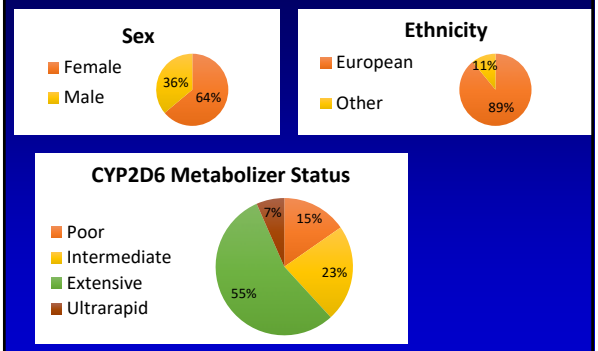
7

IMPACT Pharmacogenetics: Publications, Physicians & Patients



8

IMPACT STUDY SAMPLE CHARACTERISTICS N = 8000



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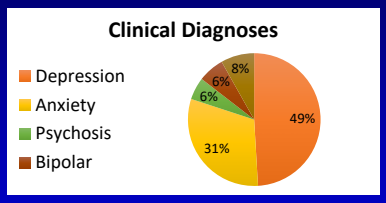
IMPACT STUDY SAMPLE CHARACTERISTICS N = 8000



Clinical diagnosis from physician referral form

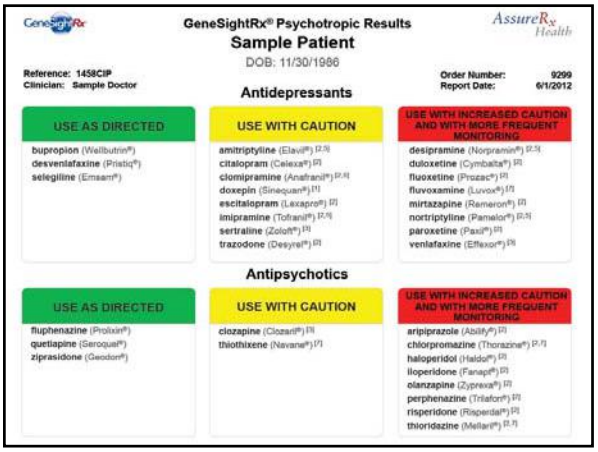
ADHD = 2%, ~ 50% comorbid with anxiety or depression

10

Example Pharmacogenetic Report

Front page Page 2

11



12

The GUIDED Study (Greden et al, 2019; *J Psychiatry Res)*

Pharmacogenomic Test RCT in Depression - 60 Sites (N = 1,167)

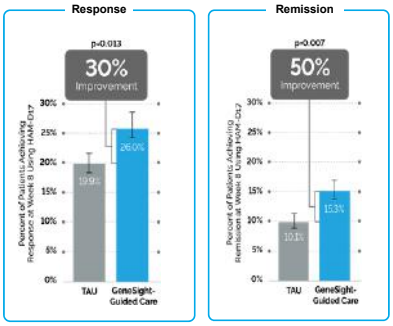
13

RESULTS

NATIONAL NETWORK OF DEPRESSION CENTERS PHARMACOGENETIC TEST RCT (Greden et al, 2019)

Treatment guided by GeneSight® Psychotropic test

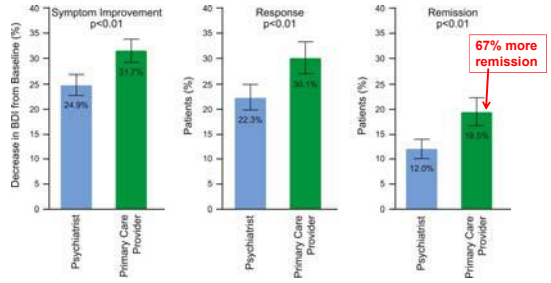
50% improvement in remission rates & 30% increase in response rates at 8 wks vs treatment as usual (TAU).



Treatment Resistant Depression pts with avg 1.7 med trials before study entry.

14

CAMH IMPACT Study: Comparison of Primary Care Physicians versus Psychiatrists Using PGx Test for Depressed Patients (Tanner et al, *J Psychiatry Res,* 2018)



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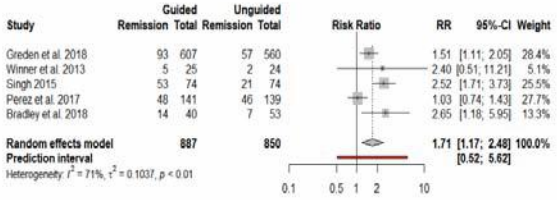
Meta-Analysis of 5 Pharmacogenetic Guided Therapy for Depression RCTs

Bousman et al, (Dec, 2018)



Forest plot of random-effects meta-analyses of five prospective, randomized controlled trials of Pharmacogenetic guided therapy on remission in major depressive disorder.

16

WHAT IS THE STATUS OF PHARMACOGENETICS OF METHYLPHENIDATE IN ADHD?

17

MOLECULAR PSYCHIATRY ORIGINAL ARTICLE

Pharmacogenetics predictors of methylphenidate efficacy in childhood ADHD

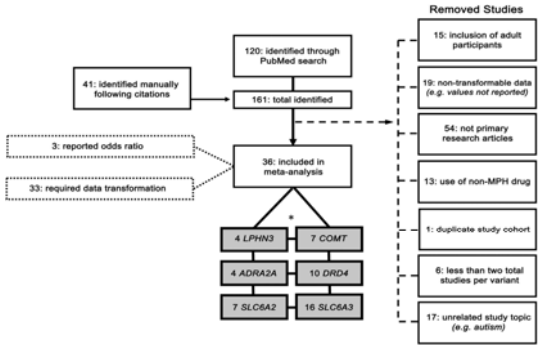
NM Myer, JR Boland and SV Faraone

Stimulant medication has long been effective in treating attention-deficit/hyperactivity disorder (ADHD) and is currently the firstline pharmacological treatment for children. Both methylphenidate and amphetamine modulate extracellular catecholamine levels through interaction with dopaminergic, adrenergic and serotonergic system components; it is therefore **likely that catecholaminergic molecular components influence the effects of ADHD treatment**. Using meta-analysis, we sought to identify predictors of pharmacotherapy to further the clinical implementation of personalized medicine. We identified 36 studies (3647 children) linking the effectiveness of methylphenidate treatment with DNA variants. Pooled-data revealed a statistically significant association between single nucleotide polymorphisms (SNPs) rs1800544 ADRA2A (odds ratio: 1.69; confidence interval: 1.12–2.55), rs4680 COMT (odds ratio (OR): 1.40; confidence interval: 1.04–1.87), rs5569 SLC6A2 (odds ratio: 1.73; confidence interval: 1.26–2.37) and rs28386840 SLC6A2 (odds ratio: 2.93; confidence interval: 1.76–4.90), and, **repeat variants variable number tandem repeat (VNTR) 4 DRD4 (odds ratio: 1.66;** confidence interval: 1.16–2.37) and VNTR 10 SLC6A3 (odds ratio: 0.74; confidence interval: 0.60–0.90), whereas the following variants were not statistically significant: rs1947274 LPHN3 (odds ratio: 0.95; confidence interval: 0.71–26), rs5661665 LPHN3 (odds ratio: 1.07; confidence interval: 0.84–1.37) and VNTR 7 DRD4 (odds ratio: 0.68; confidence interval: 0.47–1.00). Funnel plot asymmetry among SLC6A3 studies was identified and attributed largely to small study effects. Egger's regression test and Duval and Tweedie's 'trim and fill' were used to examine and correct for publication bias. **These findings have major implications for advancing our therapeutic approach to childhood ADHD treatment**.

Molecular Psychiatry advance online publication, 12 December 2017; doi:10.1038/mp.2017.23

18

Review and Meta-Analysis



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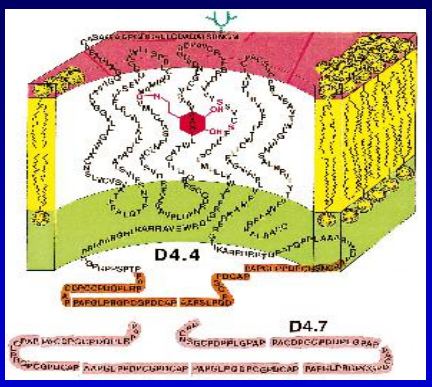
DOPAMINE D4 RECEPTOR



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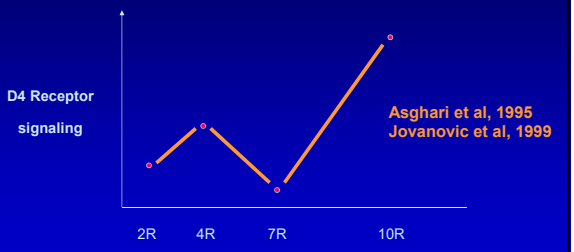
Dopamine D4 48bp Repeat Variants:
Functional differences with number of repeats



Implication: the 7R allele has a blunted response to dopamine

21

Dopamine D4 and ADHD

LaHoste G, Swanson J, Wigal S, C Glabe, King N, & Kennedy JL (1996) DRD4 Associated with ADHD *Molec. Psychiatry 1:121-124.*

22

Review of DRD4 and ADHD

Faraone et al [2005] meta analysis of the 7-repeat allele of DRD4 →case-control (odds ratio=1.45 (95% CI 1.27-1.65))

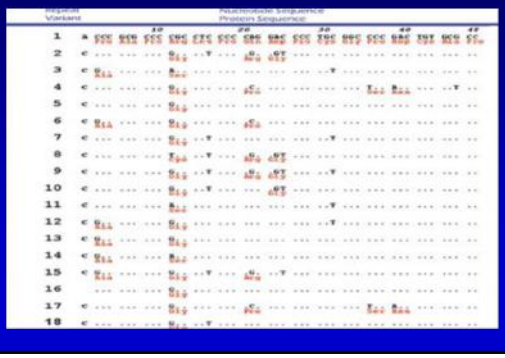
Li et al [2006] → pooled OR of 1.34 (1.23-1.45) across **33 studies.**

In genome-wide studies of ADHD, odds ratios are generally < 1.1, possibly due to heterogeneity of subjects and diagnostic methods.

Note that the widely used GWAS SNP chips do not effectively measure the variation of the repeats (eg 7R vs 4R) of DRD4.

23

DRD4 sequencing: 35 within-repeat variants identified in N=156 people



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BENEFITS TO PATIENTS AND SOCIETY

Matching the right drug at the right dosage may mean that we stand to increase our ability to:

- Treat patients right the first time
- Minimize the risk of dangerous side effects
- Reduce the risk of suicide
- Give family doctors tools they can use - increasing their ability to manage patients in the community
- Save 100s of millions of dollars in prescriptions that are ineffective or harmful
- Evidence-based biomedical test reduces stigma against people with mental illness

Ontario

25

CAMH Neurogenetics Group

Campbell Family camh

Ontario RESEARCH and INNOVATION

Larry and Judy Tanenbaum

CIHR IRSC

26

Antipsychotic Induced Weight Gain and Metabolic Syndrome

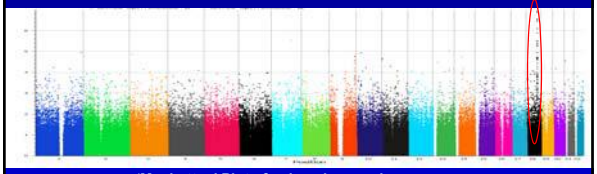
27

Antipsychotic-induced Weight Gain: Genome Wide Study

This GWAS was done on N=180 youths age 7 to 16 treated with antipsychotics (risperidone, olanzapine, quetiapine, aripiprazole) for disruptive behaviour. Nearly all gained weight to some degree. *Correll CU et al, JAMA. 2009).*

Under the chr 18, q arm

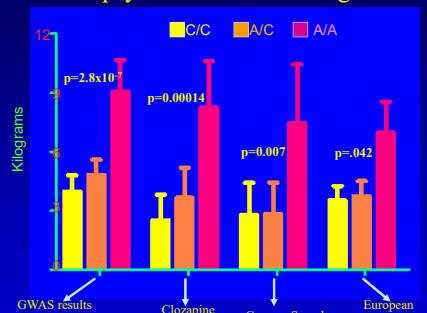
BINGO!



'Manhattan' Plot of minus log p-values
(Malhotra A... & Kennedy JL, submitted)

28

Melanocortin 4 Receptor Gene (MC4R) Predicts Antipsychotic-induced Weight Gain



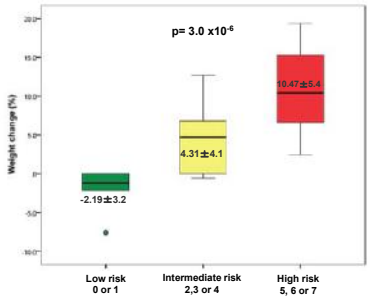
Malhotra...& Kennedy, JAMA Psy 2012.

rs489693 marker in MC4R is located downstream of coding region

Meta analysis: genome wide sig effect ($p=5.59 \times 10^{-12}$)

29

Antipsychotic Induced Weight Gain – Multi-gene test

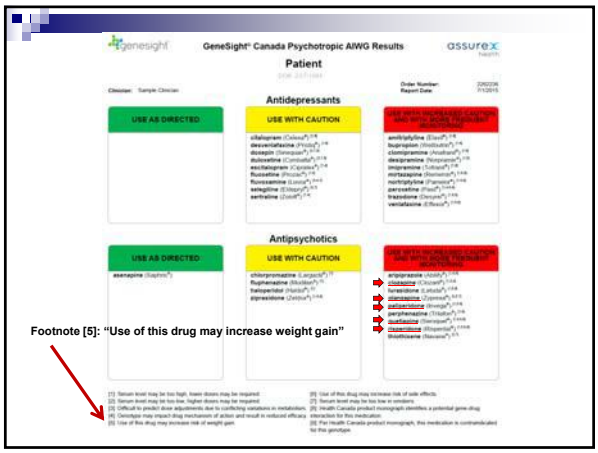


AIWG genes

MC4R	CNR1
NPY	NDUFS1
HCRTR2	GCG

Tiwari *et al.* 2010; 2013; Brandl *et al.*, 2014; Malhotra *et al.*, 2012; Tiwari *et al.*, in prep; Goncalves *et al.*, 2014

30


GeneSight® Canada Psychotropic AIWG Results
Patient
Antidepressants
USE AS DIRECTED
USE WITH CAUTION
Antipsychotics
USE AS DIRECTED
USE WITH CAUTION
Footnote [5]: "Use of this drug may increase weight gain"

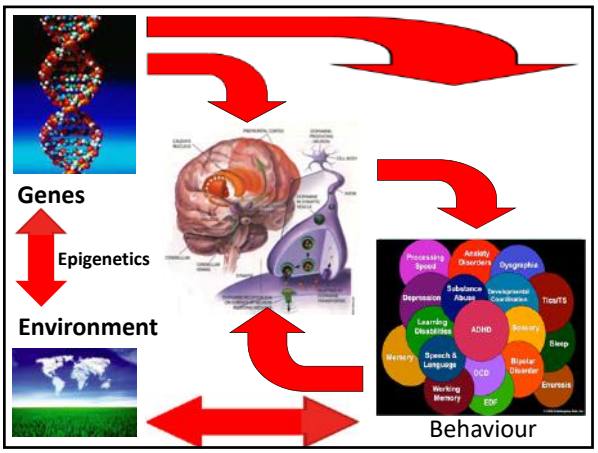
31

Relevance of Neuroimaging in Understanding ADHD

Adriana Di Martino, The Child Mind Institute, New York
Do ADHD and autism overlap in the brain connectome?

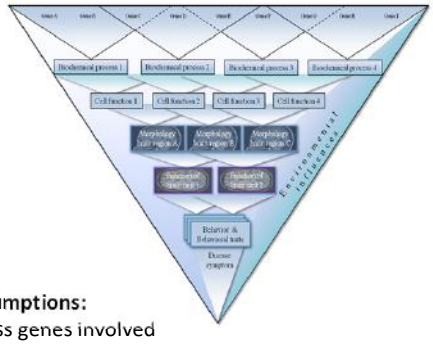
Philp Shaw, National Human Genome Research Institute, Bethesda
Growing out of ADHD

1



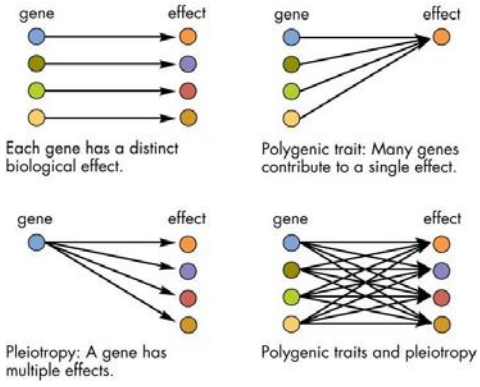
2

Endophenotype concept



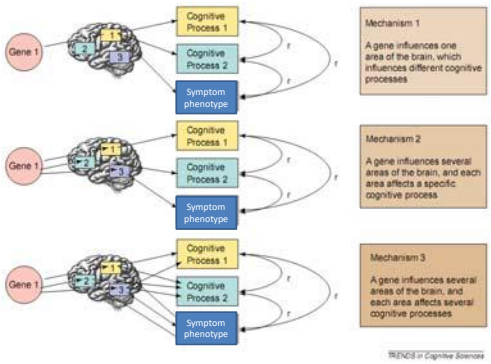
Assumptions:
- Less genes involved
- Greater genetic effect sizes

3



https://www.grossmont.edu/people/bonnie-yoshida-levine/online-lectures/genetics-mendel.aspx

4



Pleiotropy: Genetic risks effect multiple processes

Kovas and Plomin, Trends in Cognitive Neuroscience, 2006

5

Molecular Psychiatry (2010) 15, 789–797

www.nature.com/mp

FEATURE REVIEW

Endophenotype: a conceptual analysis

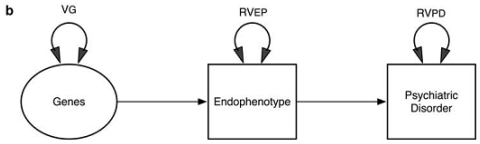
KS Kendler[1,2] and MC Neale[1,2]

[1]Department of Psychiatry, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA and [2]Department of Human and Molecular Genetics, Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA

- **Intermediate phenotype (causal)**
- **Risk index of genetic liability (pleiotropy)**

6

Intermediate endophenotype



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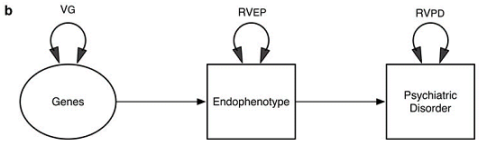
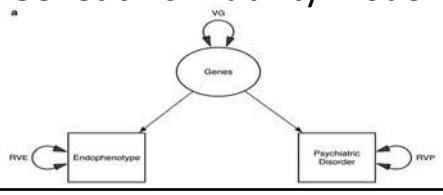
Intermediate phenotype



Genetic risk liability model



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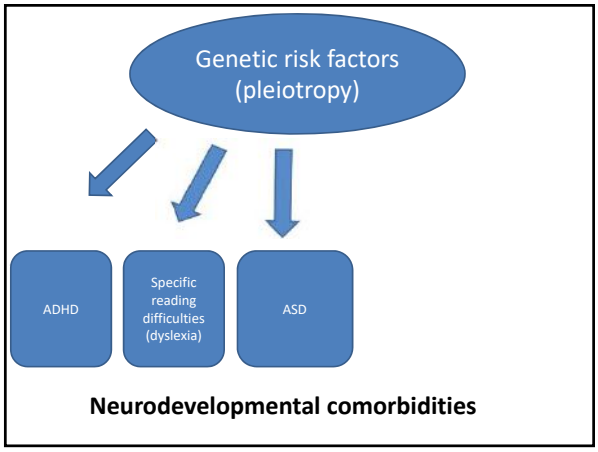

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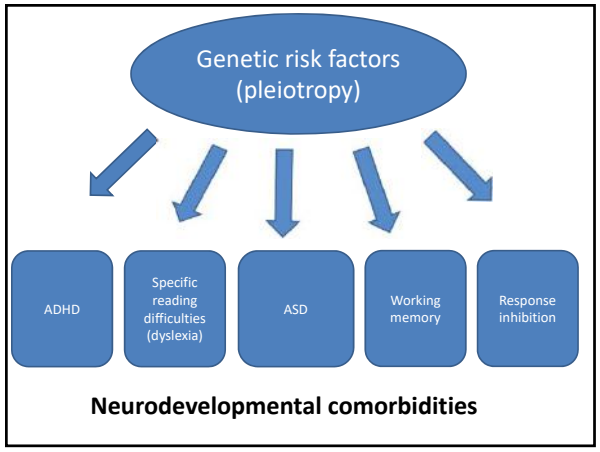

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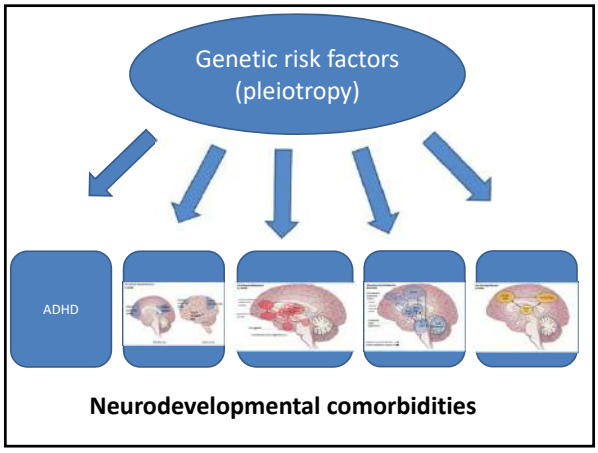


11

Adult remission from childhood ADHD: insights from multimodal imaging

APSARD
Annual Meeting
January 20th 2019

Philip Shaw BM BCh, PhD
Earl Stadtman Senior Investigator

Gustavo Sudre PhD and Eszter Szekely, PhD
Post-doctoral Fellows

Neurobehavioral Clinical Research Section, NHGRI
Adjunct faculty, National Institute of Mental Health.

Social and Behavioral Research Branch
National Human Genome Research Institute, NIH

1

- No conflicts of interest
- Funding
  - Intramural grants from the National Human Genome Research Institute and National Institute of Mental Health

2

Overview

- ADHD: remission and persistence
  - Models of remission
  - Neural correlates of remission
    - Anatomic cortical trajectories
    - White matter microstructure
    - Intrinsic functional connectivity
    - Task-related functional connectivity

3

ADHD through the lifespan

- Peter
  - Restless and fidgety since birth
  - Impulsive
  - Inattentive, poor sustained focus
  - Diagnosed ADHD age 6
- Susan
  - Physically impulsive
  - Highly distractible
  - Struggling at school
  - Diagnosed with ADHD age 6.

4

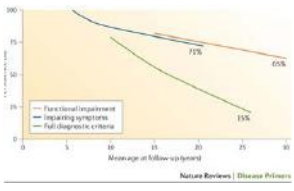
ADHD through the lifespan

- REMISSION: Peter
  - Symptom resolved around middle school
  - Stopped medication age 15
  - No other psychiatric problems
  - 25 years: symptom free
- PERSISTENCE: Susan
  - Symptoms unchanged
  - Struggled to graduate high school
  - Struggled to stay employed
  - 24- marked ADHD symptom

5

Remission vs persistence

- How frequent is remission/persistence? (Faraone et al, 2006)
  - ~15%: childhood syndrome persists into adulthood
  - ~50%: have partial remission with some symptom persistence
  - 6 recent prospective studies return similar estimates
    - Full syndrome ~20-30%
    - Impairing symptoms – 70=80%



6

Remission: importance

- Why study remission/persistence?
  - Public health importance
  - Might help prediction of prognosis
  - Stimulate novel treatment approaches
- How to study neural factors underpinning remission?
  - Interventional (does altering a neural process lead to remission?)
  - Observational:
    - Prospective: bind together clinical and imaging assessments
    - Mixed: clinical over time; image at adult endpoint

7

Models of remission

Model	Persistent brain	Remitted adult brain
Compensation/ neural reorganization	Atypical	Remitted ≠ persistent ≠ never affected brain
Convergence	Atypical	Remitted = never affected brain
Fixed anomalies	Atypical	Remitted = persistent ≠ never affected brain

Mixed models: subcortical fixed anomalies (regardless of remission) but cortical compensation (eg Halperin, Newcorn)

8

Studying remission

Childhood cohort (M=10 yrs)

ADHD, N=202;

Unaffected, N=202

Adult clinical reassessment (N=290, 24±3 years)

Multimodal imaging (N= 160-220)
White matter tract microstructure (DTI)
Intrinsic functional connectivity (FMRI and MEG)
Task based activity (FMRI and MEG)

Neuroanatomic imaging (N=280)

9

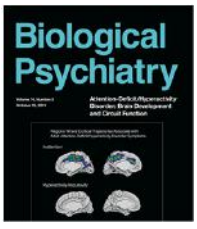
The definition of persistence/remission

- DSM IVR criteria
  - (now including DSM 5 category of in partial remission)
- Clinician interview (CAADID), SCID (for DSM-IV axis 1)
- All analyses were categorical and dimensional (hyperactive-impulsive/inattentive symptom counts)

10

Neuroanatomy and remission

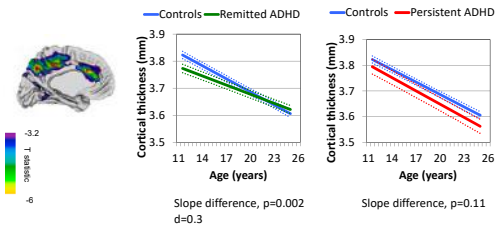
- Where is change in cortical dimensions associated with adult outcomes of ADHD?
- A longitudinal anatomic study (1.5T; CIVET- cortical thickness)



Shaw et al, 2013, Biol Psychiatry

11

Neuroanatomy and remission



Slope difference, p=0.002
d=0.3

Slope difference, p=0.11

Shaw et al, 2013, Biol Psychiatry

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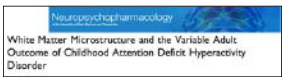
White matter microstructure

13

Remission: white matter microstructure

- Background
  - ADHD as a 'developmental dysconnectome' (di Martino et al 2016)
  - Outcome associated with neuroanatomic trajectories of multiple cortical regions (Shaw et al 2013)
  - Are structural connections in the brain, composed by white matter tracts, also associated with adult outcomes?

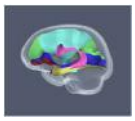


Shaw *et al*, 2015

14

Remission: white matter microstructure

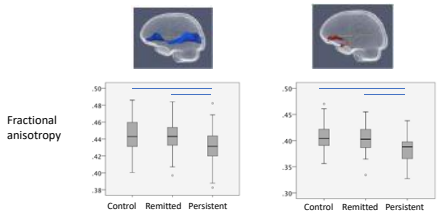
- Diffusion Tensor Imaging
  - 3 Telsa, GE scanner
  - 86 non-collinear directions
  - 43 remitted, 32 persistent; 74 never-affected
  - Quality control: excluded 51/200 data sets
  - Adjustment for age, residual head motion, medication, sex
  - Controlled for multiple comparisons (Bonferroni)
  - DTI-Tk for registration and extraction of 11 major tracts



Shaw et al, 2015, Neuropsychopharm

15

Remission: white matter microstructure



Categorical contrasts: Persistent< NV (effect sizes 0.68-0.8). Remitted =NV
No group difference when analyzed on basis of childhood history
Held when excluded those on psychostimulants, current comorbidity

Shaw et al, 2015, Neuropsychopharm

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Intrinsic functional connectivity

17

Remission: intrinsic functional connectivity

- **Intrinsic connectivity: coordinated brain activity during task free periods**:-
  - Magnetoencephalography (MEG)
  - Functional MRI (fMRI)
  - Total N=205 (variables numbers completing each modality)
- **Predictions about intrinsic connectivity in remission**
  - 'Normalization' (ie remission =never affected)?
  - Neural reorganization (ie remitted different from other groups)?
  - Fixed childhood anomalies (ie remitted=persistent)?

Sudre et al, 2017, PNAS

18

Methods

- MEG
  - Quality control: removed 32% data
    - Visual inspection for motion and muscle artifacts (boundaries marked)
  - No correlation between residual head displacement and adult symptoms
  - Analysis: activity mapped to cortex (beam former localization ;SAM tools, band passed filtered)
- fMRI
  - Volumes $\geq 0.2mm$ or 10% of voxels as outliers were excluded
  - No correlation between residual head displacement and symptoms

PNAS

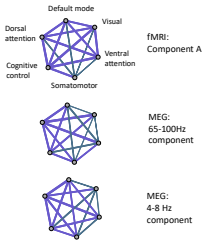
Multimodal mapping of the brain's functional connectivity and the adult outcome of attention deficit hyperactivity disorder

Sudre...Shaw, 2017

19

Methods

- **Define connectivity**
  - MNI template with 6mm gird (2146 locations; each allocated to network)
  - Connectivity = pairwise connections
    - MEG –phase coupling consistency
    - fMRI- correlations between residualized time series
- **Extract stable connectivity patterns**
  - 1,000 initializations and bootstraps- stability metric >0.85 (ICASSO)
  - Stable connectivity patterns: 6 fMRI; 56 MEG



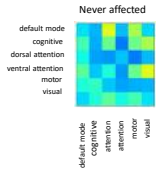
Sudre et al, 2017, PNAS

20

Adult outcome and connectivity patterns

- Association with inattention
  - 4/56 MEG (rho 0.45 to 0.54, Bonf adj p<0.05)
  - One fMRI connectivity pattern (rho=0.31, p=0.006)
  - Categorical contrasts: remitted=never affected<persistent
  - No difference between those with childhood ADHD vs never affected

Categorical contrasts



Sudre et al, 2017, PNAS

21

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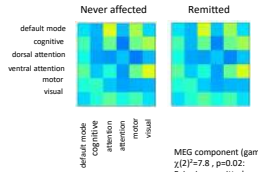

MEG component (gamma)
$\chi(2)^2$=7.8 , p=0.02:
Pairwise: remitted=never affected<persistent (o=0.001)
Inattention rho=0.45,p<10e-04

22

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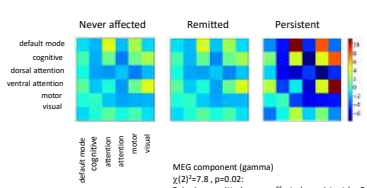
Categorical contrasts



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$\chi(2)^2$=7.8 , p=0.02:
Pairwise: remitted=never affected<persistent (o=0.001)
Inattention rho=0.45,p<10e-04

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Summary

- Intrinsic connectivity: remitters did not differ significantly from never affected
- Results held when removed those on psychostimulant medication and those with current comorbidity
- Remission
  - ➢'typical' white matter microstructure
  - ➢'typical' cortical intrinsic functional connectivity

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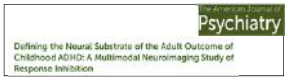
Task related neural activity

25

Adult outcome and task related processing

- Response inhibition:
  - Core cognitive deficit in ADHD
  - Recruits inferior frontal gyri/ caudate circuitry
  - Where does activation reflect adult outcome vs childhood history?
- 35 persistent; 47 remitted; 99 never affected



Szekely...Shaw,2017

26

Methods

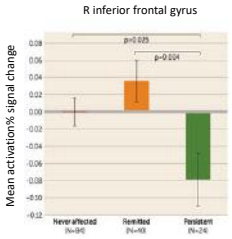
- fMRI
  - **Region of interest:**
    - **Inferior frontal gyri: activation reflects adult outcome?**
    - **Caudate: activation reflects childhood history?**
  - Whole brain: latest version 3dClustSim : voxel-wise p value ,0.05 and a cluster-corrected alpha level ,0.05 (k=1, minimum cluster size=512 voxels)
  - Data processing – quality checks as before

Sleekly et al (2017), Am J Psych

27

Behavior and fMRI

- Behavior: Remitted=never affected > persisters
  persisters less accurate (F=4,5, p-0.01), longer SSRT (F=3.46, p=0.04)
- Cortical (Inferior frontal gyri) activity reflected outcome
  - Remitted =never affected >persisters
  - Association with hyperactivity-impulsivity



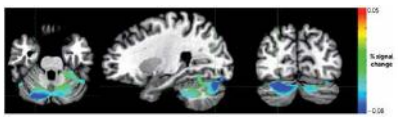
F((2,145)=4.37, *p*=0.01
Remitted=never affected

Szekely et al (2017), Am J Psych

28

Behavior and fMRI

- Caudate activity reflected childhood history
  - Childhood ADHD (remitted+persistent) vs never affected: reduced R caudate during successful inhibition (t=2.28, df=1, 146, p=0.02);i
- Whole brain level:
  - Cerebellar activation reflected outcome (also found for MEG)

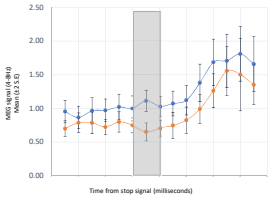


Szekely et al (2017), Am J Psych

29

MEG

- Cortical activity during successful inhibition associates with adult outcome
  - Whole brain analyses (FDR q<0.05)
  - Hyperactivity-impulsivity associated with R inferior frontal theta activation during successful inhibition



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Summary

- Inferior frontal gryal activity during inhibitory processes reflects adult outcome: remitters resemble never affected
- Cerebellar activity reflected adult outcomes (fMRI and MEG)
- Caudate anomalies found (fMRI only) in those with history of childhood ADHD, regardless of outcome
- Findings robust to excluding those on regular psychostimulants/ current comorbid major depression/ GAD

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Models of remission: summary of our studies

Model	Remitted brain	Neural finding
Compensation/ neural reorganization	Remitted ≠ persistent ≠ never affected brain	-
Convergence	Remitted = never affected brain	Cortical activity during response inhibition Intrinsic functional connectivity White matter microstructure
Fixed anomalies	Remitted = persistent ≠ never affected brain	Subcortical activity during response inhibition

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Other studies into adult outcomes….

- Five major studies of adult outcomes…
  - SUNY: Halperin/Newcorn : fMRI
  - NYU: Mannuzza/Klein/Castellanos/Cortese: aMRI, DTI
  - MGH: Biedernam/Mattfield: rsfMRI
  - IoPPN: Asherson/ Kuntsi: EEG/ERP
  - IMAGE: Euro multi-site: too young to have many remitters: aMRI/DTI/rsfMRI

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Models of remission

Model	Remitted brain	Neural finding
Convergence	Remitted = never affected brain	Schulz 2017: prefrontal activity during high cognitive demand (fMRI) Schneider (2010): prefrontal activity during response inhibition (fMRI) Cheung/Michelini (2016): EEG/ERP Indices of response preparation /vigilance (trend for indices of cognitive control) Mattfield (2014): default mode intrinsic connectivity (fMRI)

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Models of remission

Model	Remitted brain	Neural finding
Fixed anomalies	Remitted = persistent ≠ never affected brain	Clerkin (2013): thalamic activity during response preparation (fMRI) Mattfield (2014): connectivity between DMN and cognitive control Cortese (2014) focal anomAlies in white matter tracts
Compensation/ neural reorganization	Remitted ≠ persistent ≠ never affected brain	Clerkin (2013): thalamic-prefrontal connectivity during response preparation: remitters had unique pattern

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Conclusions

- Remission similar to never affected in mainly cortical/cerebellar levels
- Remission can occur despite fixed subcortical anomalies
- Future directions: Prospective multimodal imaging for a definitive mapping of the trajectories of remission

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Acknowledgements

- NHGRI
  - Post-doctoral fellows: **Gustavo Sudre, Eszter Szekely,** Marine Bouyssi-Kobar
  - Post-bac trainees: Aman Mangalmurti, Jen Frederick
- NIMH
  - Wendy Sharp
  - Ellen Liebenluft
  - MEG core facility
  - AFNI team and fMRIF center,

37

Thank you

38

Conclusions

- Convergence
  - Cortical activity during cognitive challenge
  - Intrinsic connectivity (within default mode network)
- Fixed anomalies
  - Subcortical (striato-thalamic) activity
- Compensation
  - Thalamic-frontal connectivity during response preparation
- Different processes at different brain levels

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Convergence/'normalization'

- 'Top-down': neural findings
  - Shculz 2017: fMRI: high cognitive demand: remitters=never affected > persisters
  - Schneider 2010: fMRI:response inhibition: remitters=never affected>persisters (inattention)
  - Cheung 2016/Michelini 2016: EEG?ERP indices of cognitive control (eg nogo=P3 amplitude/N2 signal): never affected>remitters>never affected

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Cognitive models of remission

- 'Bottom-up'
  - EEG/ERP: indices of response preparation and vigilance (CNV and error processing): Remitters=never affected> persistent
  - fMRI: response preparation (Clerkin et al 2013):: never affected > remitters=persisters
  - Connectivity between thalamic-prefrontal cortex: remitters had unique pattern (compensation)
- Default mode network
  - Mattfleid et al 2014: Connectivity within DMN: remitters= never affected > persisters
  - Connectivity between DMN and cognitive control: atypical in both persisters and remitters

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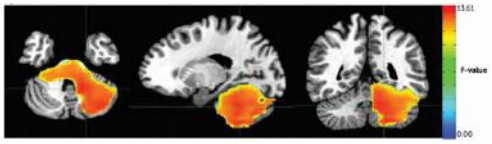
MEG

- Outcome group differences at whole brain level
- Cerebellar activation 500-600ms following stop signal (fdr corrected)
- Theta and delta bands (shown)



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STUDY	Modalities	Normalization	Compensation	Fixed anomalies
SUNY (Halperin/Newcorn/ Schulz)	Task fMRI (inhibitory and response preparation)	++ (cortical)	-Connectvity during response preparation	+ (thalamic)
MGH (Biederman/ Mattield)	Resting fMRI	++ (default mode network intrinsic)	-	+ (connectivity between networks)
NYU (Klein, Mannuzza Castellanos)	Anatomy, DTI	+ (deep structures)	-	+ (posterior cortex and focal
IoPPN London (Asherson, Kuntsi, Michelini)	Task based EEG (top down and bottom up)	++ (bottom up measures)	-	++ (top-down measures)

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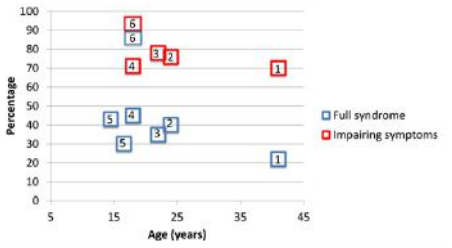
Remission vs persistence: update 2019



(1) Klein et al 2013
(2) Shaw et al 2013
(3) Halperin et al 2008
(4) Biederman et al 2010
(5) Molina et al 2009 ([a]at age 14, [b] at age 17)
(6) Francx et al 2015

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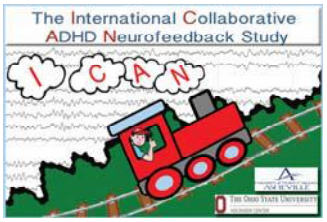

Double-Blind 2-Site Randomized Clinical Trial of Neurofeedback for ADHD

L. Eugene Arnold, M.D., M.Ed.
Professor Emeritus of Psychiatry, Ohio State University
and the Neurofeedback Cooperative Group

1

Arnold Disclosures 2019 –Past 5 Years

Source	Research funding	Advisory board, consultig	Speakr Bureau	Books Intellect Propert	In-kind Service Travel	Stock equit y	Expenses this meeting
YoungLiving	X				E. Oils		
Shire	X	X					
Supernus	X						
Thought Technology					amplifier ADHD ste		
Brainmaster					amplifier		
Noven		X					
Seaside		X					
Biomarin		X					
Arbor		X					
Tris Pharma		X					
Roche		X					
EEG Softwa					softwar		
CHADD		X					X

2

ICAN Study Design

- Two-site, parallel group, double-blind randomized comparison of Active to Sham NF
- 142 boys & girls ages 7 – 10
  - Rigorously diagnosed ADHD
- Randomization 3:2 ratio: 84 Active & 58 Sham
  - Blocks of 5, balanced on current ADHD med
- All staff with participant contact did not know the condition child was in

3

Participants – Inclusion

Sequential Inclusion / Exclusion process

- Structured Interview (ChIPS) and Clinical Evaluation (parent & child)
- Theta / Beta Ratio (TBR) of $\geq$ 4.5 at CZ or FZ in eyes open (EO) condition (also identified training site)
- T score > 65 on Conners-3 DSM-5 ADHD Inattentive criteria by both parent & teacher
- IQ $\geq$ 80
- Vitamin D in normal range ($\geq$ 30 ng/ml)

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Comparison of ICAN Treatments

	Real NF	Sham NF
Coaching	X	X
Inhibit movement	X	X
Inhibit muscle artifact	X	X
Downtraining T:B ratio:		
Contingent inhibit theta	X	
Contingent reward beta	X	
Money points	X	X
Nutrition counseling	X	X
Sleep hygiene	X	X

5

ICAN Demographics

- Mean age 8.4 years (SD = 1.14)
- 78% male
- 76% white non-Hispanic/Latino
- 8% African-American
- 4% Asian
- 13% Hispanic/Latino
- 49% receiving special education services
- Household income: <$50K=25%; $50K to $100K = 44%; >$100K=31%
- Primary parent education: HS Dip = 8%; up to 2yr College = 21%; College Grad = 39%; Adv Grad/Professional = 32%

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Blinding: Guesses About Assignment

Accuracy	Parent	Child	Trainer	Average
Unsure	42%	44%	35%	40%
Correct	34%	32%	39%	35%
Incorrect	23%	24%	26%	25%
Control Tx guessed correctly	25%	7%	24%	19%

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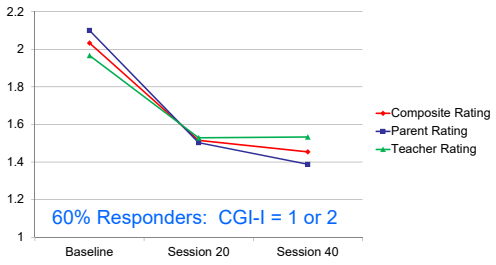
Inattentive Symptom Item Means (Primary Outcome)



60% Responders: CGI-I = 1 or 2

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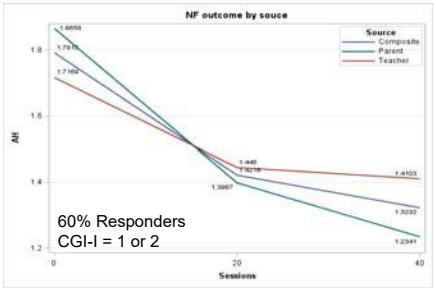
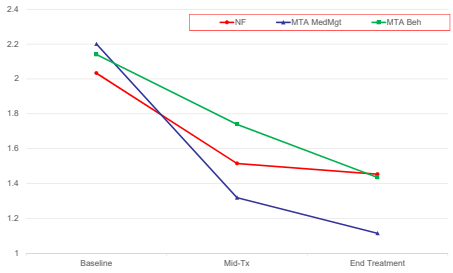
Hyperactive-Impulsive Symptoms



60% Responders
CGI-I = 1 or 2

9

Comparison to MTA: Composite P &T Rating of Inattention



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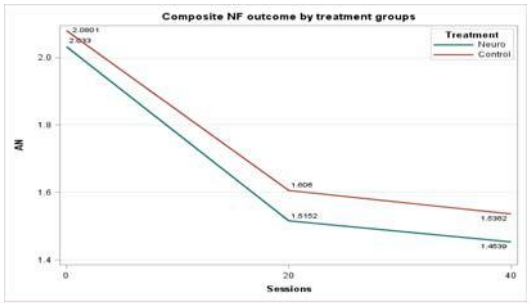
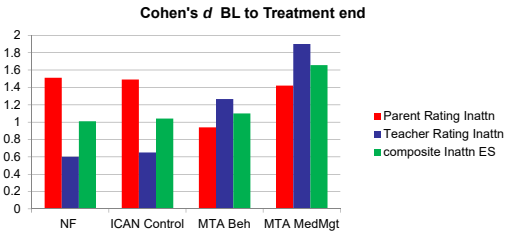
Control Does as Well as NF



11

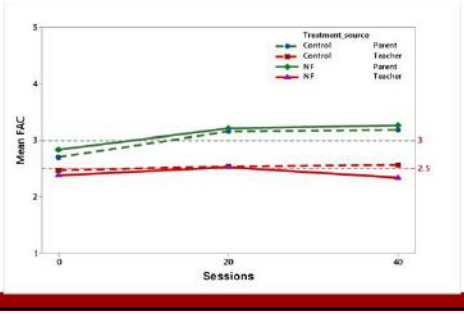
Comparing Pre-Post Effect Sizes: Inattention Improvement



MTA Cooperative Group. Archives of General Psychiatry. 56:1073-1086, Dec. 1999

12

Impairment Outcome: Functional Assessment -Higher Better



3 = Impairment threshold for parent rating
2.5 = impairment threshold for teacher rating

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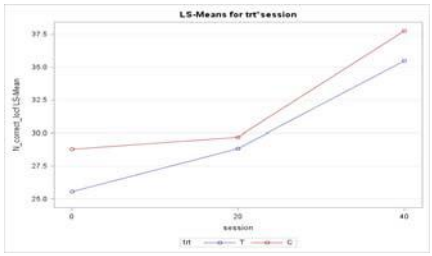
Timed Math Test: # Correct



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AEs Possibly Attributable to Tx

Possibly related Adverse Events	Control	NF
BEHAVIORAL AEs	20 (34.5%)	31 (36.5%)
NEUROLOGICAL - CNS AEs	10 (17.2%)	16 (18.8%)
GENERAL - CONSTITUTIONAL AEs	3 (5.2%)	6 (7.1%)
EYES/EARS/NOSE/THROAT AEs	1 (1.7%)	2 (2.4%)
MUSCULOSKELETAL AEs	0 (0%)	2 (2.4%)
GASTROINTESTINAL AEs	0 (0%)	1 (1.2%)
RESPIRATORY AEs	1 (1.7%)	0 (0%)
SKIN AEs	0 (0%)	1 (1.2%)
Headaches	5 (8.6%)	9 (10.6%)

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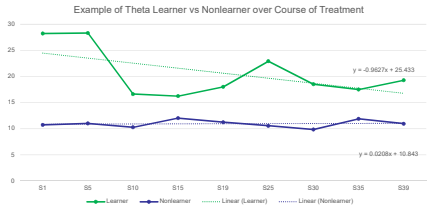
Identification of Theta Learners

"Learners": decreasing slope of theta (green)
"Nonlearners": flat or increasing slope (blue)



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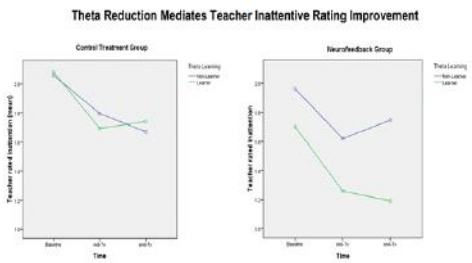
Neurofeedback Theta Learning and Inattention Improvement



Cohen's d end-Tx = 0.72

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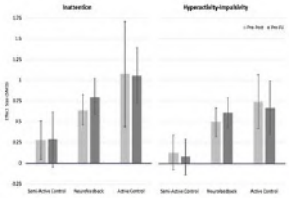
Importance of follow-ups



Geladé, K., et al (2018). 6-month follow. *European Child & Adolescent Psychiatry*, *27*(5), 581-593. doi:10.1007/s00787-017-1072-1

- RCT of Theta/Beta Neurofeedback vs. MPH vs. Sport
- Initial result post-Tx: Sport=NFB<MPH
- After 6 months: Sport<NF~MPH
  NF d 0.44 → 0.98

Van Doren, J., Arns, M., et al. (2018). Sustained effects of NF in ADHD: meta-analysis. *European Child & Adolescent Psychiatry*. doi:10.1007/s00787-018-1121-4

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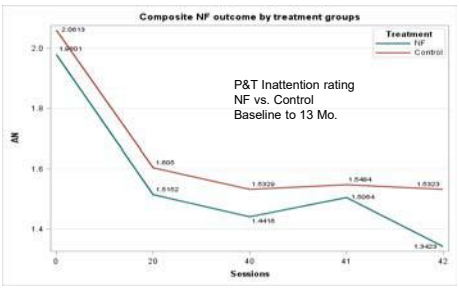
Peek at ICAN F-U: ¾ of Sample



Change Tx end to F-U:
NF d = 0.21
Control d=0.001
Difference at FU: d=0.4

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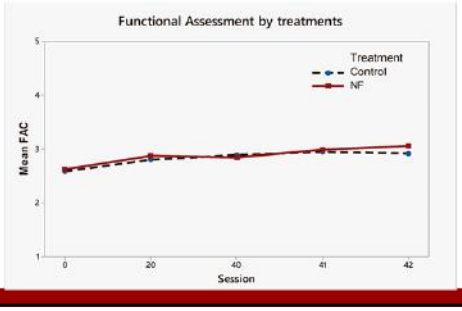
Follow-up Functional Assessment (Higher is Less Impairment)



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Summary & Conclusions

- Results apply only to Theta-Beta NF
- Both NF and control had large pre-post effect comparable to MTA behavioral treatment
- NF not significantly different from control
- Raises questions re both NF and "evidence-based" standard treatment
- Cannot conclude a specific effect of NF --at least in short term

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Summary & Conclusions -2

- May be a delayed benefit, yet to be examined in follow-up
- "Nonspecific effects" apparently as good as longer, more expensive & intensive MTA Behavioral Tx
- Control group needs further study
- What made "sham" so effective?

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Summary & Conclusions -3

- What made "sham" so effective?
  - Artifact suppression (EMG biofeedback)?
  - Bleeding through of intermittent NF?
  - Supportive coaching?
  - Practice Focusing on an uninteresting screen?
  - Attention to Nutrition & sleep hygiene?
  - Powerful sci-fi props "super placebo"?
  - Is it necessary for the child to believe in it for it to work?

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Neurofeedback for ADHD

An update of the meta-analytic evidence after ICAN

Edmund Sonuga-Barke on behalf of the European ADHD Guidelines Group

24

THE EUROPEAN ADHD GUIDELINES GROUP

KNOWLEDGABLE AND PASSIONATE ABOUT ADHD TREATMENT

Simonoff (UK; Chair); Banaschewski (Germany); Brandeis (Switzerland/Germany); Buitelaar (Netherlands); Coghill (UK); Cortese (UK); Danckaerts (Belgium); Daley (UK); Dittman (Germany); Doepfner (Germany); Ferrin (UK/Spain); Hollis (UK); Konofal (France); Lecendreux (France); Rothenberger (Germany); Santosh (UK); Sonuga-Barke (UK/Belgium); Stevenson (UK); Steinhausen (Switzerland/Denmark); Stringaris (USA); Van der Oord (Belgium); Wong (Hong Kong/UK); Zuddas (Italy); Santosh (UK); Holtman (Germany); Taylor (UK).

25

INCLUSION CRITERIA

- RCT (including non-blinded and cross over trials)
- ADHD diagnosis (or meeting validated cut-off)
- ADHD outcome
- Suitable control (placebo/attention-active/wait list/TAU)

ADHD OUTCOMES

- The primary outcome was ADHD symptom change.
- Blinding addressed by comparing two outcomes.
  - *MPROX –ADHD assessment most proximal to the intervention setting* (Typically parent ratings).
  - *P-BLIND – ADHD outcomes where the rater was likely to be unaware of treatment allocation.*
    - Where there was more than one option the best blinded was chosen.

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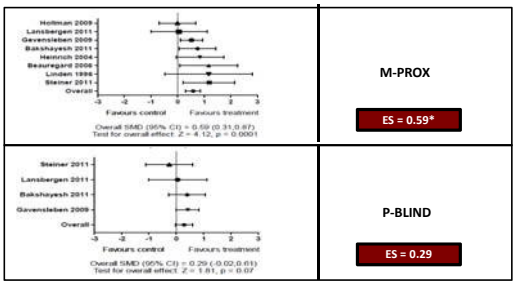
2013



M-PROX

ES = 0.59*

P-BLIND

ES = 0.29

Sonuga-Barke et al., 2013, AJP

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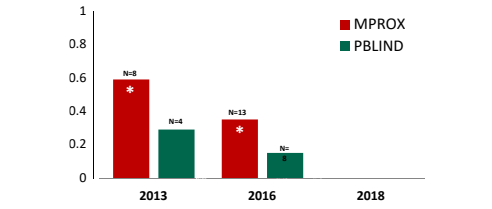
2013-2016 2018



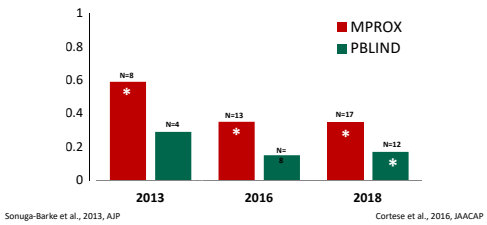
Sonuga-Barke et al., 2013, AJP

Cortese et al., 2016, JAACAP

28

2013-2016-2018

4 new trials - In total 17 RCTs with 825 participants now meet the EAGG criteria

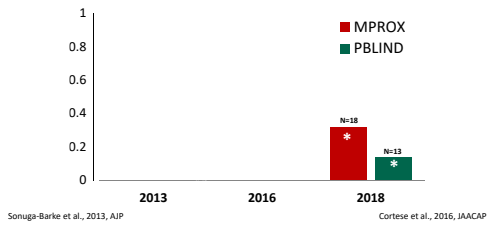


Sonuga-Barke et al., 2013, AJP

Cortese et al., 2016, JAACAP

29

2013-2016-2018(AFTER ICAN)



Sonuga-Barke et al., 2013, AJP

Cortese et al., 2016, JAACAP

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SENSTIVITY/MODERATOR ANALYSES

- This finding varied as a function of –
  - Neurofeedback type – SCP > FBT
  - Control arm type – passive (e.g. TAU) > active (e.g. sham)
- This finding did not vary as a function of –
  - Sub-dimension (inattention or hyperactivity/impulsivity).
  - evidence of neural learning.
  - Whether the training protocol was "standard".
  - Background pharma.

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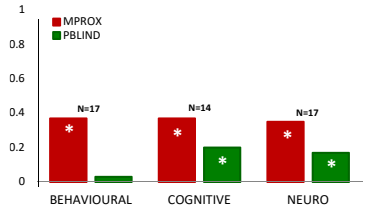
NF COMPARED TO OTHER NON-PHARMA



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SUMMARY

- Small but statistically significant effects of ADHD symptoms based on the best "blinded" evidence.
- NF similar efficacy to cognitive training.
- Clinical significance?
- Neuropsychological effects?
- Sleeper effects?

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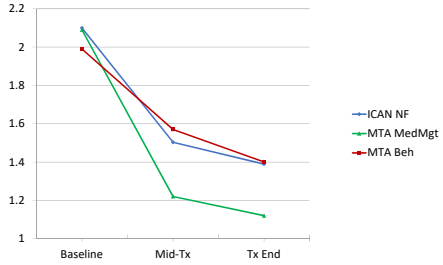
Comparison to MTA Treatments
Parent inattentive ratings



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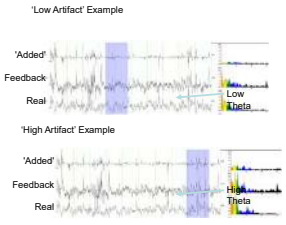
Sham integrity?



- Artifact was defined as: >Mean background Real EEG
- <Mean: Sham=Sham signal (=Feedback 'Low Artifact)
- >Mean: Amplify Sham signal (=Feedback; 'High Artifact')
- EEG signal: 1/f, Theta>>Beta (TBR>4.5)
- Unwanted effect: Theta burst triggers 'Artifact' more often then most other EEG activity

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All Adverse Events
Whether Attributable to Tx or Not

	Control	NF
BEHAVIORAL AE	45 (77.6%)	64 (75.3%)
GASTROINTESTINAL AE	35 (60.3%)	52 (61.2%)
RESPIRATORY AE	33 (56.9%)	51 (60%)
NEUROLOGICAL - CNS AE	29 (50%)	42 (49.4%)
GENERAL - CONSTITUTIONAL AE	27 (46.6%)	36 (42.4%)
EYES/EARS/NOSE/THROAT AE	17 (29.3%)	29 (34.1%)
SKIN AE	14 (24.1%)	26 (30.6%)
MUSCULOSKELETAL AE	8 (13.8%)	11 (12.9%)
RENAL/URINARY /REPRODUCTIVE	1 (1.7%)	0 (0%)
Total	209	311

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ICAN addressed Flaws in Previous NF ADHD Trials

Previous Flaws	ICAN Study
Small samples	N = 142
Lacking sham/placebo controls	Used a sham of equal duration, intensity, frequency, & likelihood of reinforcements; prerecorded EEG of active NF with the child's muscle & movement artifacts superimposed so it looked like their own
Lack of blinding	All participants, parents, teachers, trainers & investigators blinded
No RDoC EEG participant selection	RDoC = TBR $\geq$ 4.5 at FZ or CZ required for study entry

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Flaws in Previous NF ADHD Trials – 2

Previous Flaws	ICAN Study
Lack of testing of blind validity	Collected blinding information from children, parents, & trainers
Lacking identification, measurement, and control of concomitant treatments	Tracked & monitored medications, psychotherapy, and educational interventions; no psychosocial Tx allowed
Few post-treatment follow-ups	6-, 13-, and 25-month Follow-Ups

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Flaws in Previous NF ADHD Trials – 3

Previous Flaws	ICAN Study
Lacking monitoring and reporting of adverse effects (AEs)	Used pharma-like safety monitoring & adverse event tracking; monitored AEs weekly; weekly clinical panels
Large variability in NF treatment	Standardized training site (CZ or FZ); inhibit theta (4-8 Hz) and reward beta (13-21 Hz); 38 sessions; systematic session lengthening 25 to 45 min; 3X/wk; 13 wk.
No treatment fidelity monitoring	Careful fidelity monitoring by NF expert; reviewed session videos, & weekly calls with trainers; site visits

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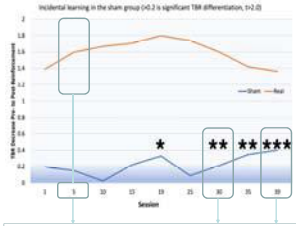
?? Re Sham Inertness



Correlation to Inattention change BL-40 (Sham: R^2=9-11%)

- Real Neurofeedback group: TBR low before reward (=contingency), higher after reward = TBR Differentiation
- Significant differentiation also for Sham group at session 20, 30, 35 & 40.
- Sham TBR differentiation correlates with overall improvement (BL to Session 40)
- Sham active?

40

ICAN Design Clinical Relevance

- Addressed many flaws of previous NF trials
- Used combined parent & teacher Conners-3 DSM-5 ADHD Inattention scale as primary outcome
- In children age 7-10 with categorically and dimensionally diagnosed ADHD
  - High proportion of high TBRs (78%)

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ICAN Design Summary

- Selected those most likely to respond to TBR NF training (RDoC)
- 142 children age 7-10 (ITT analysis)
- Diagnosed ADHD both categorically (ChIPS) & dimensionally (Conners-3)
- Randomly assigned to NF or double-blind sham of same duration, frequency, coaching, and rewards for up to 38 treatment sessions
- Blinding was successfully implemented across parents, children, and trainers

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2019 APSARD

A Gentle Introduction to FMRI Research

Jonathan Posner, MD
Columbia University

1

Disclosures

- NIH
- AACAP
- Shire Pharmaceutical
- Aevi Genomics

2

Outline

- MRI modalities
- What does functional MRI (fMRI) actually measure
- Task Design
- Resting fMRI & functional connectivity
- Potential pitfalls

3

Techniques in Magnetic Resonance Imaging

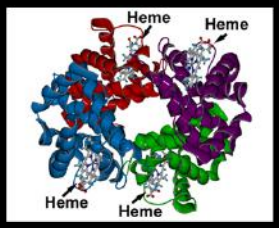
MRI Technique	Description
Magnetic Resonance Imaging	Uses strong magnetic field to align spins of hydrogen nuclei and then measures their rates of relaxation.
Anatomical MRI	Uses MRI to create images of features of brain structure.
Functional MRI	Follows changes of ratio of oxygenated and deoxygenated hemoglobin to determine blood flow and neural activity
Diffusion Tensor Imaging	Measures limitation of diffusion of water to map white matter fiber tracts.
MR Spectroscopy	Measures the concentration of metabolites.
Arterial Spin Labeling	Measures perfusion pulse-tagged hydrogen nuclei

4

What does fMRI measure?

5

Functional Magnetic Resonance Imaging (fMRI)

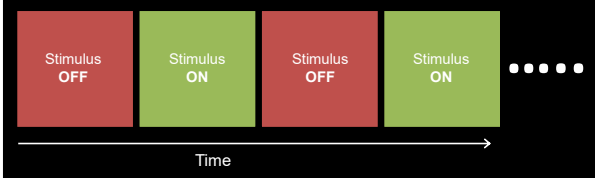


- **Changes in blood flow (proxy for neural activity)**
- **FMRI signal = Blood Oxygen Level Dependent (BOLD)**

Blood	Hemoglobin	Magnetism	
Oxygenated	Oxy	Diamagnetic	Magnetic properties suppressed
Deoxygenated	Deoxy	Paramagnetic	Magnetic Properties NOT suppressed

6

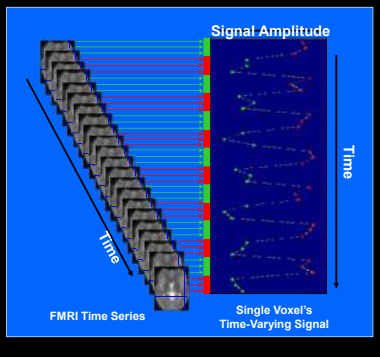
fMRI Task Design



Block Design
Subtraction Paradigm

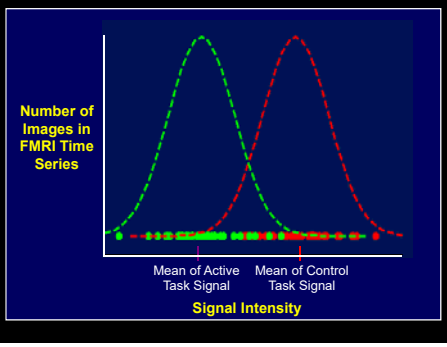
7

Functional MRI Signal



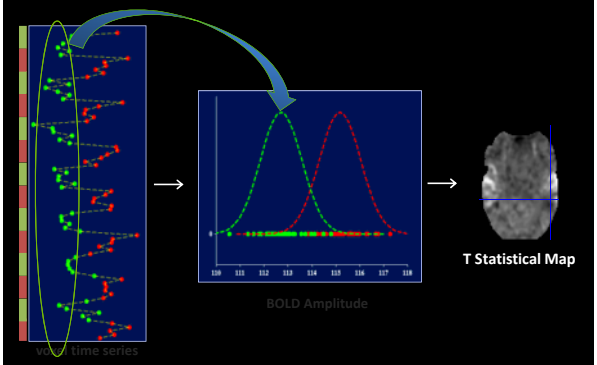
8

Functional MRI Statistical Testing



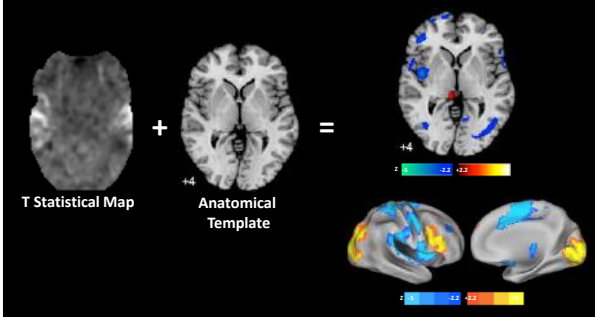
9

Statistical Analysis at One Voxel



10

Making Pretty Images



11

Task Design

12

Subtraction Logic

F. C. Donders

Two paired conditions should differ by the inclusion/exclusion of a single mental process

Example: Motion
Condition 1: View stationary rings
Condition 2: View moving rings

Condition 2 – Condition 1 = "motion"

Assumption: Linear model - Insertion of a mental process does not alter the previous process

13

Subtraction Logic

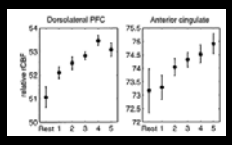
–

= ??

14

Parametric Design

- Parameters vary incrementally for a given task
- Parameters are correlated with signal intensity at each voxel
- Allows comparisons along multiple levels of a given task, rather than comparison with a single control task



Dagher, 1999

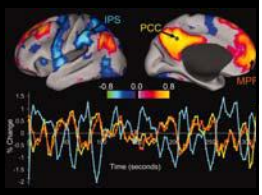
Tower of London task

15

Resting State fMRI

- No explicit task provided
- Subject thoughts freely wander (10-15 minutes)
- Correlations in low frequency (< 0.1 Hz) fluctuations in neural activity across disparate brain regions

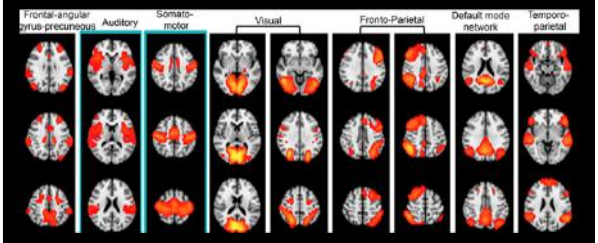
Connectivity Maps



(Fox, 2005)

16

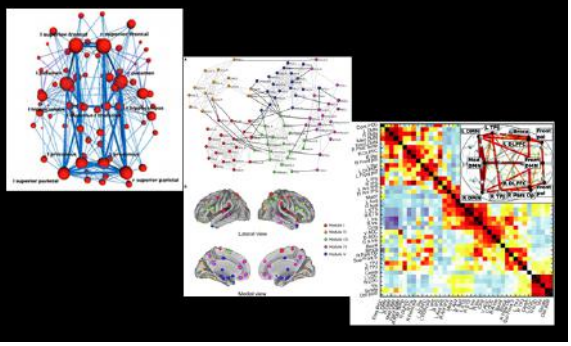
From Connectivity to Networks…



Brain regions that work together (networks) tend to fire together even at rest

17

From Networks to Graphs…



18

Statistical Issues: Potential pitfalls

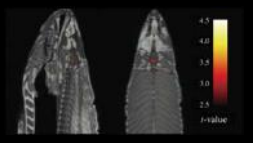
19

Multiple Comparisons

- Statistical Significance: $p < 0.05$
- Every voxel is a statistical test
  - 100,000 tests x 0.05 = 5,000 false positives

FMRI reveals…

Empathy in a dead salmon!

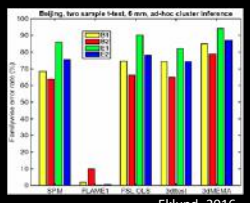


Bennett, 2009

20

Multiple Comparisons (cont)

- Bonferroni method
  - p = 0.05 / 100,000 tests = 0.0000005
  - Overly conservative?
- Cluster size correction
  - Overly lenient?
- Nonparametric



Eklund, 2016

21

Questions??

22

Geha Mental Health Center

Affiliated with the Sackler Faculty of Medicine, Tel Aviv University

* Impairment and symptoms in adult ADHD

Dr. Iris Manor

Geha Mental Health Center, Petah Tikva, Israel.
Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

1

Disclosure

Commercial interest	What was recieved	For what role
Alcobra Ltd.	$/P research support	$/P PI
Enzyotec Ltd	$/P research support	$/P PI
APSARD	Travel expenses	Board member
Janssen-Cilag	Honoraria	Consulting, Advisory board
Novartis Israel	Honoraria	Consulting
Teva Israel	Honoraria	Consulting, Advisory board
Medison Israel	Honoraria	Consulting
Eli-Lilly Israel	Honoraria	Advisory board

2

Symptoms and impairment

- ADHD is a chronic, life time, impairing disorder.
- Its' evaluation, and to a large extent its treatment, is based on symptoms.
- Several studies have already demonstrated that symptoms and impairment are not correlated enough (Gordon et al, 2006, Ben-Shitreet et al, in press)

Gordon M1, Antshel K, Faraone S, Barkley R, Lewandowski L, Hudziak JJ, Biederman J, Cunningham C. Symptoms versus impairment: the case for respecting DSM-IV's Criterion D.J Atten Disord. 2006 Feb;9(3):465-75.
Ben-Sheetrit J, Zurawel M, Weizman A, Manor I Symptoms Versus Impairment in Adults With ADHD: Intercorrelations of the BRIEF-A, CAARS, and TOVA

3

Symptoms and impairmant

- Persistence vs. remission: the percentage of symptomatic remission is significantly different than that of impairment remission (Biederman et al. 2000).
- Adults with ADHD tend to have fewer symptoms, but are even more cognitively impaired than children and adolescents (Ben Sheetrit et al, 2017)

#

Biederman J, Mick E, Faraone SV. 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.
Ben-Sheetrit J, Tasker H, Avnat L, Golubchik P, Weizman A, Manor I. Possible Age-Related Progression of Attentional Impairment in ADHD and Its Attenuation by Past Diagnosis and Treatment J Atten Disord. 2017 Dec

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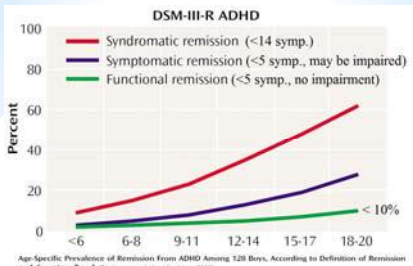


Age-Specific Prevalence of Remission From ADHD Among 128 Boys, According to Definition of Remission and Symptom Type*

5

* Symptoms vs. Impairment

- **Symptoms** are "simple" phenomena
  - representing point deficits (e.g. going off-task, impulsive reaction)
- **Impairments** are "complex" manifestations
  - representing failures of executive/cognitive functioning (e.g. sustained attention, working memory, etc.)

and

  - pathological compensations to symptoms (e.g. giving up certain activities, adapting obsessional organization to avoid careless mistakes)

- Symptoms are more easily detected in children.
- DSM criteria focus mainly on clinical symptoms.
- Impairments play a central role, especially in adult ADHD.

6

Response to Treatment difference

- The treatment of ADHD is heavily influenced by this discrepancy.
- Persistence and remission are no longer so clear cut
- Both “remitters” and “persisters” show weaker performance compared to controls, although the “remitters” tend to perform better than the “persisters” (Van Lisehout et al, 2013).
- The correlation between adults’ symptomatic response to treatment and their improvement in cognitive impairment is partial (Coghill et al, 2017).

van Lieshout M, Luman M, Buitelaar J, Rommelse NN, Oosterlaan J Does neurocognitive functioning predict future or persistence of ADHD? A systematic review. Clin Psychol Rev. 2013 Jun;33(4):539-60.
Coghill DR, Joseph A, Sikirica V, Kosinski M, Bliss C, Huss. Correlations Between Clinical Trial Outcomes Based on Symptoms, Functional Impairments, and Quality of Life in Children and Adolescents With ADHD. J Atten Disord. 2017 Aug [Epub ahead of print]

7

Response to Treatment difference

- Weiss et al (2018) studied the relationship between symptom- and functional improvement and remission in ADHD children and adolescents (C&A) treated by Methylphenidate after dose optimization
- They found that C&A treated with Methylphenidate showed moderate-to-large improvement in functioning,
- Yet, symptomatic improvement, as well as symptomatic remission, were significantly higher than the functional ones
#

Weiss M, Childress A, Mattingly G, Nordbrock E, Kupper RJ, Adjei AL.
Relationship Between Symptomatic and Functional Improvement and Remission in a Treatment Response to Stimulant Trial. J Child Adolesc Psychopharmacol. 2018 Oct;28(8):521-529.

8

Even the Placebo Response

- Measured by the “golden standard” rating scales, adults with ADHD tend to have a significant and unstable placebo response (Ben Sheetrit et al, 2018).
- Measured by objective measures, like the TOVA, the placebo response tends to exhibit an unstable and mild-to-moderate improvement pattern, is variable among the TOVA parameters and is only partially correlated with the CAARS placebo response (unpublished data)

Ben-Sheetrit J, Peskin M, Newcorn J, Rotem A, Daniely Y, Shbiro L, Weizman A, Manor I. Characterizing the Placebo Response in Adults with ADHD J Atten Disord . 2018 Jun. [Epub ahead of print]

9

The proneness of the different TOVA parameters to exhibit a PR

Response criterion \ Index	n=182 1 SD	2 SD
ACS N (%)	74 (40.7)	53 (29.1)
O-SS N (%)	35 (19.2)	21 (11.5)
C-SS N (%)	52 (28.6)	19 (10.4)
RTV-SS N (%)	43 (23.6)	19 (10.4)
RT – SS N (%)	30 (16.5)	7 (3.8)
D prime – SS N (%)	50 (27.5)	23 (12.6)

TOVA – Test of Variables Attention; ACS – Attention Comparison Score; O-SS – Omission Errors Standard Score; C-SS – Commission Errors Standard Score; RTV SS – Response Time Variability Standard Score; RT-SS – Response Time Standard Score.

10

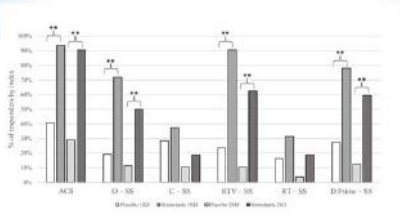
Number of CAARS responders (25% Improvement) and TOVA responders (by 1 SD, 2SD (n=182)
Note. [a] Mean with (standard deviation in parentheses);

	CAARS responders (25% Improvement)		CAARS non-responders (25% Improvement)				
Response criterion	n	%	n	%	Total	p	Phi (φ)
ACS							
1 SD	47	63.5%	27	36.5%	74	.008*	.197
2 SD	33	62.3%	20	37.7%	53	.066	.136
O-SS							
1 SD	26	74.3%	9	25.7%	35	.003*	.225
2 SD	16	76.2%	5	23.8%	21	.017*	.180
C-SS							
1 SD	28	53.8%	24	46.2%	52	.607	.039
2 SD	13	68.4%	6	31.6%	19	.105	.123
RTV-SS							
1 SD	27	62.8%	16	37.2%	43	.094	.126
2 SD	14	73.7%	5	26.3%	19	.042*	.153
RT – SS							
1 SD	16	53.3%	14	46.7%	30	.816	.017
2 SD	5	71.4%	2	28.6%	7	.279	.081
D prime - SS							
1 SD	31	62.0%	19	38.0%	50	.085	.128
2 SD	17	73.9%	6	26.1%	23	.022*	.170

Note. [a] Mean with (standard deviation in parentheses); ANOVA-RM - One-way Analysis of Variance with Repeated Measures; ACS Norm > 0; Omission, Commission, RT and RT variability norms >85; ACS - Attention Comparison Score, O-SS - Omission Errors Standard Score, C-SS - Commission Errors Standard Score, RTV SS - Response Time Variability Standard Score, RT-SS - Response Time Standard Score.

11

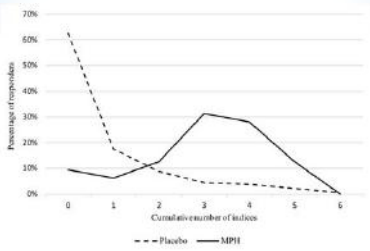
Comparison of Placebo Response and MPH response according to the TOVA parameters (1SD\2SD)



**p <.000;
ACS - Attention Comparison Score, O-SS - Omission Errors Standard Score, C-SS - Commission Errors Standard Score, RTV SS - Response Time Variability Standard Score, RT-SS - Response Time Standard Score.

12

Comparison of PR and MPH response according to the TOVA number of parameters they responded to (2SD)



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In summary

- Symptoms and cognitive impairment are two separate aspects of ADHD
- There is only a partial correlation between these aspects according to the clinical picture, the quality of life, the assessment and the response to treatment
- Hence, the issue of impairment vs. symptoms has meaningful implications on the clinical picture as well as the treatment plan
- As such, it deserves to be further studied#

14

* Thank You

15

ADHD in Older Adults

Symptoms, Impairment & Practice Considerations

Craig B.H. Surman, MD
Scientific Coordinator
Adult ADHD Clinical and Research Program
Massachusetts General Hospital

Associate Professor of Psychiatry
Harvard Medical School

1

Considering Symptoms:

Rate of screen positive for ADHD is an indicator:

- LASA Study identified ADHD using a screener in 65 yo+, followed by a structured interview. Sensitivity 0.80; specificity 0.77; test–retest validity 0.56
- Australian Personality and Total Health (PATH) Through Life Study used a screener; found that fewer older adults (68+) were identified than younger adults (48-52 yo)

Overall we can est. rate of 3% over 60 yo

LASA: Longitudinal Aging Study Amsterdam a. Michielsen M, et al. *Am J Geriatr Psychiatry*. 2014;22:1623–1632. b. Semeijn EJ, et al. *J Am Geriatr Soc*. 2013;61:882–887.
PATH: Das D, et al, PLoS One; 2014;9:e86552.
Goodman, Rhodewalt, Mitchell & Surman, 2016

2

Practical Questions:

? Will older adults notice unique patterns of symptoms or impairment vs. younger adults?

? What measures are most practical or meaningful to identify or track symptom?

3

Considering Functional Impact: we have 3 Studies on Effect of ADHD on Function: US Study

- Functional impairment: telephone interviews
  24 adults (age 60-77) with self-reported ADHD diagnosis; mean age at diagnosis 57
  - Comorbid psychiatric condition: 63%
  - Financial impact: 63%
  - Social impact: 71%

Brod M, et al. *Qual Life Res*. 2012;21:795–799.

4

Israeli Study

- Chart review of 11 older adults with diagnosis of DSM-IV-TR ADHD
- Impaired functioning
  - Mild 27%
  - Moderate 45%
  - Severe 27%

Manor I, et al. Clin Neuropharmacol. 2011;34(4):148–54.

5

Longitudinal Aging Study Amsterdam (LASA)

- Subset of >200 individuals from the LASA Study screened [a]
  - Note: For this subset, less strict interview criteria; uncertain whether symptoms could be ascribed to another condition
- In individuals age 60–94 years, ADHD diagnosis correlated with **being divorced or never married**[a]; **emotional or social loneliness**[a]; **neuroticism and social inadequacy**[b]
- ADHD was negatively correlated with self-reports of traits of **mastery, self-esteem, and self-efficacy**,[a] and **self-perceived health**[b]
- Number of ADHD symptoms was positively correlated with chronic, nonspecific lung diseases, cardiovascular diseases, and the number of chronic diseases[b]

a. Michielsen M, et al. *Am J Geriatr Psychiatry*. 2014;22:1623–1632. b. Semeijn EJ, et al. *J Am Geriatr Soc*. 2013;61:882–887.

6

Practical Questions:

? How do you apply DSM diagnostic criteria of 2 or more settings/roles in older adults?

? Should there be a higher, or lower threshold for treating some kinds of impairment than others?

? Does "retirement" reduce role impairment? Different obligations, more time to manage inefficiency or being less pro-active compensate?

? I often have people who "feel better" on the medication, should Psychological well-being be one of the domains we consider?

7

7

Some Contextual Factors Impacting Elders

Environment may exacerbate or be compensatory …

- Level of independent function
- Caregiving responsibilities
- New learning curves (internet/tech)
- Changes in peer group contact
- Financial independence

Goodman DW, et al. *Drugs Aging*. 2016;33:27–36.

8

Comorbid Disorders Are Common

- In small studies of older adults diagnosed with ADHD, comorbid disorders were common
  - **All of 9** women (ages 62-91 years) diagnosed with 'ADHD' in Texas had Axis 1: 9 with depression; 2, bipolar; 7, anxiety disorders[a]
  - **6 out of 11** adults with ADHD reported Axis I or II comorbidity in an Israeli chart review [b]
  - LASA subset (adults 60-94 years): **association of ADHD with anxiety and depression was stable over 6 years**[c]
- Survey of 149 adults over age 50 found:
  - Depression: 40%, Bipolar disorder: 24%, Anxiety: 20%[d]

a) Henry E, Jones SH. J Women Aging. 2011 23(3):246–262 ; b) Manor I,. Clin Neuropharmacol. 2011 Jul-Aug;34(4):148-54 c) Michielsen M, et al. *Am J Geriatr Psychiatry*. 2014;22:1623–1632 & Semeijn EJ, et al. *J Am Geriatr Soc*. 2013;61:882–887 d) Lensing MB et al. J Att Dis 2015;19(5):380-9.

9

Associations between adult ADHD and comorbidities in 4,864 adults aged 50 to 64 in Swedish National Registries on December 31, 2013

Comorbidity	With adult ADHD (N = 4,864)			Without adult ADHD (N = 1,661,074)			PR	95% CI
	N	Prevalence, %	95% CI, %	N	Prevalence, %	95% CI, %		
SUD	1672	35.95	34.61–37.30	50,006	3.01	2.98–3.04	11.95	11.49–12.40
Depression	1757	38.79	37.43–40.16	53,503	3.23	3.20–3.25	12.03	11.59–12.46
Bipolar Disorder	712	15.43	14.39–16.46	10,802	0.65	0.64–0.66	23.72	22.06–25.38
Anxiety	1741	38.12	36.74–39.49	49,909	3.00	2.98–3.03	12.69	12.22–13.16
T2DM	253	6.10	5.38–6.82	58,958	3.55	3.52–3.58	1.72	1.52–1.92
Hypertension	674	16.65	15.54–17.76	170,191	10.24	10.19–10.29	1.63	1.52–1.73

* Clinical diagnoses of adult ADHD and comorbid conditions were assessed between age 50 and 64. Estimates of prevalence and PR were adjusted for sex and age in years.

SUD: substance use disorder; T2DM: Type 2 diabetes mellitus; PR: prevalence ratio; CI: confidence interval

https://doi.org/10.1371/journal.pone.0204516.t004

Chen Q, Hartman CA, Haavik J, Harro J, Klungsøyr K, et al. (2018) Common psychiatric and metabolic comorbidity of adult attention-deficit/hyperactivity disorder: A population-based cross-sectional study. PLOS ONE 13(9): e0204516. https://doi.org/10.1371/journal.pone.0204516 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0204516

PLOS ONE

10

Differential Diagnosis may be broader in Older Adults:

- Effects of medications
- Sleep changes
- Mild cognitive impairment
- Dementia
- Parkinson's disease or other parkinson-plus syndromes
- Toxic/metabolic/infectious/inflammatory
- Infections
- Other encephalopathy

Goodman DW, et al. *Drugs Aging*. 2016;33:27–36.

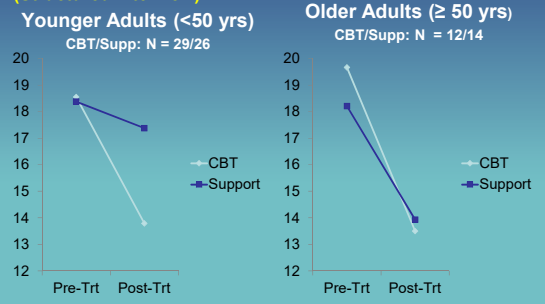
11

"What effect does treatment have?"

- Most trials exclude older adults
- Limited case study and survey data published on older adults
- Also, limited evaluation of cognitive effects of ADHD medications in older adults

12

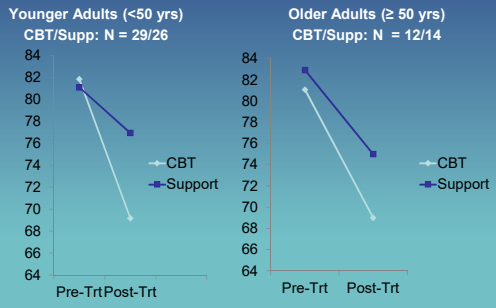
CBT vs Support group
AISRS-Inattentive Symptoms
(Structured Interview)



Solanto, Surman et al,

13

BRIEF-A Metacognitive Index



Solanto, Surman et al, submitted

14

Practical Questions Treatment:

- ? In absence of data, should we have a higher impairment threshold for medication treatment?
- ? What predicts medication benefit?
- ? What office practices will help you assess/treat ADHD in older adults?
- Are there unique forms of community support for older individuals?

15

Take Away Points

- The burden of ADHD may vary with context, including that of older age.
- There may be different contexts to consider in the life of the older adult
- We will benefit from research that describes the natural course of ADHD and how to best identify and support ADHD in older adults

16

16

Some ADHD Resources

For consumers

CADDAC.ca

CHADD.org

ADD.org

For professionals:

APSARD.com

CADDRA.ca

Contact: csurman@partners.org
www.drsurman.com

17

PSYCHOSOCIAL TREATMENT FOR ADULT ADHD:

EMERGING ADULTS AND BEYOND

20 JANUARY, 2019

APSARD, WASHINGTON, D.C.

J. Russell Ramsay, Ph.D.

Adult ADHD Treatment & Research Program
University of Pennsylvania Perelman School of Medicine

1

Continuing Education Financial Disclosure Requirement

I, (Dr. J. Russell Ramsay), have the following commercial relationship(s) to disclose from the past 12 months:

Speaker honoraria (PENN Student Disabilities Conference)

American Psychological Association Psychotherapy Video Series (honoraria)

Paid CE presentations/webinars/royalties (TZK Seminars, J&K Seminars)

Book royalties (Routledge/Taylor&Francis, American Psychological Association)

2

OBJECTIVE

How do we adapt psychosocial treatments to adults with ADHD of all ages in order to facilitate implementation of recommendations, skills, strategies, and other behaviors that will improve functioning?

3

CBT MODEL FOR ADULT ADHD

"How is the CBT model adapted to adult ADHD?"

4

CBT FOR ADULT ADHD: ADAPTED MODEL FOR ADULT ADHD *CONCEPTUALIZATION*

1. Individuals experience symptoms falling along a continuum of severity and impact, in some form, starting in childhood or adolescence.
2. ADHD makes a direct and causal contribution to functional difficulties, ranging from interference to impairment, with variation within and across domains and settings, as well as secondary skills deficits and co-existing emotional or learning issues.
3. ADHD symptoms influence experience and performance in various life roles and endeavors, with effects on sense of self, identity, and efficacy.
4. There is an ongoing, reciprocal interaction between an individual and their contexts and relationships that can magnify and/or attenuate difficulties, coping strengths, and sense of belongingness and social capital.
5. The experience of ADHD, both cumulatively and in discrete instances, has effects on information processing in the form of thoughts and beliefs, as well as concurrent emotional and behavioral experiences that affect how one acts in and reacts to various contexts and roles and relationships.

Ramsay (2020?). *Thinking through adult ADHD: How thoughts turn intentions into action (or not)*. DC: APA

5

ADHD AND EMERGING ADULTHOOD

- Childhood ADHD predicted higher depression ratings at 18 yo and at every age year during emerging adulthood (18-25yo) compared with controls[1]
  - ADHD did not predict rate of change of depressive symptoms
  - Childhood hx of ADHD remained a predictor of depressive symptoms at 18 yo after controlling for comorbidities but not for concurrent ADHD sxs and impairments
- EF deficits significantly related to inattention, hyperactivity-impulsivity, and anxiety (in that order) in structural equation modeling[2]
  - ADHD+Anxiety showed greater deficits in emotional regulation and organization/problem-solving compared with ADHD-only or Anxiety-only.
  - ADHD-only and ADHD+Anxiety showed greater deficits with self-motivation and self-restraint than Anxiety-only
  - All clinical groups differed from controls on EF deficits

[1]Meinzer et al. (2016). *J Abnorm Child Psycholo, 44*, 787-797.
[2]Jarrett (2016). *Psychological Assessment, 28*, 245-250.

6

ADHD AND EMERGING ADULTHOOD (2)

- Empirically-derived symptoms of ADHD in Emerging Adulthood[1]

- **Cognitive Inflexibility**
  - Trouble organizing my thoughts or thinking clearly
  - When shown something complicated to do, cannot keep information in mind to do it
  - Not very flexible in my behavior or approach to a situation
  - Unable to come up with or invent as many solutions to problems as others
  - Have trouble putting my thoughts down in writing as well or as quickly as others
  - I am not able to think of as many ways to accomplish goals or assignments as others
  - Have difficulty explaining things in their proper order or sequence
  - Unable to "think on my feet" or respond effectively to unexpected events

[1]Fedele et al. (2010). *J Psychopathol Behave Assess, 32*, 385-396.

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ADHD AND EMERGING ADULTHOOD (3)

- Empirically-derived symptoms of ADHD in Emerging Adulthood[1] (cont.)

- **Disinhibition**
  - Make decisions impulsively
  - Unable to inhibit my reactions or responses to events or others
  - Make impulsive comments to others
  - Likely to do things without considering the consequences
  - Change my plans at the last minute on a whim or last minute impulse
  - Quick to get angry or become upset
  - Over react emotionally
  - Get silly, clown around, or act foolishly when I should be serious
  - Accident prone

[1]Fedele et al. (2010). *J Psychopathol Behave Assess, 32*, 385-396.

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ADHD AND EMERGING ADULTHOOD (4)

- Clinically-relevant domains/issues[1]
  - Education/college
  - Occupation
  - Concurrent problems (psychiatric, substance use)
  - Health (sexual behaviors/health, sleep)
  - Legal

- Clinical challenges[1]
  - Engaging in treatment
  - Instability in support
  - Impulsivity, risky behaviors (risk-seeking due to poor decision-making[2])
  - Accurate assessment
  - Addressing comorbidities
  - Adequate treatment

[1]Knouse & Fleming (2016). *Cognitive & Behavioral Practice, 23*, 300-315.
[2]Dekkers et al. *J of Attention Disorders*. Advance Online.

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ADHD AND EMERGING ADULTHOOD (5)

- *Negative self-concept and depression* fully mediated the association between past academic functioning (previous GPA) and self-report of overall functioning at follow-up in a sample of college students with ADHD tracked for an academic year. Negative self-concept was seen as an important precursor to depression, which itself first stemmed from the experience of living with ADHD.[1]

- Not necessarily GPA but its effects on depression and self-concept that predicts functioning

- *Internalizing symptoms and self-concept* may be important targets for treatment

[1]Eddy et al. (2018). *J of Attention Disorders, 22*, 323-333.

10

WHAT ARE WE TARGETING?

BROAD-BAND TREATMENT

- Do not focus on a set of specific sxs, behaviors, or impairments
- Seek overall reductions in ADHD sxs and thereby improve functioning
  - Medications
  - Traditional Chinese Medicine
  - Omega 3 supplementation
  - Diet

NARROW-BAND TREATMENT

- Focus on a subset of sxs, behaviors, or impairments
- Aim to improve skills, adaptive behaviors and/or decrease maladaptive behaviors
  - Psychosocial treatments/CBT
  - Coaching
  - Social skills training
  - School based interventions

Faraone & Antshel (2014). *Child Adolesc Psychiatric Clin N Am 23*, 965-972.

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LIFE OUTCOMES: ADULT ADHD

- Workplace problems
- Relationship problems
- Lower educational attainment
- Employment problems
- **Lower self-esteem**
- Lower social functioning
- Lower satisfaction in life domains
- **Physical health issues**
- Legal issues
- Lower SES
- Psychiatric comorbidity (anxiety, depression, substance use)
- Substance use disorders
- Risk for suicide (ADHD + SUD + psychiatric comorbidity)
- **Disengagement**

Barbaresi et al. (2013). *Pediatrics, 131*, 637-644.
Barkley & Fischer (2018). *J of Attention Disorders*, advance online.
Barkley et al. (2008). *ADHD in adults: What the science says*. New York: Guilford.
Biederman et al. (2006). *Journal of Clinical Psychiatry, 67*, 524-540.
Biederman et al. (2012). *Journal of Clinical Psychiatry, 73*, 941-950.
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Harpin et al. (2013). *Journal of Attention Disorders*, online ahead of print.
Nigg (2013). *Clinical Psychology Review, 33*, 215-228.
Klein et al. (2012). *Archives of General Psychiatry, 69*, 1295-1303.
Weiss & Hechtman (1993). *Hyperactive children grown up* (2nd ed.). New York: Guilford.

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CBT FOR ADULT ADHD: PREMISES FOR THE ADAPTED MODEL

- CBT – Implementation Focus (or CBT Extended Release [CBT-XR])
- Main cognitive issue/theme = **impaired self-regulatory efficacy** [**Self-Distrust** cognitions; **Self-Mistrust** schema]
- Main behavioral issue = **engagement**, scripting, challenging avoidance/escape
- Main emotional issue = tolerating **discomfort**, emotional flexibility
- Main implementation issue = transform **plan into action**, switching modes
- Main interpersonal issue = managing **social capital**, self-advocacy/compassion

Ramsay (2020?). *Thinking through adult ADHD: How thoughts turn intentions into action (or not)*. DC: APA

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ADULT ADHD: COGNITIVE THEME

- **Personal agency**: The ability to effect change through one's action
- **Self-efficacy**: Belief in one's ability to exercise control over the events in one's life (in order to pursue goals)
- ***Self-regulatory efficacy***: Belief in one's ability to organize and carry out actions necessary to effect change in one's life (and not from lack of skill)
- Gain education → Enroll in class → Attend and complete work

Bandura (1997). *Self-efficacy: The exercise of control*. NY: Freeman

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ADULT ADHD: COGNITIVE THEME (2)

- **Self-regulatory efficacy**:
- "… to plan and structure activities, to enlist needed resources; to regulate one's motivation through proximal challenges and self-incentives; and to manage the emotionally and cognitively disruptive effects of obstacles, setbacks and stressors." (p. 53)
- "In many spheres of functioning, people know full well how to perform the needed behavior. Here, **the relevant efficacy beliefs concern self-regulatory capabilities** – can people get themselves to stick with the behavior given the many dissuading conditions they will encounter? ... (T)hose who **distrust** their capacities to surmount unpleasant factors have little reason to put themselves through misery. In familiar activities that must be performed regularly to achieve desired results, it is perceived **self-regulatory efficacy,** rather than perceived efficacy for the activity per se, that is most relevant." (p. 64)

Bandura (1997). *Self-efficacy: The exercise of control*. NY: Freeman

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"BOOSTING" PSYCHOSOCIAL EFFECTS

- Between sessions phone/coaching contacts[1]
  - Fostering and externalizing implementation between sessions
  - Point of performance engagement
- Coordinated individual and group treatment for college students[2,3]
  - Balance personalization and sense of community
  - Unique educational/social context for young adults with ADHD
- Internet-based CBT (iCBT, either self-help or self-help + group) for adult ADHD[4]
  - Ready access to coping tools
  - Coping resource/library
  - Providing "smart content" vs. self-monitoring

[1]Cherkasova et al. (2016). *J of Atten Disord*. Online. doi: 10.1177/1087054716671197
[2]Anastopoulos & King (2015). Cognitive & Behavioral Practice, *22*, 141-151.
[3]Anastopoulos et al. (2018). *J of Atten Disord*. online. doi: 10.1177/1087054717749932
[4]Pettersson et al. (2017). *J of Atten Disord, 21*, 508-521. doi: 10.1177/1087054714539998

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CONCLUSION

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ADHD and Tics: Boundaries, Overlap and Disentanglement
January 20, 2019

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Disclosures (Past 12 Months)

- Abide Therapeutics: Scientific Advisory Board
- American Academy of Child and Adolescent Psychiatry: Honoraria
- Bracket: Honoraria
- Cincinnati Children's Hospital: Honorarium
- Harvard Medical School /Psychiatry Academy: Honoraria
- Neurocrine Biosciences: Research Support
- Nevada Psychiatric Association: Honorarium
- NIMH: Research Support
- Partners Healthcare: Honoraria
- Teva/Nuvelution: Research Support; Scientific Advisory Board
- Tourette Association of America: Co-Chair, Medical Advisory Board; TAA-CDC Partnership

- ***Off label indications will be discussed***

THE NEW YORKER

"Young man, go to your room and stay there until your cerebral cortex matures."

WEDNESDAY JUNE 18

ADHD and Tics: Boundaries, Overlap and Disentanglement
Learning Objectives

- At the end of this session, the participant should be able to:
- 1) Describe what is known about **boundaries and overlapping neurobiology, phenomenology and course** of ADHD and tic disorders, including Tourette's Disorder (TD)
- 2) Discuss importance of disentangling ADHD and tic symptoms, as this may help elucidate **similarities and differences** and guide treatment
- 3) Interpret relevance of these findings **for application to treatment of patients** with ADHD and tic disorders

THE NEW YORKER

"I need you to line up by attention span."

THURSDAY MAY 15

Neurodevelopmental Disorders: Epidemiology
Bi-Directional Overlap of ADHD and Tic Disorders

- Rates of **tic disorders are higher (10-30%) in children** with **Attention Deficit Hyperactivity Disorder** (ADHD) than in children without ADHD (1-10%). *(Spencer T., Biederman, J. Coffey, B. et al., Arch Gen Psych; 1999, 56: 842-84)*
- **ADHD is the most highly prevalent** (50-75%) **comorbid disorder** in children with Tourette's Disorder (TD), in both community and clinical samples. (*Coffey, B. Biederman, J. 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)*
- Lifetime prevalence **of any psychiatric comorbidity among individuals with TS: 85.7%**. **72.1% met criteria for OCD or ADHD.** *(Hirschtritt, ME et al. (2015). JAMA Psychiatry. 2015;72(4):325-333)*

Table 1. Lifetime Prevalence of Psychiatric Disorders by Sex

Comorbid Disorder	No./Total No. With Available Data (%)			
	All TS-Affected Participants	Sex		*P* Value[a]
		Male	Female	
Obsessive-compulsive spectrum[b]	904/1368 (66.1)	645/1001 (64.4)	259/367 (70.6)	.03
Attention-deficit/hyperactivity	713/1314 (54.3)	564/962 (58.6)	149/352 (42.3)	<.001
Mood[c]	277/930 (29.8)	184/690 (26.7)	93/240 (38.8)	<.001
Anxiety[d]	343/949 (36.1)	225/703 (32.0)	118/246 (48.0)	<.001
Disruptive behavior[e]	185/622 (29.7)	157/493 (31.8)	28/129 (21.7)	.03
Eating[f]	19/937 (2.0)	2/693 (0.3)	17/244 (7.0)	<.001
Psychotic[g]	7/931 (0.8)	5/689 (0.7)	2/242 (0.8)	.88
Substance use[h]	59/948 (6.2)	42/701 (6.0)	17/247 (6.9)	.62
Elimination[i]	108/668 (16.2)	90/531 (17.0)	18/137 (13.1)	.28

Abbreviation: TS, Tourette syndrome.

[a] The χ^2 or Fisher exact test was used to compare rates of each disorder in males vs females.

[b] Obsessive-compulsive disorder and subclinical obsessive-compulsive disorder.

[c] Major depressive disorder, dysthymia, and bipolar disorder I and II.

[d] Generalized anxiety disorder, panic disorder, agoraphobia without panic, posttraumatic stress disorder, separation anxiety disorder, social phobia, and specific phobia.

[e] Oppositional defiant and conduct disorders.

[f] Anorexia and bulimia nervosa.

[g] Schizophrenia and psychotic disorder, not otherwise specified.

[h] Alcohol and other substance use or dependence, excluding tobacco use.

[i] Enuresis and encopresis.

Hirschtritt, E. et al. Lifetime Prevalence, Age of Risk, and Genetic Relationships of Comorbid Psychiatric Disorders in Tourette Syndrome (2015). JAMA Psychiatry. 2015;72(4):325-333. doi:10.1001/jamapsychiatry.2014.2650

Gilles de la Tourette Syndrome Robertson et al. (2017)

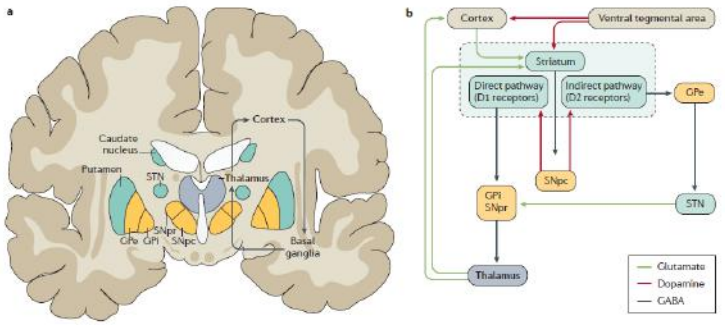
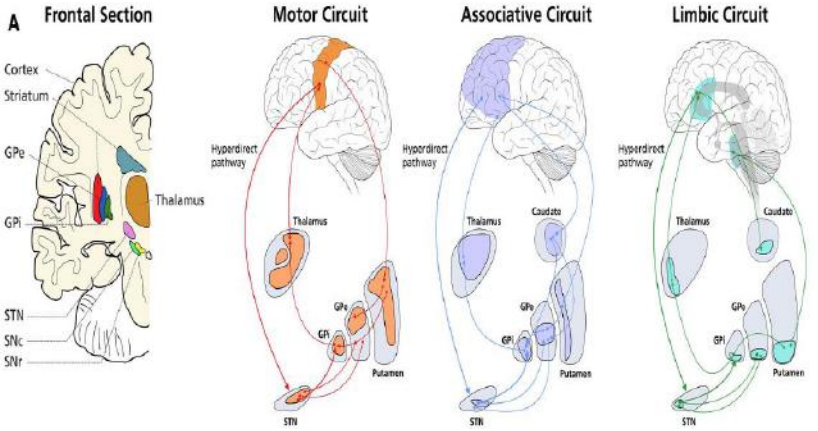


Figure 4 | **CSTC circuit.**



Rowshanak, Hashemiyoon et al. Putting the Pieces Together in Gilles de la Tourette Syndrome: Exploring the Link Between Clinical Observations and the Biological Basis of Dysfunction. 2017. Brain Topography; 30:3-29

ADHD and TD/Tic Disorders: Neurocircuitry

(Leckman, J. et al; JCAP, 2010; 20 (4); 237-247; Robertson, M. Nature Reviews; 2017 (3); 1-20; Malhany, N. et al Eur J Pediatr 2015; 174; 279-288)

- **Inhibition**: core deficit in both disorders; thought to result from fronto-striatal and frontal-parietal network dysfunction in **Cortical-Striatal-Thalamic-Cortical (CSTC)** tracts**.**
- **ADHD:** Imaging studies: Reductions in total cerebral volume, PFC, BG, dACC, CC, and cerebellum reported in ADHD patients are consistent with **fronto-striatal models**. Some studies also showed reduction in right cerebral volume, and right caudate nucleus in ADHD.
- **TD:** Mixed results; reduced caudate nucleus volume frequently reported.
- Individuals with TD+ADHD have smaller caudate nuclei.
- **TD+ADHD:** hyper-functioning/overactive circuits in BG in TD result in motor/cognitive/emotional disinhibition, worsened by frontal hypo-activity in ADHD.
- **Both TD and ADHD** tend to improve with time, which may be a result of increased myelinization of prefrontal regions.

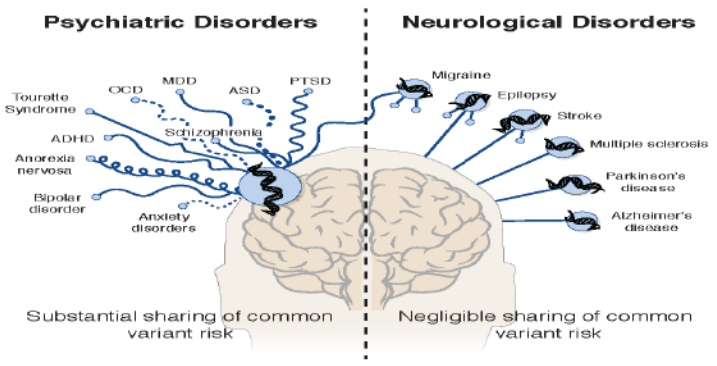
Table 3 Main brain regions implicated in the pathogenesis of TS and ADHD

Brain areas	TS	ADHD	Ref.
Prefrontal areas	+	+	[19, 29, 56]
Inferior frontal gyrus	+	+	[100]
Sensorimotor areas	+	+	[19, 29, 55]
Anterior cingulated cortex	+	+	[19, 29, 55]
Posterior cingulated cortex	+	+	[91]
Basal ganglia	+/−	+	[19, 29, 73]
Cerebellum	−	+	[29]

(+) implicated region, (−) not implicated region, (+/−) findings contradictory

El Malhany, N. at al. Tourette syndrome and comorbid ADHD: causes and consequences. 2015; Eur J Pediatr 174; 279-288

From a genetic standpoint, TS is a psychiatric disorder (C. Mathews, 2018, AACAP)



Gilles de la Tourette Syndrome. Nature Reviews; Robertson, M. et al. 2017; (3) 1-20

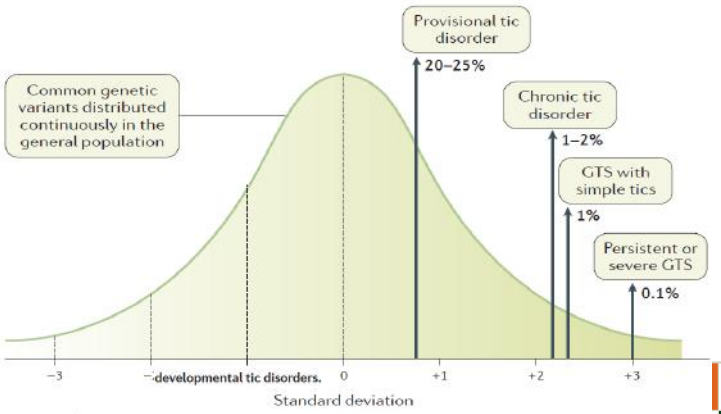


Figure 3 | Genetic architecture of Gilles de la Tourette syndrome and related

Table 2 Candidate genes implicated in the pathogenesis of TS and ADHD

Genes	Gene functions	TS	ADHD	Ref.
Dopamine receptors				
DRD1 (dopamine D1 receptor gene)	Encodes the D1 subtype of the dopamine receptor. D1 receptors regulate neuronal growth and development, mediate some behavioral responses, and modulate dopamine receptor D2-mediated events	−	−	[61, 67, 95]
DRD3 (dopamine D3 receptor gene)	Encodes the D3 subtype of the dopamine receptor. This receptor is localized to the limbic areas of the brain, which are associated with cognitive, emotional, and endocrine functions	−	−	[61, 67]
DRD4 (dopamine D4 receptor gene)	Encodes the D4 subtype of the dopamine receptor. Mutations in this gene have been associated with various behavioral phenotypes, including autonomic nervous system dysfunction, attention deficit/hyperactivity disorder, and the personality trait of novelty seeking	+/−	+	[61, 67, 25]
Dopamine-associated transporter				
SCL6A3/DAT1 (dopamine-associated transporter)	This gene encodes a dopamine transporter which is a member of the sodium- and chloride-dependent neurotransmitter transporter family. Variation in the number of repeats is associated with idiopathic epilepsy, attention deficit hyperactivity disorder, dependence on alcohol and cocaine, susceptibility to Parkinson disease, and protection against nicotine dependence	+/−	+	[61, 67, 104]
Catecholamine transporter				
COMT (catechol-*O*-methyltranferase)	Catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine. This *O*-methylation results in one of the major degradative pathways of the catecholamine transmitters	−	−	[61, 67, 95]
SLC6A2/NET (norepinephrine transporter)	Encodes a member of the sodium: neurotransmitter symporter family. This member is a multi-pass membrane protein, which is responsible for reuptake of norepinephrine into pre-synaptic nerve terminals and is a regulator of norepinephrine homeostasis	−	−	[61, 67, 95]
MAOA (monoamine oxidase A)	Is one of two neighboring gene family members that encode mitochondrial enzymes which catalyze the oxidative deamination of amines, such as dopamine, norepinephrine, and serotonin. This gene has also been associated with a variety of other psychiatric disorders, including antisocial behavior	+	−	[61, 67, 95]

(+) positive association, (−) negative association, (+/−) findings contradictory

El Malhany, N. at al. Tourette syndrome and comorbid ADHD: causes and consequences. 2015; Eur J Pediatr 174; 279-288

Table 1 Pre-perinatal risk factors implicated in the pathogenesis of TS and ADHD

Pre-perinatal risk factors	TS	ADHD	Ref.
Alcohol during pregnancy	+	+	[78]
Smoking during pregnancy	+	+	[9, 53]
Prematurity	+	+	[36]
Low birth weight	+	+	[41]

(+) implicated factor

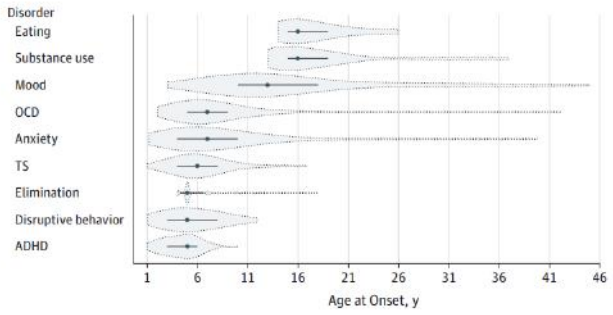
El Malhany, N. at al. Tourette syndrome and comorbid ADHD: causes and consequences. 2015; Eur J Pediatr 174; 279-288

Lifetime Prevalence, Age of Risk, and Genetic Relationships of Comorbid Psychiatric Disorders in Tourette Syndrome

(Hirschtritt, ME et al. (2015). JAMA Psychiatry; April 2015 Volume 72, Number 4)

- **DESIGN:** Structured diagnostic interviews with TS (n =1374) and TS-unaffected family members (n=1142).
- **RESULTS**: Lifetime prevalence **of any psychiatric comorbidity among individuals with TS was 85.7%**; 57.7% had 2 or more psychiatric disorders. 72.1% met criteria for OCD or ADHD. Other disorders: mood, anxiety, and disruptive behavior, each occurred in about 30%.
- **Age of greatest risk for onset of most comorbid psychiatric disorders was between 4 and 10 years.**
- TS was associated with increased risk of anxiety (odds ratio [OR], 1.4; P = .04) independent of comorbid OCD and ADHD; high rates of mood disorders (29.8%) may be accounted for by OCD (OR, 3.7; P < .001).
- **CONCLUSION**: Psychiatric comorbidities are common among individuals with TS, and most comorbidities begin early in life.

Figure 2. Ages at Onset for Comorbid Disorders Among Individuals With Tourette Syndrome (TS)



Hirschtritt, E. et al. Lifetime Prevalence, Age of Risk, and Genetic Relationships of Comorbid Psychiatric Disorders in Tourette Syndrome (2015). JAMA Psychiatry. 2015;72(4):325-333. doi:10.1001/jamapsychiatry.2014.2650

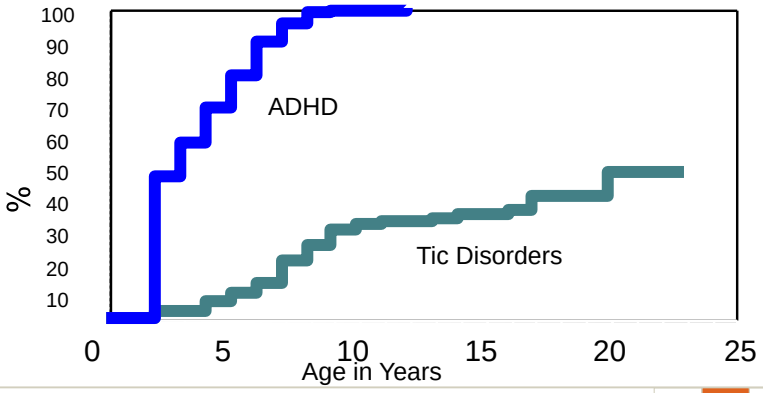
Course of ADHD and Tic Disorders: What Happens to Tics in the Context of ADHD Over Time?

(Spencer, T. Biederman, J. Coffey, B. 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; mean ages 9-13.
- **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

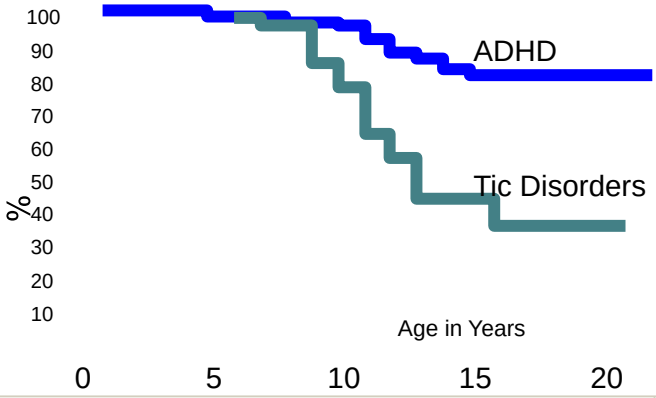
Onset of ADHD and Tic Disorders in ADHD Probands

(Spencer, T. Biederman, J. Coffey, B. et al. Arch Gen Psych 1999, 56: 842-847)



Offset of ADHD and Tic Disorders in ADHD Probands

(Spencer, T. Biederman, J. Coffey, B. et al. Arch Gen Psych 1999, 56: 842-847)



Chronic Tic Disorders (CTD) in Children with ADHD

(Poh, W., Payne, J. et al. Arch Dis Child; 2018; 0; 1-6)

Aim: To examine 1) prevalence of chronic tics in a community based cohort in children with ADHD compared to children with non-ADHD at ages 7 and 10, and 2) additional psychiatric and functional burden of CTD in children with ADHD.

Methods: N=179 children age 6-8 with ADHD and 212 healthy controls

Recruited through 43 schools using parent and teacher Conners followed by case confirmation with DISC-IV. Baseline and 36 month follow up evaluations: tic measures; CBCL; academic performance; quality of life.

Results: Compared with controls, **children with ADHD were 4 times more likely to have CTD at age 7 and 5.9 times more likely at age 10.**

Concurrent CTD symptoms contribute to higher rates of internalizing disorders, more peer problems and reduced quality of life in children with ADHD.

Conclusions: Clinicians should be aware of and manage both symptoms.

Table 1 Sample characteristics for ADHD+CTD and ADHD-only children

	ADHD+CTD (n=23)	ADHD-only (n=92)	P
ADHD			
Combined subtype, n (%)	7 (30.4)	31 (33.7)	0.79
Inattentive subtype, n (%)	7 (30.4)	30 (32.6)	0.60
Hyperactive/impulsive subtype, n (%)	5 (21.7)	3 (3.3)	0.005
Symptom severity, parent report, mean (SD)	13.7 (5.7)	12.1 (5.5)	0.23
Symptom severity, teacher report, mean (SD)	10 (6.1)	11.0 (6.5)	0.51
Medications			
Medication use (any), n (%)	5 (21.7)	27 (29.3)	0.43
ADHD medication, n (%)	4 (17.4)	16 (17.4)	0.98
ASD symptoms			
SCQ score >15, n (%)	4 (17.4)	7 (7.6)	0.48
Primary caregiver characteristics			
Single parent family, n (%)	4 (17.4)	18 (19.6)	0.49
Did not complete high school, n (%)	7 (30.4)	25 (27.2)	0.83
Completed high school, n (%)	7 (30.4)	26 (28.3)	0.92
Completed higher education, n (%)	6 (26.1)	26 (28.3)	0.75
SEIFA score, mean (SD)	1018.1 (40.3)	1016.6 (46.5)	0.61

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CTD, chronic tic disorder; SCQ, Social Communication Questionnaire; SEIFA, Socio-Economic Indexes for Areas.

Poh W, *et al. Arch Dis Child* 2018;0:1–6. doi:10.

Table 2 ADHD+CTD versus ADHD-only—psychiatric outcomes

	ADHD+CTD (n=23)	ADHD-only (n=92)	Mean difference* (95% CI)	P
Psychiatric outcomes, n (%)				
Internalising disorder	11 (52.4)	20 (23.8)	28.3 (6.1 to 50.6)	0.007
Generalised anxiety disorder	4 (19.1)	3 (3.2)	13.4 (−2.6 to 29.6)	0.03
Separation anxiety disorder	4 (19.1)	9 (10.7)	8.3 (8.5 to 25.1)	0.26
Social anxiety	3 (14.3)	6 (7.1)	5.3 (−9.7 to 20.3)	0.44
Obsessive compulsive disorder	3 (14.3)	7 (8.3)	6.5 (−8.3 to 21.4)	0.31
Post-traumatic stress disorder	0 (0)	0 (0)	-	-
Dysthymia	1 (4.4)	1 (1.1)	3.2 (−5.6 to 11.8)	0.36
Major depression	1 (4.4)	1 (1.1)	3.2 (−5.6 to 11.8)	0.36
Hypomania	0 (0)	0 (0)	-	-
Mania	0 (0)	0 (0)	-	-
Externalising disorder	14 (66.7)	37 (44.0)	11.5 (−11.3 to 34.4)	0.33
Oppositional defiant disorder	14 (66.7)	38 (41.3)	19.6 (−11.3 to 34.4)	0.33
Conduct disorder	3 (13.0)	5 (5.4)	7.6 (−8.3 to 21.3)	0.32

*Difference in mean prevalence (ADHD+CTD minus ADHD).
ADHD, attention-deficit/hyperactivity disorder; CTD, chronic tic disorder.

Poh W, *et al. Arch Dis Child* 2018;0:1–6. doi:10.1136/archdischild-2017-314139

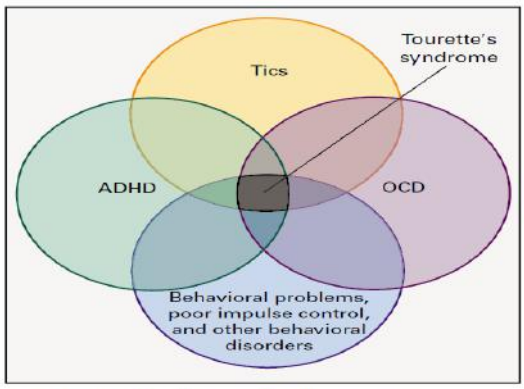


Figure 1. Clinical Hallmarks of Tourette's Syndrome. The diagnosis is based on the occurrence of tics along with behavioral disorders, including attention-deficit–hyperactivity disorder (ADHD) and obsessive–compulsive disorder (OCD). Other behavioral disorders include anxiety and mood disorders, learning disorders, sleep disorders, conduct and oppositional behavior, and self-injurious behavior.

Jankovic J.NEJM; 2001.

Disentangling the Overlap between Tourette's Disorder and ADHD

(*Spencer, T. Biederman, J. et al. J Child Psychol Psychiatr; 1998; 39; (7); 1037-1044*

Aim: Identify **similarities and differences** in neuropsychiatric correlates in children with ADHD and TD.

Methods: 1) N=79 children with **ADHD+TD**; 2) N=18 children with **TD**; 3) N=563 children with **ADHD**; 4) N=212 children with **psychiatric referral**; 5) N=140 **healthy controls**.

Results: Children with TD had higher rates of OCD and phobias.

DBDs, mood and anxiety disorders, neuropsychological and psychosocial functioning were indistinguishable in children with TD+ADHD and ADHD alone.

Children with **TD+ADHD** had more comorbidity and lower psychosocial functioning overall than those with ADHD.

Conclusions: Findings confirm previous association of TD and OCD; DBDs and mood/anxiety disorders may be accounted for by comorbidity with ADHD. **TD+ADHD** may be a more severe condition than ADHD alone.

Table 1
Demographics

	TS minus ADHD (N = 18)		TS plus ADHD (N = 79)		ADHD (N = 563)		Psychiatric controls (N = 212)		Normal controls (N = 140)		Significance (p)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	3df	2df
Age	11.9	2.8	10.7	3.2	10.4	3.7	11.1	3.1	11.7	3.6	n.s	n.s.
SES	2.2	0.9	2.1	1.1	1.9	1.1	1.9	1.0	1.6	0.8	n.s.	n.s.
Males: No. (%)	15 (83)		71 (90)		429 (76)		166 (78)		115 (82)		n.s.	n.s.

Overall analyses were done excluding the normal control group ($df = 3$) and excluding the normal control group and TS without ADHD groups ($df = 2$) using ANOVA or chi-square analyses.

Spencer, T. Biederman, J. et al. J Child Psychol Psychiatr; 1998; 39; (7); 1037-1044

Table 2
Rates of Psychiatric Diagnoses

	TS minus ADHD (N = 18)		TS plus ADHD (N = 79)		ADHD (N = 563)		Psychiatric controls (N = 212)		Normal controls (N = 140)		Significance (p)	
Diagnosis	N	%	N	%	N	%	N	%	N	%	χ^2 3df	χ^2 2df
Mood disorders												
Major depression (severe)	1	6	23	29	147	26	35	18	2	1	.04	n.s.
Bipolar	1	6	15	19[c]**	78	14[c]**	8	4	0	0	.0001	.0001
Dysthymia	3	17	9	11	51	9	18	9	1	1	n.s.	n.s.
Disruptive disorders												
Conduct disorder	2	11	16	20[c]*	109	19[c]**	18	8	4	3	.002	.001
ODD	7	39[a]*	56	71[c]**	324	58[c]**	51	24	14	10	.0001	.0001
ADD	0	0	79	100	563	100	0	0	0	0	n.a.	n.a.
Anxiety disorders												
Multiple anxiety	7	39	33	42[c]**	168	30	44	21	6	4	.002	.001
Separation anxiety	5	28	20	25	133	24	36	17	6	4	n.s.	n.s.
Overanxious	5	28	27	34[c]*	160	28[c]*	38	18	8	6	.01	.003
Social phobia	1	6	14	18	81	14	23	11	4	3	n.s.	n.s.
Simple phobia	4	22	26	33[c]**	81	14	22	10	8	6	.0001	.0001
Agoraphobia	6	33[a]*	17	22[c]*	87	15	21	10	3	2	.008	.03
Panic disorder	3	18	7	9	21	4	10	5	0	0	.02	n.s.
OCD	5	28[a]**[c]**	16	21[c]**	32	6	14	7	3	2	.0001	.0001
Elimination disorders												
Enuresis	2	11	28	35[c]*	153	27[c]*	38	18	16	11	.004	.003
Encopresis	1	6	14	18	53	9	14	7	3	2	.03	.02
Language disorders												
Language	1	6	16	20	136	24	32	15	12	9	.02	.02
Stuttering	0	0	8	10	29	5	8	4	5	4	n.s.	n.s.
Psychosis	3	17[c]**	10	13[c]**	32	6[c]*	2	1	1	1	.0001	.0001

[a] vs. TS plus ADHD; [b] vs. ADHD; [c] vs. psychiatric controls.
* $p < .01$; ** $p < .001$.
Overall analyses and pairwise analyses were done excluding the normal control group ($df = 3$) and excluding the normal control group and TS minus ADHD groups ($df = 2$) using chi-square analyses.

Spencer, T. Biederman, J. et al. J Child Psychol Psychiatr; 1998; 39; (7); 1037-1044

Phenotype Development in Adolescents with Tourette Syndrome: A Large Clinical Longitudinal Study

(*Groth, C. Mol Debes, N. et al ; Journal of Child Neurol; 2017; 32 (3) 1047-1057)*

Aim: Description of TS phenotype development and tic-related impairment in a longitudinal study of 226 children and adolescents followed up after 6 years.

Methods: Participants examined for tic severity, impairment, OCD and ADHD.

Results: Phenotype development changed toward **less comorbidity:**

at baseline 40% had TS only (no OCD or ADHD); 55% TS only at follow up.

Tic related impairment scores did not reflect tic decline. Sex, vocal and motor tics, and OCD and **ADHD severity** were highly significantly correlated with tic related impairment score.

Conclusion: Knowledge of phenotype development may be useful in clinical settings.

Table 1. Baseline Characteristics of Participants and Nonparticipants at Follow-Up.

Characteristics	Participants	Nonparticipants	*P* value
Sample size	227	87	—
Age, years, mean(SD)	12.5 (2.7)	12.3 (2.9)	.69
Male, number (%)	185 (81.5)	72 (82.8)	.87
IQ, mean (SD)	90.0 (18.4)	85.3 (16.1)	.07
SES, mean (SD)	2.5 (1.0)	2.7 (1.0)	.10
ADHD, number (%)	93 (41.2)	42 (48.3)	.31
OCD, number (%)	89 (39.2)	33 (37.9)	.90
OCD, CY-BOCS score, mean (SD)	8.4 (8.0)	8.2 (7.9)	.82
Tics YGTSS score, mean (SD)	24.5 (18.2)	25.6 (17.6)	.68

There were no significant differences ($P < .05$) between any of the demographic variables examined between participants and nonparticipants using Fisher's exact test for sex, SES, ADHD, OCD, and CY-BOCS; and *t*-test for age, tic severity, OCD severity, IQ, and YGTSS.[25] Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; IQ, intelligence quotient; OCD, obsessive compulsive isorder; SES, socioeconomic status; YGTSS, Yale Global Tic Severity Scale.

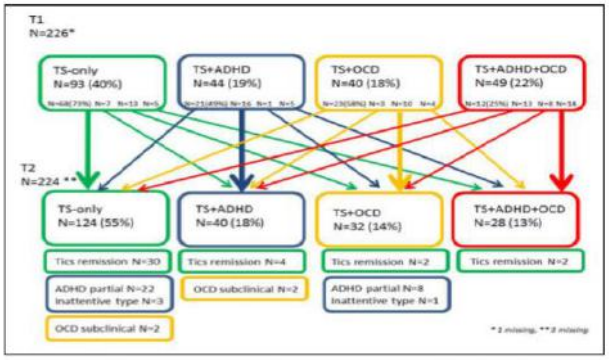
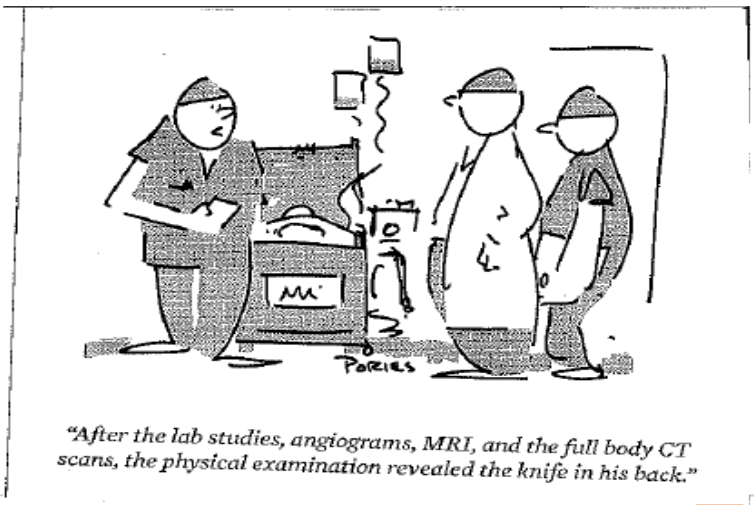


Figure 1. The development of phenotypes from baseline (T1) to follow-up (T2). At follow-up, the groups were subdivided illustrating the subclinical symptoms into full tic remission (tic score on YGTSS = 0), partial ADHD remission (subthreshold symptoms and impairment according to DSM-IV), inattentive type (ADHD predominantly inattentive type), and subclinical OCD (OCD-score8-9 on Y-BOCS). No participants fulfilled criteria at T2 for ADHD predominantly hyperactive/impulsive type. Abbreviations: ADHD, attention-deficit/hyperactivity disorder; OCD, obsessive compulsive disorder; TS, Tourette syndrome.



"After the lab studies, angiograms, MRI, and the full body CT scans, the physical examination revealed the knife in his back."

Neurodevelopmental Disorders: Diagnostic Evaluation: Tic Disorders and ADHD

- **Diagnoses** of both disorders are made on basis of **classical history.**
- **Structured or semi-structured diagnostic interviews,** such as the DISC or 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); the "gold standard" assesses domains of: tic number, frequency, intensity, complexity and interference (0-50), and tic related impairment (0-50). **Tic Symptom Self Report** (TSSR) derived.
- **SNAP, ADHD-RS and Conners** (Parent and Teacher) are helpful for quantitative evaluation of ADHD symptoms.
- ***Quantitative ratings of tics and ADHD can facilitate disentanglement for overall treatment planning and use of targeted combined pharmacotherapy.***

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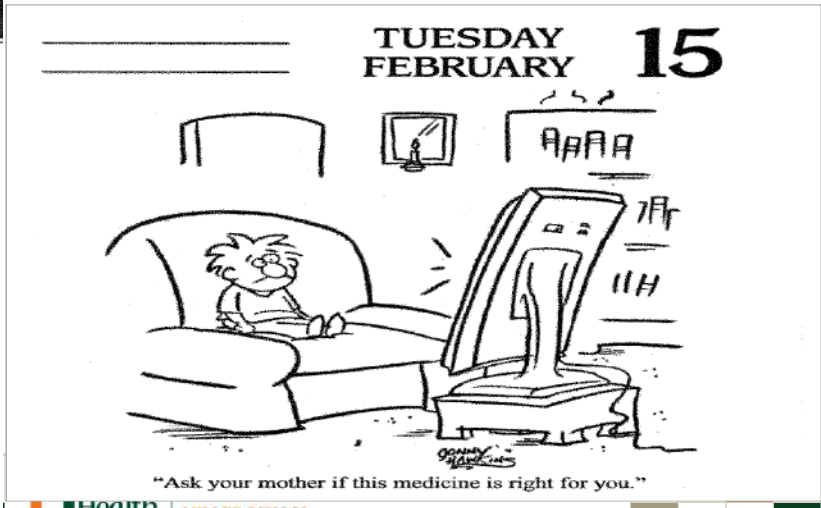

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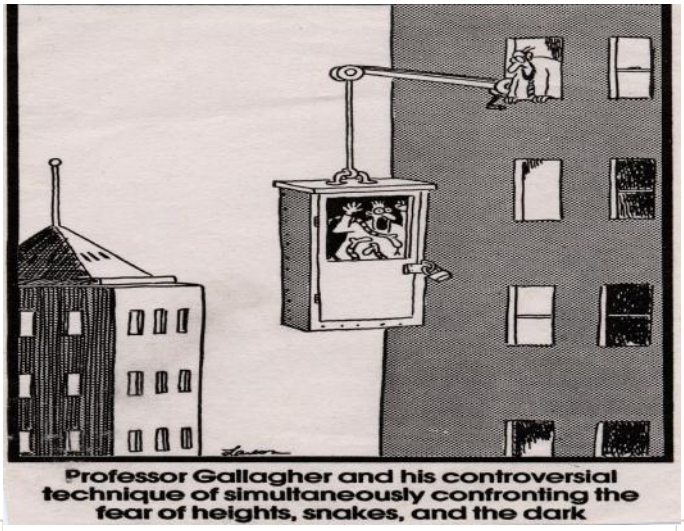
TD/Tics and ADHD: Impact on Management

- **Tics:** Most patients with mild tic symptoms need only monitoring, education, and guidance. Those with moderate to severe symptoms will usually need treatment.
- ***ADHD**: Since ADHD symptoms are more likely to persist and cause significant functional impairment, treatment is recommended.
- **Behavioral treatment of tics (Comprehensive Behavioral Intervention for Tics (CBIT))** is now established as **first line treatment** for tic disorders. This may be particularly relevant to patients with tics and ADHD, since pharmacotherapy may be challenging. ADHD did not moderate response to CBIT. *(Sukholdosky, D. et al, Neurology, 2017)*
- There are no controlled studies of comorbid ADHD and tic disorders of pharmacotherapy plus behavioral treatment.
- **Pharmacotherapy for Tic Disorders and ADHD**:
- 1) stimulants
- 2) alpha agonists
- 3) atomoxetine
- 4) combinations



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Comprehensive Behavioral Intervention for Tics Study (CBIT)

(Piacentini, J. Woods, D. Scahill, L. et al. JAMA; 2010; 303 (19):1929-1937)

Three phases:

1) Awareness training

2) Competing response training

3) Social support

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

Daily Doses of Frequently Prescribed Tic Medications

(Egolf, A. Coffey, B. Current Pharmacotherapeutic Approaches to the Treatment of Tourette Syndrome: Drugs Today; 2014 Feb; 50 (2):159-79. doi: 10.1358/dot.2014.50.2.2097801). ***off label**

Medication	Range of daily dosing
Haloperidol	0.25-4.0mg
Pimozide	0.5-8.0mg
*Risperidone	0.125-3.0mg
Aripiprazole	1.0-15.0mg
*Clonidine	0.025-0.4mg
*Guanfacine	0.25-4.0mg

Meta Analysis: Risk of Tics Associated with Stimulant Use in Randomized, Placebo-Controlled Trials

(Cohen, S. Mulqueen, J. Ferracioli-Oda, E. Stuckelman, Z. Coughlin, C, Leckman, J. Bloch, M. JAACAP; 2015; 54(9); 728-736)

Design: Meta-analysis of RCTs of stimulants in treatment of ADHD.

Results: N=22 studies with 2385 children with ADHD.

New onset or worsening of tics were commonly reported with ***stimulants (5.7%) and placebo groups (6.5%)***.

Risk of new onset or tic worsening associated with stimulants was similar to that of placebo (risk ratio=0.99, p=.962).

Results: Stimulant type, dose, duration and age did not affect risk.

Cross over studies were associated with a significantly greater risk than parallel group trials.

Conclusion: There is **no evidence** for support of an association between new onset or worsening of tics with stimulant use in patients with ADHD.

Practical Tips on Treating ADHD and Tics/TD with Stimulants

- **Methylphenidates (MPH)** are recommended.
- For adolescents, MPH can be initiated at 10 mg (or equivalent) and titrated upward gradually.
- For tic increase with upward titration: if ADHD symptoms have improved, hold the dose and monitor, or temporarily reduce the dose and re-titrate.
- There are no controlled trials of extended release stimulants, but they may be less likely than IR to be associated with tic increase that occurs in some children?
- Guanfacine or clonidine can be added if the tic increase is sustained.

How To Decide? Systematic Review: Pharmacological Treatment of Tic Disorders: Efficacy of Antipsychotic and Alpha 2 Agonist Agents

(Weisman, H. Qureshi, I. Leckman, J. Scahill, L. Bloch, M. Neuroscience and Biobehavioral Reviews; 2013; 37; 1162-1171)

- **Design:** Meta-analysis of RCTs in treatment of chronic tic disorders and examination of moderators
- **Results:** Significant benefit of antipsychotics vs. placebo. **SMD=0.58.**
- No significant difference in efficacy of risperidone, pimozide, haloperidol and ziprasidone.
- Significant benefit of alpha 2 agonists vs. placebo. Significant **moderating effect of comorbid ADHD**.
- **With comorbid ADHD SMD: 0.68. No ADHD: 0.15.**
- **Conclusion**: Significant benefits of both medication types, but alpha 2 agonists may have minimal benefit in patients without ADHD.

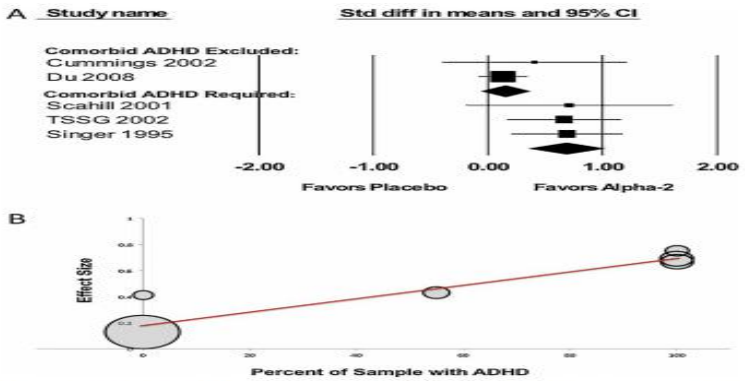

Fig. 7. (A) Efficacy of alpha2-agonists for the treatment of tics in trials stratified by ADHD comorbidity. Trials that required tic patients to have comorbid ADHD (SMD = 0.68 (95%CI: 0.36–1.01), $z = 4.10$, $p < 0.001$) demonstrated a significantly greater effect (test for subgroup differences $\chi^2 = 7.27$, df = 1, $p = 0.007$) of alpha-2 agonists in reducing tic symptoms than trials that excluded subjects with comorbid ADHD (SMD = 0.15 (95%CI: −0.06 to 0.36), $z = 1.40$, $p = 0.16$). (B) Meta-regression of alpha-2 agonist efficacy in treating tics versus percent of subjects with comorbid ADHD in trial. Meta-regression demonstrated that trials enrolling a larger proportion of subjects with comorbid ADHD reported a greater efficacy of alpha-2 agonists in treating tics ($\beta = 0.0053$ (95%CI: 0.0015–0.0091), $z = -2.72$, $p = 0.006$).

Extended-Release Guanfacine (GXR) Does Not Show a Large Effect on Tic Severity in Children with Chronic Tic Disorders

(Murphy T, Fernandez T, Coffey B, et al. JCAP. 2017;27(9):762–770.)

- **Methods:** 8-week RCT in N=34 youth ages 6 to 17 years (mean = 11.1) with CTD.
- **Results:** At baseline, mean YGTSS total score was 26.3 for GXR group vs. 27.7 for placebo.
- GXR group: (mean final daily dose 2.6 mg.); mean YGTSS total score declined to 23; **p = 0.08; effect size = 0.35**.
- PBO group: declined to 24.7; **p = 0.08; effect size = 0.38.**
- There was **no significant difference** in the rate of positive response on CGI-I between GXR and PBO (19% vs. 22%; p = 1.0).
- **Adverse Effects (AE):** Most common: fatigue, drowsiness, dry mouth, headache, and irritability.
- **Conclusion:** This pilot study **did not confirm a clinically meaningful effect size** within GXR group. These results **do not support launch** of a larger efficacy trial for tics in youth with CTD.

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TABLE 1. CHARACTERISTICS OF STUDY PARTICIPANTS AT BASELINE (N=34)

	Guanfacine, n = 16	Placebo, n = 18	Test statistic, p-value[b]
Age, M (SD)	11.5 (3.03)	10.8 (3.2)	$t(32) = 0.62$, $p = 0.5$
Gender, males, n (%)	11 (69)	12 (67)	$\chi^2(1) = 0.02$, $p = 0.9$
Race, n (%)			
Caucasian	16 (100)	17 (94)	Fisher's exact test, $p = 1.0$
African American	—	1 (6)	
Ethnicity, Hispanic	3 (19)	4 (22)	
Tic disorder, n (%)			
TD	14 (87.5)	15 (83)	Fisher's exact test, $p = 1.0$
Chronic motor TD	2 (12.5)	2 (11)	Fisher's exact test, $p = 1.0$
Chronic vocal TD	—	1 (6)	Fisher's exact test, $p = 1.0$
ADHD, n (%)	8 (50)	4 (22)	Fisher's exact test, $p = 0.15$
Generalized anxiety disorder, n (%)	3 (19)	1 (6)	Fisher's exact test, $p = 0.3$
OCD, n (%)	3 (19)	3 (17)	Fisher's exact Test, $p = 1.0$
ODD, n (%)	3 (19)	4 (22)	Fisher's exact test, $p = 1.0$
Separation anxiety disorder, n (%)	3 (19)	1 (6)	Fisher's exact test, $p = 0.3$
Tanner stage, N stage 1 or 2, n (%)	10 (63)	11 (61)	Fisher's exact test, $p = 1.0$
YGTSS total score, M (SD)	26.3 (6.61)	27.7 (8.7)	$t(32) = -0.53$, $p = 0.6$
YGTSS motor score, M (SD)	15.2 (2.61)	17.2 (3.44)	$t(32) = -1.92$, $p = 0.06$
YGTSS phonic score, M (SD)	11.1 (6.13)	10.4 (6.73)	$t(32) = 0.28$, $p = 0.8$
YGTSS impairment, M (SD)	29.8 (8.18)	28.6 (8.01)	$t(32) = 0.43$, $p = 0.7$
CGI severity, n (%)			
Moderately ill	12 (75)	9 (50)	$\chi^2(2) = 3.7$, $p = 0.2$
Markedly ill	4 (25)	6 (33)	
Severely ill	—	3 (17)	
TSSR (parent), M (SD)[a]	26.9 (22.83)	24.6 (16.94)	$t(31) = 0.33$, $p = 0.7$
PUTS, M (SD)	19.8 (5.39)	20.9 (8.18)	$t(32) = -0.47$, $p = 0.6$
ADHD RS (parent), M (SD)	19.7 (12.29)	17.5 (13.65)	$t(32) = 0.49$, $p = 0.6$
DBRS, M (SD)	8.8 (6.59)	5.6 (7.37)	$t(32) = 1.33$, $p = 0.19$
CY-BOCS, M (SD)	9.6 (10.41)	10.5 (11.43)	$t(32) = -0.25$, $p = 0.8$
ROARS, M (SD)	3.1 (2.87)	2.2 (2.87)	$t(32) = 0.97$, $p = 0.3$

[a]Owing to missing items, the TSSR phonic and total scores could not be calculated for one subject.
[b]$p < 0.05$.

ADHD RS, attention-deficit/hyperactivity disorder rating scale; CGI, clinical global impressions; CY-BOCS, Children's Yale-Brown Obsessive Compulsive Scale; DBRS, Disruptive Behavior Rating Scale; M, mean; OCD, obsessive compulsive disorder; ODD, oppositional defiant disorder; PUTS, Premonitory Urge for Tics Scale; ROARS, Rage Outbursts and Anger Rating Scale; SD, standard deviation; TD, tic disorder; TSSR, Tic Symptom Self-Report; YGTSS, Yale Global Tic Severity Scale.

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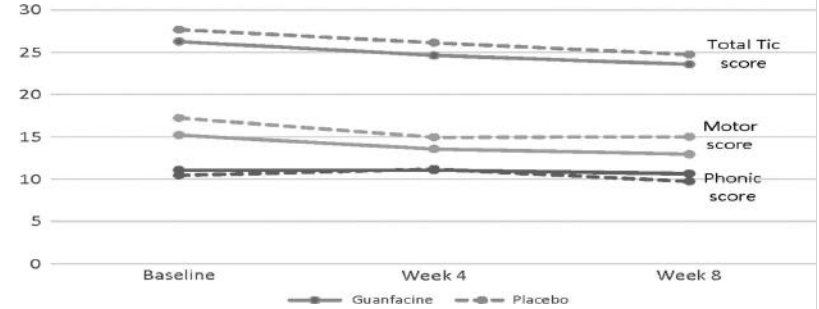

FIG. 2. YGTSS total score, motor, and phonic; guanfacine vs. placebo. YGTSS, Yale Global Tic Severity Scale.

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Summary: ADHD and Tics: Boundaries, Overlap and Disentanglement

There is **bi-directional overlap of ADHD and Tic Disorders:** neurobiology, including genetics and neurocircuitry, and phenomenology, including clinical course and psychiatric comorbidity.

ADHD symptoms tend to persist, but **tic symptoms** tend to remit over time.

Much of the **associated psychopathology (behavioral, emotional, neurocognitive**) in Tourette's Disorder is secondary to ADHD.

Children and adults with **ADHD+CTD** are more likely to have higher rates and severity of psychopathology and reduced quality of life than those with either ADHD or CTD alone.

Tic and ADHD symptoms should be carefully **disentangled,** by severity and potential outcomes, for best management and intervention.

Behavioral treatment of tics is recommended; **stimulants** can be used safely for pharmacotherapy, but there are several other options including combination.

Epilepsy and ADHD: Bidirectional Interface and Opportunity

Joseph Gonzalez-Heydrich, MD

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Department of Psychiatry
Children's Hospital Boston

Associate Professor of Psychiatry
Harvard Medical School

1

Joseph Gonzalez-Heydrich Disclosures:

- In the past 3 years, received grant support from the Tommy Fuss Fund. He has equity in Neuro'motion, Inc., a company working on emotional regulation training tools.
- In previous years, he has served as a consultant to Abbott Laboratories, Pfizer Inc, Johnson & Johnson (Janssen, McNeil Consumer Health), Novartis, Parke-Davis, Glaxo-SmithKline, AstraZeneca, and Seaside Therapeutics; has been a speaker for Abbott Laboratories, Pfizer Inc, Novartis, Bristol-Meyers Squibb; and has received grant support from Abbott Laboratories, Pfizer Inc, Johnson & Johnson (Janssen, McNeil Consumer Health), Akzo-Nobel/Organon and the NIMH.

2

Epilepsy Definition

- Any one of the following:
- At least two unprovoked (or reflex) seizures occurring >24 hours apart.
- One unprovoked (or reflex) seizure and a≥60% chance of recurrent seizures over the next 10 years.
- Diagnosis of an epilepsy syndrome

3

Epilepsy Causes

- No identifiable cause for Epilepsy in 50%
- In the other 50%:
  - Genetic conditions
  - Perinatal Injury
  - Later aquired brain conditions (e.g. head trauma, strokes, tumors, infections, autoimmunity)

4

Epilepsy: common and comorbid

- By the age of 20 years, 1% of children in the USA and Western Europe will develop epilepsy.
- Behavioral Problems in Children:
  - general child population 6.6% (Rutter et al 1970)
  - with non-neurological illness 10.3%
  - with epilepsy, no other CNS prob. 28.6%
  - with epilepsy + other CNS prob. 58.3%
- Risk increases with additional neurological and psychosocial deficits.

5

ADHD and Epilepsy are Associated

- 2-4% of children with ADHD have epilepsy
- 30-40% of children with epilepsy and no ID have ADHD
- When both occur together, the chance of identifying the cause of the ADHD increases
  - The shared liability between ADHD and epilepsy is frequently environmental
  - It can also be genetic
  - It is unlikely to be due to current ADHD medications

6

Many Levels of ADHD-Epilepsy Association

- ADHD often precedes and increases risk for epilepsy arguing that the cause predisposes to both in many patients.
- ADHD can also follow seizures arguing that seizures can disrupt ADHD associated brain circuits-a form of epileptic encephalopathy
- Antiepileptic drugs can cause ADHD symptoms
- All three processes can be at play
  - E.G. Dravet syndrome, due to dominant mutation in SCN1A,is an example of these combined phenomenon

7

Epilesy and ADHD Genetics

- Not much correlation between common risk variants for ADHD and for epilepsy
- Rare, sometimes inherited, CNVs and single gene mutations have been implicated in many neurodevelopmental disorders, including ASD, ID, ADHD, epilepsy and psychosis
- The same mutation can predispose to all of these, complicating risk considerations for probands and family members

8

List of Actionable Genetic Epilepsies Increasing

- Next-generation sequencing (NGS) has transformed Epilepsy Genetics
  - A decade ago 10-20 epilepsy genetic mutations known
  - Now over 300.
- Translation of genetic lesion to treatment increasing
- These treatments may improve ADHD as well as epilepsy in these patients.

9

Selecting a Psychotropic

- Prior to Genomics: If psychotropic needed, Four Considerations:
  - **Efficacy**
  - Lowering seizure **threshold**
  - **Interactions**: Pharmacodynamic (eg. sedation), Pharmacokinetic Interactions
  - **Side effects**
- New Consideration: Is there an identifiable genetic cause of the epilepsy and if so what are the associated risks to consider

10

Knowing Associated Mutation Risks Important: Clinical Example

- 16p13.11 deletion is associated with Epilepsy, ASD, Psychosis, ID and ADHD.
- CNV found in patient and his father; neither had psychosis until
- Father at age 47 is treated with Adderall 80 mg per day and has a manic-psychotic break with symptoms that persist after stopping Adderall.
  - Fears of poisoned food/poisoned bottled water, Hallucinations, Mania
  - Symptoms continued for several months until stabilized on antipsychotic
- 8 months into increase stress due to his father's psychotic episode his 22 year old son started hearing voices insulting his mother and telling him to jump out of window. Hallucinations remitted on clozapine but he still thinks they were real.
- If Father's clinical team had known of increased risk for psychosis a different medication choice or closer monitoring may have prevented two psychotic disorders

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Can risk of psychosis from Known Mutations be reduced?

- **Set up alert**
- **Contact parents**
- **Give clinical consultation preventive advice monitoring**


ORIGINAL ARTICLE

American Journal of medical genetics

Overlapping 16p13.11 Deletion and Gain of Copies Variations Associated With Childhood Onset Psychosis Include Genes With Mechanistic Implications for Autism Associated Pathways: Two Case Reports

Catherine A. Brownstein, Robin J. Kleiman, Elizabeth C. Engle, Meghan C. Towne, Eugene J. D'Angelo, Timothy W. Yu, Allan H. Beggs, Jonathan Picker, Jason M. Fegter, Devon Carroll, Rachel C. O. Schmitt, Robert R. Wolff, Yiping Shen, Vu Lip, Kaya Bilguvar, April Kim, Sahil Tembulkar, Kyle O'Donnell, and Joseph Gonzalez-Heydrich

12

Childhood epilepsy Increases Risk for Adult Social Problems

- **Even in patients with normal intelligence**
  - **decreased employment, marriage, social relationships, and independent living.**
  - **not clearly related to remission or any other biologic factor except learning disorder**
- **The influence of epilepsy on social outcome is greater than in other childhood chronic disease control groups.**

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Even if seizures remit, challenges remain

- 24 patients with JME followed ~25 years-
- Despite 87% high school graduation,
- 31% were unemployed.
- Eleven pregnancies (80%) were unplanned, outside of a stable relationship.
- At least 1 major unfavorable social outcome was noted in 76%.

Camfield CS and Camfield Pr. Neurology September 29, 2009 vol. 73 no. 13 1041-1045

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Psychiatric disorders are associated with epilepsy

- **Disruptive behavior disorders**
  - ADHD in 39% of children with epilepsy without ID
  - Prevalence of explosive anger & aggression is unknown but seems to be elevated
- **Internalizing disorders also elevated**
  - Depression in 20%
  - Anxiety in 60%
  - Suicidal ideation 20%, with plan 7.4%, completed suicide risk markedly elevated
- **Pervasive Developmental Disorders:** seizures in 5-10% of high functioning patients with Autism

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Lack of Treatment for Psychiatric Disorder in Epilepsy Patients.

- **Psychiatric disorders are often undiagnosed and poorly managed**
- **Evidence base for psychotropic treatments in patients with Epilepsy sparse.**
  - **Essentially only Methylphenidate Studied and only few small studies.**

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Sources of reluctance to treat psychiatric disorders in children with epilepsy

- It is often unclear if the psych symptoms are the effects
  - of a common pathology underlying both
  - of chronic seizures,
  - of non-convulsive epileptiform discharges,
  - and/or of antiepileptic drugs (AEDs) (Schubert, 2005).
  - Most importantly, the safety and efficacy of the standard psychopharmacologic treatments have not been adequately studied in children with epilepsy.
- Yet, psychiatric symptoms may be more impairing in the long-term than seizures.

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Placebo Controlled Trial for ADHD+epilepsy:

- Feldman et al. (1989) studied 10 children with well-controlled epilepsy on one AED in a double blind placebo cross over trial of MPH.
- A 0.3mg/kg/dose of MPH was administered on school days at 8am and noontime for four weeks.
- During the study period, there were no seizures or side effects other than mild appetite suppression and emotional lability.
- There were no effects on AED plasma levels or on the EEG.
- The Teacher's Conner's Rating Scale was improved in 70% of the children while on the MPH

18

Prospective observation period followed by open label trial

- Gross-Tsur et. al. (1997) studied 30 children with both ADHD and epilepsy.
- The children were observed for 8 weeks prior to starting open label a single morning 0.3 mg/kg/day dose of MPH for 8 weeks.
- None of the children who were seizure free during the observation period had seizures during MPH treatment.
- Of the 5 children who were still having seizures during the observation period, 3 had an increase in seizure activity during MPH treatment
  - These 5 patients had an average of 1.8 seizures/wk during the observation period and 3/wk on MPH, p=NS.
  - would need 31 patients in the study with this baseline seizure frequency to have adequate power to find this magnitude of difference statistically significant.
- There were no significant changes in EEG findings or in AED levels.
- 70% of the children had an improvement in ADHD symptoms by parent report.

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Outcomes in "Real World Care": Stimulant Effectiveness in Well Controlled Vs. Poorly Controlled Pediatric Epilepsy

- Review of data entered prospectively in an electronic medical record system (EMRS) during routine care
- Records of patients seen between November of 1998 and October of 2001 were searched for patients with:
  - Epilepsy
  - Age less than 18 years
  - Receiving Methylphenidate (MPH) or Amphetamine (AMP)
  - Baseline and treated visits available in the EMRS

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Stimulant Effectiveness in Well Controlled vs. Poorly Controlled Pediatric Epilepsy (Continued):

- 79 youth with epilepsy were found.
- 23 had baseline and treated visits with MPH
  - Average dose 0.6±0.3 mg/kg/day
- 19 had baseline and treated visits with AMP
  - Average dose 0.4±0.2 mg/kg/day
- 6 had baseline and treated visits on with both,
- Total of 36 patients included in the study.
- Effectiveness and tolerability of MPH and AMP for the patients who were seizure free for 6 months (SzFree), not seizure free (NotSzFree) and the total sample were compared

21

Stimulant Type = Best Predictor of Response

- **Entered Three Predictors into Multivariate Logistic Regression:**
  - Stimulant Type: MPH vs Amph
  - Seizure Free v Not Seizure Free
  - Cognitive Level (6 point likert from high to severe MR)
- **Seizure status was not significant in predicting response.**
  - There was no significant difference in responder rates in SzFree patients (53%) and NotSzFree patients (37%).
  - **However: trend for a seizure in the 6 months previous to the trial to predict worsening on stimulant (p=0.08)**
- **Type of stimulant was significant for predicting whether a patient was a responder even after controlling for confounders (χ^2=4.7, df=1, p=0.03).**
  - There was a significantly higher percentage of responders to MPH (63%) than to AMP (24%).
- **There was a trend for higher cognitive level to predict that a patient would be a responder (χ^2=2.3, df=1, p=0.13).**

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Tolerability

- Patients' discontinuation of medication due to worsening agitation or emotional lability was predicted by lower cognitive level (χ^2=3.9, df=1, p=0.048) and not medication type or seizure status.
- Discontinuation rates due to adverse events for SzFree was 35% and NotSzFree 53% (p=ns).
- Three of 19 NotSzFree patients had an increase in seizures while on a stimulant. One had anticonvulsants adjusted and became seizure free while she was still taking AMP. One each on MPH and AMP discontinued the stimulant due to increase in seizures and promptly returned to his baseline seizure frequency.
- For both groups, the most common reason for discontinuation of MPH and AMP was increased agitation not increase in seizures.

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Observed Clinical Response to Amphetamine and Methylphenidate			
	AMP	MPH	
Number of Patients	17	19	
Average Dose	0.37±0.26 mg/kg/day	0.62±0.28 mg/kg/day	
CGI Severity Start	4.71±0.92	4.79±0.86	
	median: 5	median: 5	p=ns
CGI Severity End	**4.65±0.93**	**3.79±1.03**	
	median: 5	**median: 4**	**p=0.02**
CGI Improvement	**3.41±1.73**	**2.47±1.74**	
	median: 3	**median: 2**	**p=0.05**
Responders %	**24%**	**63%**	**p=0.02**
Worsened %	41%	27%	ns
Unchanged %	24%	5%	ns
Discontinuation due to AE	53%	37%	ns

Study 3

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Adapting Clinical Trial Methods to Higher Risk Populations: RCT of OROS-MPH for ADHD plus Epilepsy

–Stage I, dose finding trial of XR-MPH

- IRB concerned that safety of lower doses be established before patients exposed to higher doses.
- Traditional Phase I design adopted.
- Crossover design
  - –used so as to control for heterogeneity of ADHD + epilepsy patients
  - –Unblinding at the end of each patients trial so that each individual patient receives a benefit to balance risk.
- No patient exposed to more the 2 mg/kg/day of MPH

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Seizure Data: Closer Look

- There was no significant worsening of epilepsy or any serious adverse event.
- longer exposure to placebo than to OROS-MPH.
  - Adverse events leading to early discontinuation occurred earlier and more frequently on the OROS-MPH arm of the crossover, leading to longer exposure to placebo than to OROS-MPH.
- Five seizures occurred while on OROS-MPH and 3 while on placebo.
- Average number of days with a seizure per 100 days of exposure were
  - 0.53 for placebo,
  - 0.54 for doses less than 1.2 mg/kg/day
  - 1.63 for doses of 1.2 to 2mg/kg/day of OROS-MPH.
- Higher doses predicted increased risk of seizure ($p<0.01$).

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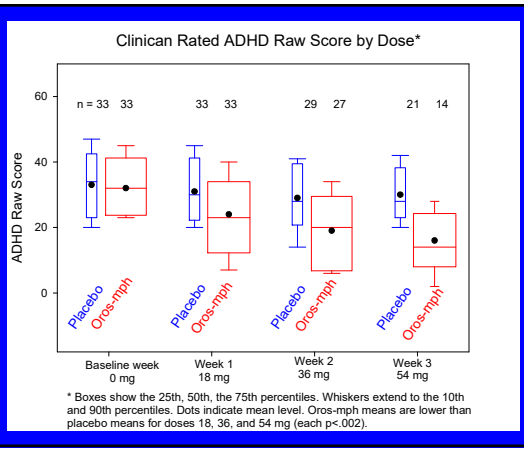

27

Stimulant Effectiveness in Poorly Controlled Pediatric Epilepsy

- Review of data entered prospectively in an electronic medical record system (EMRS) during routine care
- Medical records through 2/06 searched for patients with:
  - Epilepsy, and seizure frequency > 1 per month
  - Receiving Methylphenidate (MPH) preparation for treatment of ADHD
  - Baseline and treated visits available in the EMRS

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Stimulant Effectiveness in Poorly Controlled Pediatric Epilepsy

- N=8
- 3 experienced a worsening of seizures during MPH treatment (2 with increase in sz frequency, 1 with increase in severity)
- 2 of these unlikely due to MPH and 1 possibly.
- No permanent sequelae
- 5/8 (63%) with positive, robust response of ADHD symptoms to MPH (close to the 70% seen in non-epilepsy ADHD patients)
- % Responding seems not related to having frequent seizures

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Atomoxetine: open label case series in ADHD+Epilepsy 1

- Study 1 (abstract) : Hernandez and Barragan studied 17 patients, 6 to 15 years old, with epilepsy (degree of seizure control not specified in the abstract) given open label atomoxetine
  - starting at 0.5 mg/kg/day and increased to a maximum of 1.8 mg/kg/day.
  - Significant ADHD improvement starting at 3 weeks and maintained for up to 12 weeks.
  - Only one patient showed an increase in seizures

ILAE Meeting Paris 2005

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Atomoxetine: open label case series in ADHD+Epilepsy 2

- Study 2 (Paper): Torres, Whitney, Rao, Lobel, Tilley, and Gonzalez-Heydrich
- **27 patients** (10±4 years, 63% male) treated with atomoxetine for 4-141 weeks, median 26 weeks). **90% were stimulant non-responders**.
- Seizure frequency at baseline was from no seizure in 11 years to 90 seizures per month. No patient discontinued due to increase in seizures.
- **The overall rate of discontinuation for atomoxetine was 63%.**
  - **inadequate response (n=7, 23%), behavioral worsening (n=8, 30%),** appetite decrease and tremor (n=1, 4%), or noncompliance (n=1, 4%).
  - non-significant trend for more discontinuations due to non response among ADHD-I patients and mood disorders to predict discontinuation.
- Of the 10 patients continuing Atomoxetine 8 were responders. Response rate is modest but almost all the patients previously failed stimulants.

Epilepsy and Behavior 2010

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Question of Treatment for those with ADHD and Epilepsy

- Methylphenidate (MPH) → currently the most widely studied and prescribed stimulant for ADHD
- Data surrounding MPH for those diagnosed with epilepsy is still somewhat controversial
  - Gucuyener et al. (2003 found that MPH does not affect seizure frequency in those with ADHD and epilepsy
  - Gonzalez-Heydrich (2013) found a positive correlation between seizure frequency and MPH dosage
  - Animal models demonstrate that MPH prolongs the length of seizures by more than 150% of baseline

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Follow Up Study: Use of MPH in Patients with Epilepsy and ADHD

- Retrospective chart review--examine effectiveness/safety of MPH in those diagnosed with epilepsy and ADHD
  - Examined seizure aggravation, pre/post treatment EEGs, and effectiveness of MPH
  - Participants: 105 subjects diagnosed with epilepsy at the Department of Pediatric Neurology at Asan Medical Center and then diagnosed with ADHD
    - Exclusion criteria
      - Those who took less than 50% of the prescribed MPH dose over the study period
      - Those with an additional diagnosis of a major psychiatric disorder (ex. Schizophrenia, Bipolar disorder)

Park, Jangho, Hae-Won Choi, Mi-Sun Yum, et al. Relationship Between Aggravation of Seizures and Methylphenidate Treatment in Subjects with Attention Deficit/Hyperactivity Disorder and Epilepsy. *Journal of Child and Adolescent Psychopharmacology.* 2018; 28(9): 637-646

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Results

- Seizures were aggravated in 34 out of 105 subjects (32.4%)
  - **21 related to MPH (20%)**
  - 10 related to AED dose reduction or poor adherence
- Those with **aggravated seizures**:
  - Higher prevalence of: anxiety disorders, epileptic encephalopathy
- EEG results: **32.3% showed EEG worsening** related to MPH treatment
  - Those who had **worsening of their EEGs** → had baseline epileptiform charges, anxiety disorders, or were naïve for AEDs
- MPH was effective in improving ADHD symptoms regardless of its effects on seizure aggravation

Park, Jangho, Hae-Won Choi, Mi-Sun Yum, et al. Relationship Between Aggravation of Seizures and Methylphenidate Treatment in Subjects with Attention Deficit/Hyperactivity Disorder and Epilepsy. *Journal of Child and Adolescent Psychopharmacology.* 2018; 28(9): 637-646

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Why are these rates of aggravated seizures higher?

- Rates currently reported are: 0-18% with an average of 8% (Ravi and Ickowicz, 2016)
- Potential reasons why they found aggravated seizures in 20% of their cohort:
  - Included those with uncontrolled seizures and epileptiform discharges → known risk factors
  - Included those with ID, MRI abnormalities, or multiple AED medications → additional risk factors
  - Higher average MPH dosage [i.e. 0.86 mg/kg/day]→previous studies ranged from 0.3-0.56 mg/kg/day

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10-step road map to the pharmacologic treatment of a psychiatric disorder comorbid with a seizure disorder: 1-3

1. Know as much about the epilepsy as possible including
   - Any known cause and its associated risks,
   - The plan for its treatment.
2. Integrate this information into a biopsychosocial formulation and medication treatment plan
3. I would not let the patient's seizures prevent my treating psychiatric problems unless the seizures were occurring more frequently than one per month and there was a plan to change the antiepileptic drug (AED) regimen to decrease the seizure frequency.

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10-step road map: 4-5

4. Assess for additional comorbid illnesses
   - Such as learning, anxiety, depressive, bipolar, and psychotic disorders
   - Intervention for the latter two disorders will likely be needed prior to treating the ADHD symptoms.
5. Try to understand the longitudinal course of the psychiatric symptoms and epilepsy in order to better plan the treatment.
   - Even if psych symptoms preceded the first recognized seizure, didthey worsened after seizures started?
   - Did they improve as seizures were brought under control?
   - Is there a relationship between increases in psych symptoms and changes in AED therapy?

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10-step road map: 6

6. Look for opportunities to improve psych symptoms through better seizure control, decreasing AED polypharmacy, or switching to an AED with fewer cognitive or behavioral effects.
   - Some AEDs have more potential for behavioral (e.g. phenobarbitol) or cognitive (e.g topiramate) adverse effects than others.
   - However, these measures, even if successful, will not obviate the need for psych medication in most children.

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10-step road: 7-10

7. If a patient experiences deterioration in psych symptoms, consider if it could be due to a worsening of a neurological condition. Discuss this with the neurologist and consider the merit of repeating an EEG and other studies.
8. Ask parents and teachers to fill out an rating scales at the start of treatment and periodically during treatment.
9. Implement behavioral interventions and parent guidance along with medication treatments.
10. Include in the informed consent discussion an explanation of the limits of our evidence-base for using psychotropics in children with epilepsy.

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If a patient's seizures seem to worsen during psychotropic treatment

- Response depends on
  - Severity of the seizures,
  - How much of a departure they were from prior pattern,
  - Benefit observed from the psychotropic medication.
- Consider discontinuing if
  - clinically meaningful intensification in seizure frequency or duration.
- Consider increasing the AED regimen and continuing the psychotropic if
  - Observed benefits is great

40

Once An Apparently Effective ADHD Medication Has Been Found

- I would consider on-off trials to carefully establish efficacy in each patient.
- It is likely that the ADHD treatment will need to continue long-term even in patients whose seizures are completely controlled and who are able to come off their AED treatment.
- However, it is important to try decreasing or discontinuing the dose of ADHD medications during the summer holidays to see if it is still needed.

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Attention Deficit Hyperactivity Disorder in Children and Adolescents with Obsessive Compulsive Disorder: Fact or Artifact?

APSARD, Washington DC, January 2019

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1

Disclosures-Geller

Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose

NIMH, NICHD, Neurocrine Bioscience, Biohaven Pharmaceuticals, Teva &Syneos, AACAP, TAA

2

Disclosures-Pliszka

Research support and/or consultant:

Shire NLS Supernus

Ironshore Sunovion

Astra-Zeneca

3

DSM 5 OCD in Children

Obsession:

- Unwanted, fixed, intrusive, repetitive ideas, thoughts, urges, images or impulses
- From obsedere (L) to beset, occupy or besiege
- Subjective mental experience causing negative affect

Compulsion:

- A repetitive irresistible impulse to act regardless of the rationale for the motivation
- From compellere (L) to exert an irresistible force, to sway or to drive
- Objective behavior that moderates the affect
- A potentially confusing colloquial term

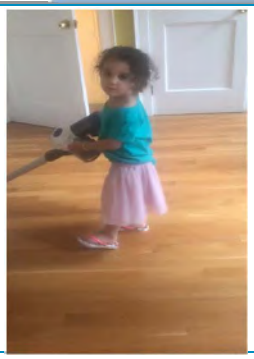
4

Compulsion vs Addiction?

- OCD
  - Fear conditioning and anxiety drives compulsion
  - Insight generally maintained
  - Ego-dystonic
  - Internal resistance
  - Anxiety relief from rituals reinforces repetition (-ve reinforcement)
  - Treatment involves fear extinction learning (habituation)
- Addiction (IAD)
  - gratification drives repetitive behavior (+ve reinforcement)
  - dopaminergic nucleus accumbens mediated
  - Denial prominent, insight poor
  - Ego-syntonic
  - Little internal resistance
  - Treatment involves cognitive and motivational intervention and externally managed behavioral approaches

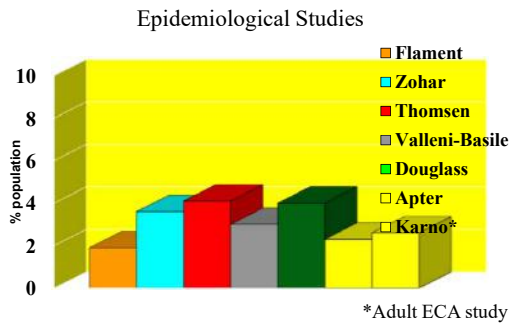
5

OCD can start early



6

Prevalence of Pediatric OCD



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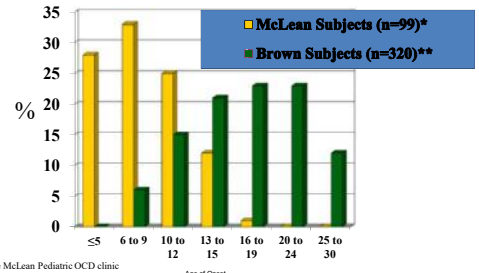
Age at Onset of OCD in Children & Adults



*From the McLean Pediatric OCD clinic
**Rasmuusen, Steven, MD & Eisen, Jane, MD, The Epidemiology and Clinical Features of Obsessive-Compulsive Disorder, *Obsessive-Compulsive Disorders: Practical Management, ed.3,1998*

8

Common Categories of Obsessions in Youth

C	P	Contamination Obsessions
		Concern with dirt, germs, certain illnesses (e.g., AIDS)
		Concern or disgust with bodily waste or secretions (e.g., urine, feces, saliva)
		Excessive concern with environmental contaminants (e.g., asbestos, radiation, toxic waste)
		Excessive concern with household items (e.g., cleaners, solvents)
		Excessive concern about animals/insects
		Excessively bothered by sticky substances or residues
		Concerned will get ill because of contaminant
		Concerned will get others ill by spreading contaminant (aggressive)
		No concern with consequences of contamination other than how it might feel*
		Other (Describe)
		Aggressive Obsessions
		Fear might harm self
		Fear might harm others
		Fear harm will come to self
		Fear harm will come to others (may be because of something child did or did not do)
		Violent or horrific images
		Fear of blurting out obscenities or insults
		Fear of doing something else embarrassing*
		Fear will act on unwanted impulses (e.g., to stab a family member)
		Fear will steal things
		Fear will be responsible for something else terrible happening (e.g., fire, burglary, flood)
		Other (Describe)

C	P	Sexual Obsessions
		[Are you having any sexual thoughts? If yes, are they routine or are they repetitive thoughts that you would rather not have or find disturbing? If yes, are they:]
		Forbidden or perverse sexual thoughts, images, impulses
		Content involves homosexuality*
		Sexual behavior towards others (Aggressive)
		Other (Describe)
		Hoarding/Saving Obsessions
		Fear of losing things
		Other (Describe)
		Magical Thoughts/Superstitious Obsessions
		Lucky/unlucky numbers, colors, words
		Other (Describe)
		Somatic Obsessions
		Excessive concern with illness or disease*
		Excessive concern with body part or aspect of appearance (e.g., dysmorphophobia)*
		Religious Obsessions (Scrupulosity)
		Excessive concern or fear of offending religious objects (God)
		Excessive concern with right/wrong, morality
		Other (Describe)
		Miscellaneous Obsessions
		The need to know or remember
		Fear of saying certain things
		Fear of not saying just the right thing
		Intrusive (non-violent) images
		Intrusive sounds, words, music, or numbers
		Other (Describe)

9

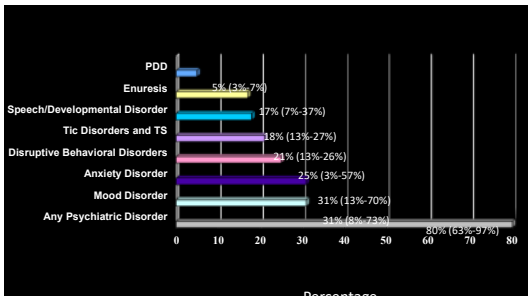
Common Categories of Compulsions in Youth

C	P	Washing/Cleaning Compulsions
		Excessive or ritualized handwashing
		Excessive or ritualized showering, bathing, toothbrushing, grooming, toilet routine
		Excessive cleaning or items; such as personal clothes or important objects
		Other measures to prevent or remove contact with contaminants
		Other (Describe)
		Checking Compulsions
		Checking locks, toys, school books/items, etc.
		Checking associated with getting washed, dressed, or undressed
		Checking that did not/will not harm others
		Checking that did not/will not harm self
		Checking that nothing terrible did/will happen
		Checking that did not make mistake
		Checking tied to somatic obsessions
		Other (Describe)
		Repeating Rituals
		Rereading, erasing, or rewriting
		Need to repeat routine activities (e.g., in/out of doorway, up/down from chair)
		Other (Describe)
		Counting Compulsions
		Objects, certain numbers, words, etc.
		Ordering/Arranging
		Need for symmetry/evening up (e.g., lining items up a certain way or arranging personal items in specific patterns)
		Other (Describe)

C	P	Hoarding/Saving Compulsion
		[distinguish from hobbies and concern with objects of monetary or sentimental value]
		Difficulty throwing things away, saving bits of paper, strings, etc.
		Other (Describe)
		Excessive Games/Superstitious Behaviors
		[distinguish from age appropriate magical games]
		(e.g., array of behavior, such as stepping over certain spots on a floor, touching an object/self certain number of times as a routine game to avoid something bad from happening.)
		Other (Describe)
		Rituals Involving Other Persons
		The need to involve another person (usually a parent) in ritual (e.g., asking a parent to repeatedly answer the same question, making mother perform certain meal time-rituals involving specific utensils).*
		Other (Describe)
		Miscellaneous Compulsions
		Mental rituals (other than checking/counting)
		Need to tell, ask, or confess
		Measures (not checking) to prevent harm to self; harm to others; terrible consequences
		Ritualized eating behaviors*
		Excessive list making*
		Need to touch, tab, rub*
		Need to do things (e.g., touch or arrange) until it feels just right)*
		Rituals involving blinking or staring*
		Trichotillomania (hair pulling)*
		Other self-damaging or self-mutilating behaviors*
		Other (Describe)

10

Comorbid Disorders in Pediatric OCD Review of Clinical Studies



11

Compulsive or Impulsive or Both?

- Kids can be both impulsive and compulsive
- 30% of children and adolescents with OCD satisfy diagnostic criteria for ADHD
- However, ADHD symptoms such as inattention in OCD may be artifacts of intrusive obsessional thoughts or anxiety and not true ADHD at all…
- Do OCD children with concomitant "ADHD-like" features have true ADHD or not?

12

Exclusion Criteria in Pediatric OCD Randomized Drug Trials

	MDD	Bipolar	TD	Psychosis	ADHD	Autism
CMI*	+	+	+	+	+	+
Fluoxetine	+	+	+	+	+	+
Sertraline*	+	+	+	+	+	+
Fluvoxamine	+	+	+	+		
Paroxetine*	+	+	+	+	+	+

*Any predominant psychiatric disorder other than OCD.

(adapted from Geller & Spencer 2004)

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Comorbid OCD and ADHD: Implications

Clinical

- Drug treatments diverge so accurate identification of each syndrome could lead to better outcome
- RCTs do not reflect comorbid cases
- SSRIs may cause behavioral activation
- Stimulants could aggravate anxiety/compulsions

Scientific

- comorbid ADHD may provide a marker of heterogeneity in OCD useful for clarifying the course, outcome and etiology of the disorder
- Comorbid kids may be more at risk for problematic use of the internet

14

Original Research

Does Comorbid Attention-Deficit/Hyperactivity Disorder Impact the Clinical Expression of Pediatric Obsessive-Compulsive Disorder?

by Daniel A. Geller, MBBS, FRACP, Barbara Coffey, MD, Stephen Faraone, PhD, Lisa Hagermoser, BA, Noreen K. Zaman, BA, Colleen L. Farrell, BS, Benjamin Mullin, BA, and Joseph Biederman, MD

ABSTRACT

What is the impact of attention-deficit/hyperactivity disorder (ADHD) on the phenotypic expression of pediatric obsessive-compulsive disorder (OCD). We examined phenotypic features, and functional and clinical correlates in youths with OCD, with and without comorbid ADHD, from a large sample of consecutively referred pediatric psychiatry patients. Although comorbid ADHD had no meaningful impact on the phenotypic expression or clinical correlates of OCD, it was associated with higher rates of compromised educational functioning compared with other OCD youths. Our findings suggest that the OCD phenotype runs true and is not impacted by comorbid ADHD in youths diagnosed with both OCD and ADHD. As such affected youths, both disorders contribute to morbid dysfunction and require treatment. More work is needed to determine whether OCD plus ADHD represents a developmentally and etiologically distinct form of the OCD syndrome.

CNS Spectrums 2003;8(4):259-264

Despite these observations, it has been argued that ADHD symptoms in youth with OCD may represent secondary phenomena to OCD psychopathology; that is, OCD youths may be inattentive and distractible due to interference of obsessional thoughts. However, because ADHD symptoms typically appear several years before the onset of OCD symptoms in childhood OCD cases, the contention that ADHD symptoms are simply an artifact of obsessional ideation is not supported. Rather, since the phenotype of ADHD is not moderated at all by the presence of OCD, these symptoms may represent true ADHD.* This study also documented that children with OCD and comorbid ADHD had more impaired global functioning scores than youths with OCD alone, suggesting that ADHD contributes in an additive fashion to morbid dysfunction in pediatric OCD subjects.

An inverse correlation between age at onset of OCD and the rate of comorbid ADHD has been identified. For exam-

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Methods to Explore OCD±ADHD

- Examine the comorbidity of ADHD and OCD using
  - clinical correlates
  - phenotypic features
  - endophenotypic features (neuropsychology)
  - family genetic patterns
  - course and outcome
- To clarify the association we used several large cohorts of children
  - with ADHD, with and without OCD, and
  - with OCD, with and without ADHD
  - consecutively referred pediatric & psychiatry patients.

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A Family Genetic Study of OCD and ADHD

- Subjects derived from consecutive referrals to specialty pediatric OCD program
- Total N=96
  - OCD+ADHD n=34
  - OCD-ADHD n=62
- All subjects met full DSM-IV criteria for OCD and/or ADHD
- Controls were non-referred siblings of non-ADHD controls in a large concurrent ADHD study

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A Family Genetic Study of OCD and ADHD

- Subjects evaluated using:
  - structured diagnostic interviews w/parent(K-SAD-E)
  - clinical interview w/ subject & parent
  - CY-BOCS and ADHD rating scale w/parent & subject
- Psychosocial functioning assessed w/GAF score
- School functioning assessed by repeated grades, tutoring, special class placement or special ed placement
- OCD & ADHD impairments recorded minimal (1) to severe (3)

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Demographics features of OCD Children with and without ADHD

	OCD without ADHD N=62		OCD with ADHD N=34		
	Mean	SD	Mean	SD	P value §
Current Age	12.3	3.2	12.0	3.1	0.67
SES (1-5) †	1.6	0.7	1.8	0.9	0.42
Age of OCD onset £	8.6	3.3	7.9	2.9	0.32
Age of referral	11.4	3.1	11.4	2.9	0.97
	N	%	N	%	P value §
Male	31	50.0	21	61.8	0.27

† OCD without ADHD N=59
£ OCD without ADHD N=60
§ P-values derived using logistic regression

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Psychiatric Comorbidity in OCD Children with and without ADHD

Anxiety Disorders	OCD without ADHD (N=62) N	%	OCD with ADHD (N=34) N	%	P value *
Panic Disorder	5	8.1	7	20.6	0.049
Social Phobia	6	9.7	5	14.7	0.16
Specific Phobia	14	22.6	8	23.5	0.95
Agoraphobia	19	30.7	9	26.5	0.60
Separation Anxiety	24	38.7	5	14.7	0.018
Disruptive Disorders					
Conduct	1	1.6	0	0.0	0.32ª
Oppositional	23	37.1	17	50.0	0.11

* P values derived using logistic regression, unless otherwise stated
ª P values derived using t-test

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Psychiatric Comorbidity in OCD Children with and without ADHD

Mood Disorders	OCD without ADHD (N=62) N	%	OCD with ADHD (N=34) N	%	P value *
MDD	20	32.3	14	41.2	0.32
Any Bipolar Disorder	7	11.3	6	17.7	0.39
Dysthymia	2	3.2	3	8.8	0.33
Tic Disorders Simple Tic Disorder	3	4.8	3	8.8	0.45
Chronic Motor or Vocal Tic Disorder	7	11.3	2	5.9	0.39
Tourettes Disorder	10	16.1	9	26.5	0.23
Psychosis	2	3.2	2	5.9	0.31

* P values derived using logistic regression

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Symptomatic Impairment in OCD Children with and without ADHD

C-YBOCS Impairment	OCD without ADHD N=60 Mean	SD	OCD with ADHD N=34 Mean	SD	P value Ω
C-YBOCS Total Score	21.1	4.8	21.7	5.6	0.57
C-YBOCS Obsession Subtotal	11.0	2.6	11.4	2.8	0.52
C-YBOCS Compulsion Subtotal	10.1	2.5	10.4	2.8	0.65
C-YBOCS Insight ª§ (rated 0-4)	1.5	0.9	1.7	0.9	0.22

Ω P-values derived using logistic regression
§OCD without ADHD N=59
ª 0=Excellent insight, 1=Much Insight, 2=Moderate Insight, 3=Little Insight, 4=Absent Insight

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Functional Impairment in OCD Children with and without ADHD

	OCD without ADHD N=62 Mean	SD	OCD with ADHD N=34 Mean	SD	P value Ω
OCD Impairment ª	2.4	0.7	2.4	0.6	0.87
¶ADHD Impairment ª	N/A	N/A	2.0	0.7	N/A
†GAF Score ᵇ	50.6	6.6	48.7	4.4	0.15
Educational Indices	N	%	N	%	P valueΩ
Repeated Grade	4	6.5	5	14.7	0.20
Special Class	2	3.2	10	29.4	*0.002*
Extra Help	20	32.3	18	52.9	*0.050*

Ω P-values derived using logistic regression
¶ OCD with ADHD N=32
† OCD without ADHD N=58; OCD with ADHD N=33
ª 1=minimal impairment, 2=moderate impairment, 3=severe impairment
ᵇ Global Assessment of Functioning Scale 0-100

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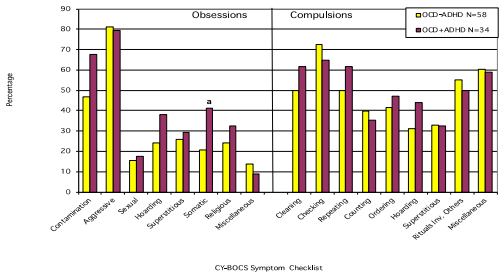
Frequency of Obsessions and Compulsions in OCD Children with and without ADHD



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Clinical Correlates of OCD±ADHD Summary

- OCD+ADHD participants had higher rates of:
  - Special class placement (p=0.002)
  - Extra help in class (p=0.05)
  - Panic Disorder (21% vs. 8%, p=0.049)
  - But not tics or Tourette's
- OCD-ADHD participants had higher rates of:
  - Separation Anxiety Disorder (39% vs. 15%, p=0.018)
- OCD was phenotypically similar with or without ADHD
- ADHD adds to the morbidity & educational burden of OCD in youth with both disorders

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ADHD in Children & Adolescents ± OCD

	ADHD (n=54)		ADHD + OCD (n=67)		Z-Score	P value
	Mean	SD	Mean	SD		
# of Attentional Symptoms	7.7	1.4	7.6	1.8	-0.35	0.73 [a]
# of Hyperactive/ Impulsive Symptoms	5.9	2.8	5.9	2.4	-0.01	1.00 [a]
Total # of ADHD Symptoms	13.6	3.2	13.5	2.9	-0.20	0.85 [a]

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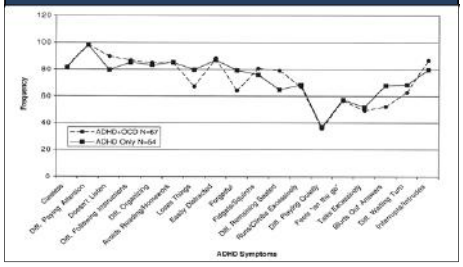
Attention-Deficit/Hyperactivity Disorder in Children and Adolescents With Obsessive-Compulsive Disorder: Fact or Artifact?

Fig. 1 Frequency of ADHD symptoms in ADHD children with and without OCD



Geller et al. (2002)

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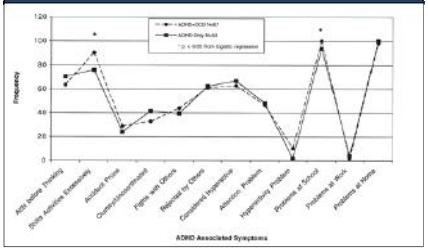
Attention-Deficit/Hyperactivity Disorder in Children and Adolescents With Obsessive-Compulsive Disorder: Fact or Artifact?

Fig. 2 Frequency of associated functional symptoms in ADHD children with and without OCD



Geller et al. (2002)

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Attention-Deficit/Hyperactivity Disorder in Children and Adolescents With Obsessive-Compulsive Disorder: Fact or Artifact?

Table 3: Functional Impairment in ADHD Children With and Without OCD

	ADHD (n = 54)		ADHD+OCD (n = 67)		Z Score	p Value
	Mean	SD	Mean	SD		
ADHD impairment[a]	2.1	0.6	2.1	0.6	0.43	.67[c]
GAF score[b]	51	8.2	47	6.1	−3.06	.002[c]
Educational indices	No.	%	No.	%		
Repeated grade	8	15	15	22	0.96	.34[c]
Special class	16	30	17	25	−0.59	.56[c]
Extra help	38	70	47	70	0.26	.79[c]
Average grades from 2nd–5th grade	No. (n = 39)	%	No. (n = 47)	%		
A/B	15	28	21	31		
B/C	18	33	16	24		
					−0.11	.92[c]
C/D	3	6	7	10		
D/F	3	6	3	4		

Geller et al. (2002)

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ADHD in Children & Adolescents with OCD

	ADHD (n=54)		ADHD + OCD (n=67)		Z-Score	P value
	Mean	SD	Mean	SD		
ADHD Impairment[a]	2.1	0.6	2.1	0.6	0.43	0.67 [c]
GAF Score[b]	51	8.2	47	6.1	-3.06	*0.002*[c]
Educational Indices	N	%	N	%	Z-Score	P value
Repeated Grade	8	15	15	22	0.96	0.34 [c]
Special Class	16	30	17	25	-0.59	0.56 [c]
Extra Help	38	70	47	70	0.26	0.79 [c]

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ADHD in Children & Adolescents ± OCD

- No differences found in:
  - frequency of individual DSM-IV ADHD symptoms
  - mean # of ADHD symptoms
  - frequency of DSM-IV ADHD types
  - frequency of functional symptoms of ADHD
- Interpretation
  - The ADHD phenotype runs true, irrespective of comorbid OCD
  - ADHD is an additive educational burden
  - Children presenting with OCD+ADHD truly have both disorders
  - Youth with both disorders are more globally impaired

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The World Journal of Biological Psychiatry

Neurocognitive function in paediatric obsessive-compulsive disorder

Daniel A. Geller, Amitai Abramovitch, Andrew Mittelman, Abigail Stark, Kesley Ramsey, Allison Cooperman, Lee Baer & S. Evelyn Stewart

Table 1. Demographic and clinical characteristics of the OCD and control groups.

Measure	OCD (N = 102)	Controls (N = 161)	$F(1,261)/\chi^2(1)$	P value
Age M (SD)	11.39 (3.05)	11.61 (3.03)	0.34	0.56
Gender N (% Males)	57 (55.9%)	92 (57.0%)	<0.01	0.98
Estimated IQ M (SD)[a]	110.07 (14.34)	112.18 (13.76)	1.41	0.26
CY-BOCS total score M (SD)	20.88 (5.04)	-	-	-
CY-BOCS obsessions M (SD)	10.91 (2.71)	-	-	-
CY-BOCS compulsions M (SD)	9.88 (2.66)	-	-	-

[a]Estimated IQ (based on WISC Vocabulary test score).
CY-BOCS: Children's Yale-Brown Obsessive Compulsive Scale.

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Group comparison on neuropsychological measures

Table 2. Group comparison on neuropsychological measures.

	OCD M (SD)	Controls M (SD)	OCD N	Controls N	t/z(df)	P value	Cohen's d
Processing speed							
Coding scaled score	9.25 (3.75)	11.66 (2.87)	102	161	34.85 (1, 261)	<0.001	0.72
Symbol Search scaled score	10.23 (3.40)	11.80 (2.90)	102	95	9.65 (1, 166)	0.001	0.50
Visuospatial abilities							
RCFT copy accuracy	61.55 (4.28)	62.52 (7.36)	94	67	1.11 (1, 159)	0.29	0.16
Block Design scaled score	10.76 (3.21)	13.70 (3.27)	102	161	5075 (1, 261)	<0.001	0.91
Working memory							
Digit Span scaled score	10.68 (3.03)	10.39 (3.00)	102	161	0.59 (1, 261)	0.44	0.10
Arithmetic scaled score	11.35 (3.30)	12.58 (2.83)	102	161	13.90 (1, 261)	<0.001	0.46
Non-verbal memory							
RCFT delay accuracy	43.08 (10.64)	46.94 (12.11)	93	68	4.58 (1, 159)	0.03	0.34
Executive functions							
Stroop Word (t score)	46.91 (7.11)	46.98 (7.10)	99	78	.01 (1, 175)	0.94	0.01
Stroop Colour (t score)	43.70 (8.25)	42.23 (7.62)	99	78	1.67 (1, 175)	0.23	0.19
Stroop Colour-Word (t score)	45.20 (8.51)	45.87 (9.61)	99	77	.24 (1, 174)	0.63	0.07
Stroop Interference (t score)	48.78 (6.36)	50.51 (7.27)	99	77	2.82 (1, 174)	0.09	0.25
WCST Categories completed	4.88 (1.69)	5.00 (1.56)	64	62	.19 (1, 124)	0.67	0.07
WCST Percent perseverative errors	14.44 (9.75)	14.00 (8.71)	63	62	.09 (1, 123)	0.77	0.05
WCST Trials to complete 1st category	24.93 (27.48)	18.66 (20.60)	64	62	1.62 (1, 124)	0.20	0.23
WCST Failure to maintain set	.98 (1.15)	1.29 (1.27)	64	62	2.01 (1, 124)	0.16	0.26
RCFT Copy organisation score	8.27 (3.47)	8.93 (3.79)	95	68	1.30 (1, 161)	0.26	0.18
RCFT Delayed organisation score	6.57 (3.70)	8.04 (3.92)	94	68	5.81 (1, 160)	0.02	0.38

OCD: obsessive-compulsive disorder; RCFT: Rey complex figure test; WCST: Wisconsin Card Sorting Test.

Geller et al 2017

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The World Journal of Biological Psychiatry

Neurocognitive function in paediatric obsessive-compulsive disorder

Daniel A. Geller, Amitai Abramovitch, Andrew Mittelman, Abigail Stark, Kesley Ramsey, Allison Cooperman, Lee Baer & S. Evelyn Stewart

Results:

Compared to controls, youth with OCD exhibited

- underperformance on tasks assessing processing speed.
- On tests of VSA and WM, underperformance was found only on timed tasks.
- There were no differences on NVM and EF tasks. Notably, the OCD group's standardized scores were in the normative range.
- Test performance was not associated with any demographic or clinical variables.
- Comorbid MDD, Anxiety, ADHD and Tics/Tourette's did not moderate the test scores

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JOURNAL of CHILD PSYCHOLOGY and PSYCHIATRY

Research Review: Neuropsychological test performance in pediatric obsessive–compulsive disorder – a meta-analysis

Amitai Abramovitch,[1,2,3] Jonathan S. Abramowitz,[4] Andrew Mittelman,[2] Abigail Stark,[2] Kesley Ramsey,[2] and Daniel A. Geller[1,2]
[1]Department of Psychiatry, Harvard Medical School, Boston, MA; [2]Department of Psychiatry, Massachusetts General Hospital, Boston, MA; [3]Department of Psychology, Texas State University, San Marcos, TX; [4]Department of Psychology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

J Child Psychol Psychiatr 2015; 56(8): 837–47

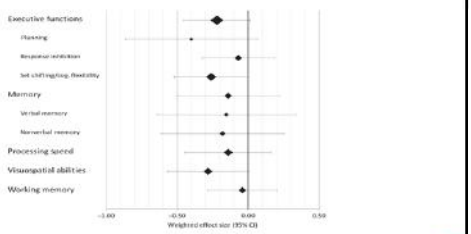

Figure 2 Forest plot of major domains and sub domains' weighted effect sizes and corresponding 95% confidence intervals. 'Diamond' sizes correspond to sample size. Negative effect sizes indicate that patients with OCD underperformed control groups.

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Heritability of OCD

Heritability of Early Onset OCD = 45% - 65%

Heritability of Adult Onset OCD = 27% - 47%

Heritability for Obsessions = 33%

Heritability for Compulsions = 26%

Family studies find 24-28% risk for OCD in relatives of pediatric OCD probands (Nestadt et al., 2000; Hanna et al., 2005; Do Rosario-Campos et al., 2005)

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Age-Corrected Risk of OCD, TS, tics & ADHD in Relatives of Youth with OCD

Subthreshold or Full OCD: Lifetime	Age-corrected rate (SE) in relatives of cases
OCD	26.3% (2.7%)
Tourette's Syndrome	1.7% (0.8%)
Chronic Tics	7.5% (1.5%)
Tourette's OR Chronic Tics	8.9% (1.6%)
ADHD	17.5% (2.1)

(Geller et al 2004)

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Competing Hypotheses of Familial Transmission

- If ADHD is secondary to OCD
  - Expect no familial transmission of ADHD in the families of OCD probands *with or without ADHD*.
- If ADHD and pediatric OCD share common underlying genetic risk
  - Expect familial transmission of both ADHD *and* OCD at similarly elevated rates in first-degree relatives of probands with *either* ADHD *or* OCD compared with controls.
- If ADHD and OCD are distinct conditions with independent transmission
  - Expect equally high rates of OCD in first-degree relatives of probands with OCD with or without ADHD,
  - Prevalence of ADHD should be elevated *only* in the relatives of probands with OCD *and* ADHD
  - When occurring together, ADHD and pediatric OCD may represent a distinct familial subtype as evidenced by co-segregation and nonrandom mating between parents.

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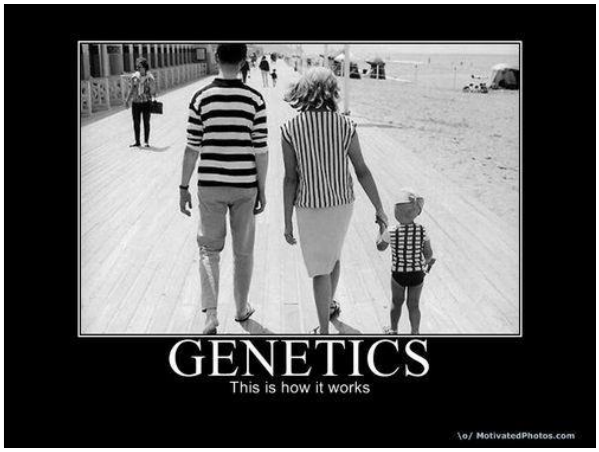

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Clinical Features of Relatives of Controls, ADHD-OCD and ADHD+OCD Probands

	Proband Diagnosis						P value
	Control (N=716)		ADHD without OCD (N=791)		ADHD with OCD (N=33)		
Gender*	N	%	N	%	N	%	
Male	360	50.3	412	52.1	16	48.5	0.39
Onset** (y)	Mean	SD	Mean	SD	Mean	SD	
ADHD	3.9	2.9	3.5	2.7	2.2	2.4	0.14
OCD	11.0	2.6	15.3	8.3	7.2	10.6	0.60
Impairment***	Mean	SD	Mean	SD	Mean		
ADD past	1.9	0.7	2.2	0.7	2.5	0.5	0.06
OCD past	2.0	1.0	1.9	0.7	2.2	1.0	0.79
ADD current	1.6	0.6	1.9	0.6	2.3	0.6	0.06
OCD current	1.0	0.0	1.8	0.4	1.8	0.5	0.66
GAF**	Mean	SD	Mean	SD	Mean		
Past	63.8	10.8	58.2 [a]	12.0	54.2 [ab]	8.8	<0.001
Current	71.0	7.5	67.2 [a]	9.5	63.5 [ab]	9.7	<0.001

Logistic Regression, ** Linear Regression, ***Ordinal Logistic Regression
[a] p≤ 0.001 compared to control group
[b] p≤ 0.05 compared to ADHD without group

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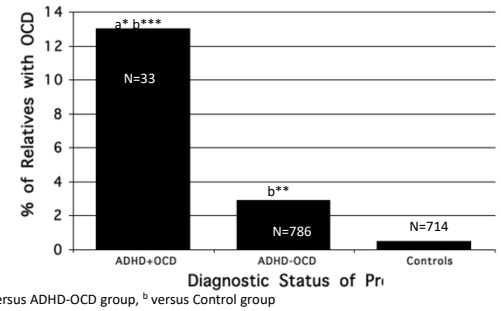
Figure 2. Kaplan-Meier estimates of obsessive-compulsive disorder (OCD) among first-degree relatives of ADHD probands with and without OCD and control probands with neither disorder.



[a] versus ADHD-OCD group, [b] versus Control group
* p≤0.05, ** p≤0.01, ***p≤0.001

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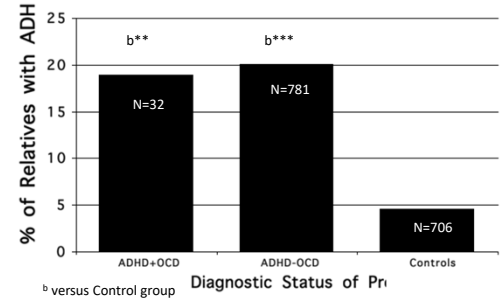
Figure 1. Kaplan-Meier estimates of attention-deficit/hyperactivity disorder (ADHD) among first-degree relatives of ADHD probands with and without OCD and control probands with neither disorder.



[b] versus Control group
**p<0.01, ***p≤0.001

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Examining the Relationship Between Obsessive-Compulsive Disorder and Attention-Deficit/Hyperactivity Disorder in Children and Adolescents: A Familial Risk Analysis

Daniel Geller, Carter Petty, Fe Vivas, Jessica Johnson, David Pauls, and Joseph Biederman

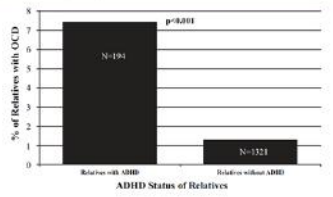

Figure 3. Kaplan-Meier estimates of obsessive-compulsive disorder (OCD) among relatives with and without attention-deficit/hyperactivity disorder (ADHD).

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Pharmacotherapy of OCD

Serotonergic medications are effective in short, medium and long term treatment*

NNT ~ 3. Mean improvement on CY-BOCS is 6 points over placebo

Multimodal treatment (CBT plus medication) is recommended if CBT fails to achieve clinical response after several months and for more severe cases should be considered the "default" treatment

* (Apter et al., 1994; Como and Kurlan, 1991; DeVeaugh-Geiss et al., 1992; Flament et al., 1985; Geller et al., 1995; Leonard et al., 1989; Leonard et al., 1991; Liebowitz et al., 1990; Riddle et al., 1996; Riddle et al., 1992; Riddle et al., 1990b, Thomsen 1997, Scahill et al 1997, March et al 1998, Rosenberg 1999, Riddle et al 2001, Geller et al 2001a,b,c, Geller et al 2002)

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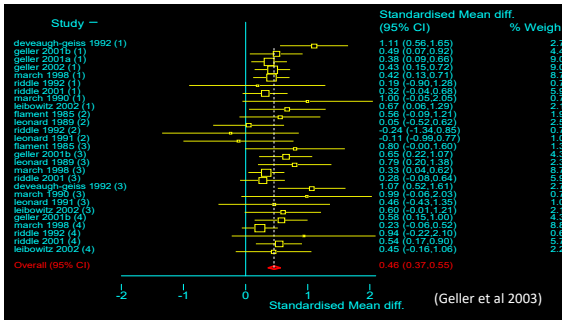
Meta-analysis of Pediatric OCD Trials



(Geller et al 2003)

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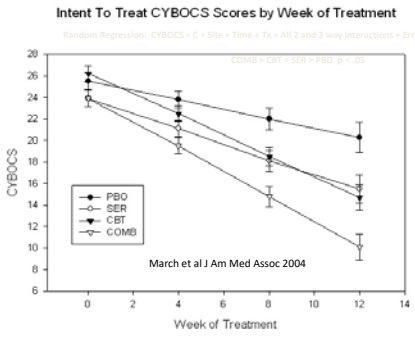
The Pediatric OCD Treatment Study (POTS)



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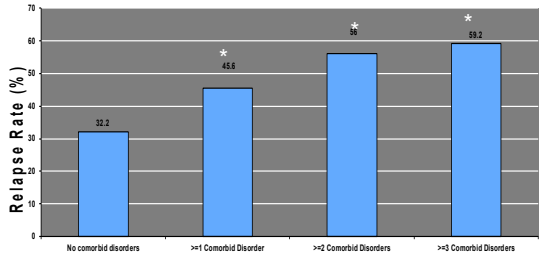
Relapse Rate (%) By Number of Comorbid Psychiatric Disorders - All Patients

Paroxetine in Pediatric OCD



(Geller et al. 2003)

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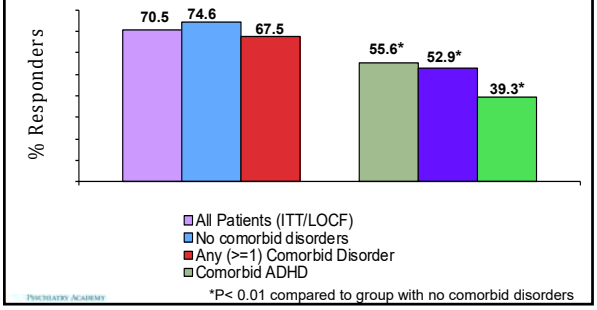
Proportion (%) of CGI Responders To Paroxetine Treatment by Psychiatric Comorbidity

(Geller et al. 2003)



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SSRI's and Suicidality

FDA black box warnings for all antidepressants but *no* suicides occurred in any of the pediatric OCD RCTs of SSRIs

Bridge et al. (2007) *found no statistically increased risk of suicidal thinking or behavior* in the pooled pediatric OCD trials

Pooled absolute rate of suicidal ideation/attempt in OCD trials:

SSRI 1% (4/362) (95%CI 0-2%),Placebo 0.3% (1/339) (95%CI -0.3-1%), pooled risk difference 0.7% (95%CI -1%-2%, p=.57 NNH = 143-200)(Bridge et al 2007)

It remains unknown as to whether comorbid ADHD alters the risk of SSRIs in youth with OCD

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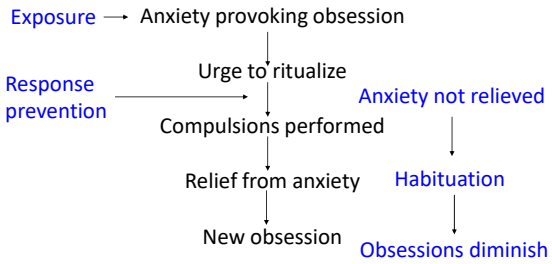
CBT: Exposure & Response Prevention (ERP)

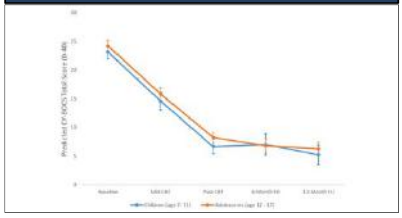


50

Nordic Long-Term OCD Treatment Study

One-Year Outcomes for Responders of Cognitive-Behavioral Therapy for Pediatric Obsessive-Compulsive Disorder

Figure 2 Estimated CY-BOCS total scores in children and adolescents who responded to acute CBT, by age group with 95% CI



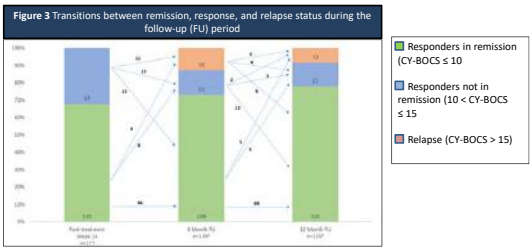
Højgaard et al. (2017)

51

Nordic Long-Term OCD Treatment Study

One-Year Outcomes for Responders of Cognitive-Behavioral Therapy for Pediatric Obsessive-Compulsive Disorder

Figure 3 Transitions between remission, response, and relapse status during the follow-up (FU) period

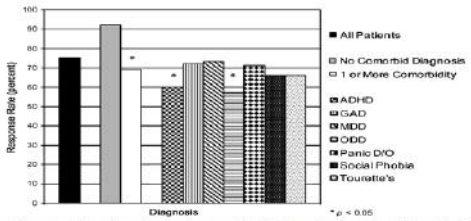


Højgaard et al. (2017)

52

Impact of Comorbidity on Cognitive-Behavioral Therapy Response in Pediatric Obsessive-Compulsive Disorder

ERIC A. STORCH, PH.D., LISA J. MERLO, PH.D., MICHAEL J. LARSON, M.S., GARY R. GEFFKEN, PH.D., HEATHER D. LEHMKUHL, PH.D., MARNI L. JACOB, B.S., TANYA K. MURPHY, M.D., AND WAYNE K. GOODMAN, M.D.



Storch et al 2008

53

Compulsion vs Addiction?

- OCD
  - Fear conditioning and anxiety drives compulsion CAN BECOME HABITUAL
  - Insight generally maintained NOT ALWAYS
  - Ego-dystonic NOT ALWAYS
  - Internal resistance RESISTANCE CAN VARY
  - Anxiety relief from rituals reinforces repetition CAN BE GRATIFYING
  - Treatment involves fear extinction learning IF COMPLIANT
- Addiction (IAD)
  - gratification drives repetitive behavior NOT ALWAYS
  - dopaminergic nucleus accumbens mediated
  - Denial prominent NOT ALWAYS
  - Ego-syntonic NOT ALWAYS
  - No internal resistance NOT ALWAYS
  - Treatment involves cognitive and motivational intervention and externally managed behavioral approaches MAY RESPOND TO MEDS

54

Health risks of online gaming: Fortnite

Displaces important daily activities
- school and homework
- chores
- socializing in person
- family time
- adequate sleep
- physical activity
- junk food diet
- lack of exercise
- obesity
- postural pain syndromes in cervical or lumbar spine ("gamer slouch")
- repetitive stress injury

45 million players
Rated T for teens, violent content
Fast action with visual effects
Highly accessible to all formats/consoles
Limitless choices inspire creativity
groups of 2-4 provide limited socialization
Random treasure introduces gambling
Social status with increased competency

55

Health risks of online gaming in youth

Boys are more susceptible
ADHD and Autism spectrum are risk factors
Consequences for mental health include
mood disorders (depression)
social anxiety
online bullying
school failure
social withdrawal

BUT bidirectional influence
Are OCD + ADHD youth more at risk?

Increased risk for aggressive ideation or behavior in susceptible youth

From top: Red Dead Redemption 2, Call of Duty, Black Ops 4

56

Non gaming Problematic Internet Use

- Social media (girls more susceptible)
  - cyberbullying
  - sexting
  - sexual predators
- Online pornography
- Online gambling
- Netflix bingeing
- Workaholism
- Internet shopping
- Identity theft
- Phishing/fraud
- Influencing elections..!

57

Conclusions

- When you see ADHD with OCD both conditions are present and real
- Both need treatment
- Affected youth have additive functional and educational burdens
- They are harder to treat with meds and CBT
- Treat anxiety/OCD first as a general rule
- May be at increased risk for AEs and PUI
- Good luck!

58

My spouse/partner and I have the following relevant financial relationships with commercial interests to disclose:

For Janet Wozniak MD

Research support: PCORI
Author: "Is Your Child Bipolar" published May 2008, Bantam Books.

Spouse royalties: UpToDate
Spouse consultation fees: Advance Medical, FlexPharma, Merck
Spouse research support: UCB Pharma, NeuroMetrix, Luitpold, NIMH, RLS Foundation

1

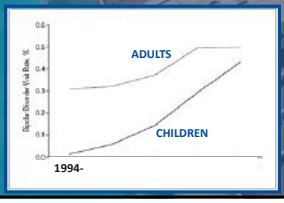
Pediatric bipolar disorder occurs (and co-occurs with ADHD)

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

Joseph Biederman MD, Harvard Medical School
Cesar Soutullo MD PhD, University of Navarra
Kathleen Merikangas PhD, NIMH

MASSACHUSETTS GENERAL HOSPITAL

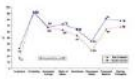
Rising Rates of Pediatric Bipolar Disorder



2

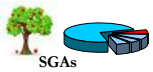
Overview: Pediatric Bipolar disorder is a highly morbid, valid condition that affects a significant minority of young children and is often comorbid with ADHD

Scope: Pediatric Bipolar Disorder is now in the differential diagnosis for moody children



Diagnostic description: Pediatric bipolar disorder can be reliably diagnosed and is often mixed and irritable and comorbid with ADHD

Persistence, Familiability, Treatment: Pediatric onset of bipolar disorder is familial, persists over time and responds to mood stabilizers



Biomarkers: We have progress towards objective identification with rating scale and biomarkers

3

Bipolar disorder is now considered in the differential diagnosis of youngsters with mood symptoms

MGH clinical studies using structured interview diagnoses (KSADS) led a paradigm shift

Consecutively referred children ≤ 12 years:

76% ADHD

1991-1995 16% Bipolar Disorder (N=262)
1995-2002 17% Bipolar Disorder (N=768)

Wozniak, 1995; Biederman, 2004

4

The symptoms of mania are the same in children and adults with presentations appropriate to developmental stage

A. A *distinct period* of abnormally and persistently elevated, expansive or irritable mood and persistently increased goal-directed activity or energy

B. At least 3/7 (4/7 if mood is irritable)

1) D Distractibility
2) I Increased activity/psychomotor agitation
3) G Grandiosity or inflated self-esteem
4) F Flight of ideas or racing thoughts
5) A Activities with painful consequences
6) S Sleep decreased
7) T Talkative or pressured speech

Diagnostic and Statistical Manual (DSM-5)

5

What we learned about children with mania:

- IRRITABLE: • The major mood disorder chief complaint of the parents was severe irritability (rather than euphoria)
- MIXED: • The children had mostly mixed states (mania and depression overlapped in time)
- CHRONIC: • The children were seldom well due to mixed states, many cycles and comorbidity (chronicity)

Wozniak, 1995; Biederman, 2004

6

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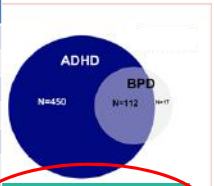
- MIXED: • The children had mostly mixed states (mania and depression overlapped in time)
- CHRONIC: • The children were seldom well due to mixed states, many cycles and comorbidity (chronicity)
- ADHD: • Almost all of them had ADHD (especially when the onset of mania was prior to age 12)

Wozniak, 1995; Biederman, 2004

7

Despite a substantial bi-directional overlap, bipolar disorder is a different more impairing condition from ADHD alone

	MANIA	ADHD
Depression	**86%**	38%
Psychosis	**16%**	0
Defiance (ODD)	**88%**	48%
Conduct Disorder	**37%**	15%
Anxiety	**56%**	26%
Hospitalization	21%	2%
Functioning	Very poor	fair
Learning Disability	42%	14%



Most young children with bipolar disorder also have comorbid ADHD

Wozniak, 1995; Biederman, 2004

8

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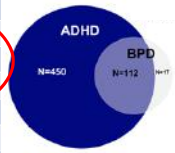

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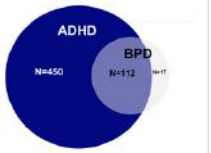


Most children with bipolar disorder also have comorbid ADHD

Wozniak, 1995; Biederman, 2004

10

Pediatric bipolar disorder often co-occurs and overlaps with ADHD, but requires mood symptoms to diagnose

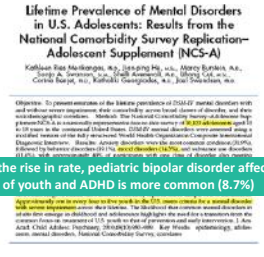
There are overlapping symptoms between ADHD and BPD

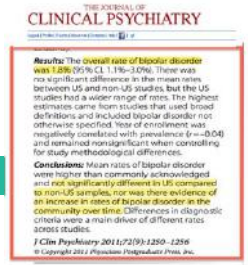
- Distractibility: very severe in bipolar disorder
- Hyperactivity: vs. increased energy/activity in bipolar disorder
- Talkativeness: vs. pressured speech in bipolar disorder
- Bipolar disorder requires severe **mood symptoms**: euphoria/irritability/melancholy

Biederman JAACAP 1996

11

In study of 10,000+ US adolescents, 2.9% were bipolar and in a meta-analysis of international studies, the rate of pediatric bipolar disorder was 1.8%


Lifetime Prevalence of Mental Disorders in U.S. Adolescents: Results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A)


JOURNAL OF CLINICAL PSYCHIATRY

Despite the rise in rate, pediatric bipolar disorder affects a minority of youth and ADHD is more common (8.7%)

Merikangas 2010: Van Meter J Clin Psych 2011

12

DSM-5 Workgroup Rationale: "reduce the number of bipolar diagnoses" DMDD is "common, transient, difficult to distinguish from ODD and CD

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, MSW; Jessica C. Hauser-Harrington, PhD; Judith Depew; Shawn M. Kennedy, MA; Brittany A. Gron, BS; Brieana M. Rowles, MA; and Boris Birmaher, MD

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

- **Temper outbursts ≥3 per week**
- **Persistently irritable mood**
- 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

Exclusionary:
Euphoria for 1+ day with 3/7 B criteria
During MDD episode
History of (hypo)mania

Axelson JClinPsych 2012

13

A framework for the validation of psychiatric disorders can be applied to pediatric bipolar disorder

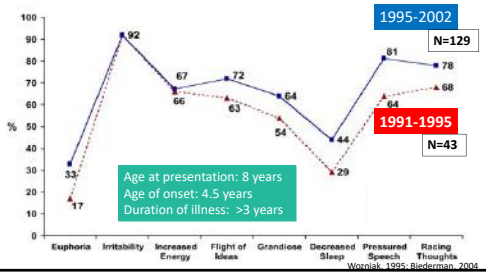
Establishment of Diagnostic Validity in Psychiatric Illness: Its Application to Schizophrenia

1. *Unique Clinical characteristics*
2. *Familiality*
3. *Course (persistence)*
4. *Unique Pharmacological Responsivity*
5. *Laboratory Studies*

Robins & Guze, Am J Psych 1970

14

The symptoms of mania are the same in two cohorts of pre-adolescent age (<12 years) youth with bipolar disorder



Wozniak, 1995; Biederman, 2004

15

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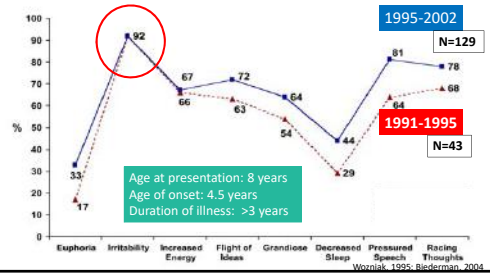
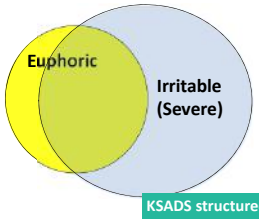


Wozniak, 1995; Biederman, 2004

16

Irritability lasting "7 days or longer most of the day most every day" is more common than euphoria in BPD Youth



KSADS structured interview data

Wozniak, 1995; Biederman, 2004

17

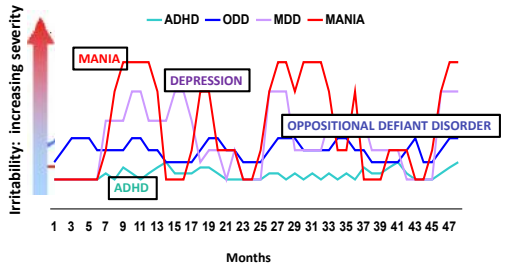
The type of irritability observed in manic children is very severe, persistent and often violent

- Outbursts often include threatening or attacking behavior towards others: kicking, hitting, biting, spitting, swearing, disrespectful, wild, out of control, destructive **explosions**
- Outbursts are frequent often daily and long lasting, 30-60+ minutes

Biederman JAACAP 1996; 35(8): 997-1008

18

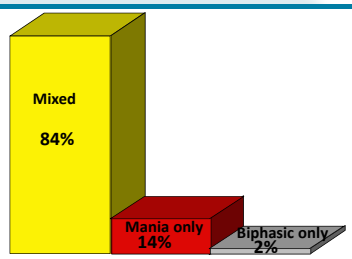
All forms of irritability are not the same but can co-exist and overlap, creating a 'never well' condition



Mick 2007

19

Mixed presentations are common



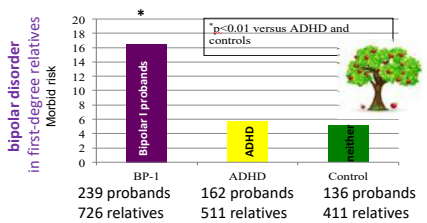
Wozniak, 1995; Biederman, 2004

20

Pediatric bipolar disorder familial, a feature of a valid diagnosis

Familial risk of bipolar I disorder is greatest in first-degree relatives of pediatric BP-I probands versus ADHD and control probands

Pediatric probands with subthreshold bipolar disorder have rates of familiality similar to full syndrome probands

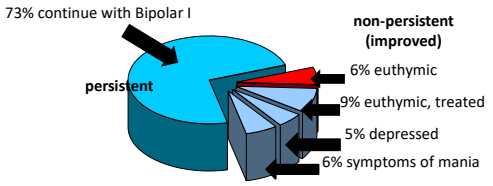


Wozniak J Clin Psych 2012

21

Pediatric bipolar disorder is highly persistent in our 4-year MGH longitudinal study and few improved without treatment

N=78, Baseline age 10 years, 76% male, Age of onset 5 years



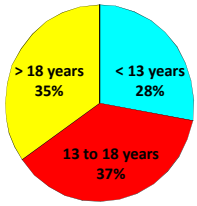
Consistent with studies by Geller (WashU) and Birmaher (COBY)

Wozniak JPsychiatrRes 2011; Geller ArchGenPsychiatry 2008; Birmaher AmJPsychiatry 2009

22

Most bipolar adults in STEP-BD (N=983) reported onset in childhood or adolescence demonstrating continuity

Age of onset of bipolar disorder for bipolar adults



9.5% lifetime prevalence comorbid ADHD

BPD+ADHD Adult patients:

- had earlier onset BPD by 5 years
- had shorter periods of wellness (chronic)
- had more comorbidity (anxiety and substance)
- were more likely to be male
- were more likely to have Bipolar I
- had more days irritable and more days elated
- had lower GAF
- more suicide attempts
- more violence
- more legal problems (conduct disorder)

Perlis Biol Psych 2004; Nierenberg 2005

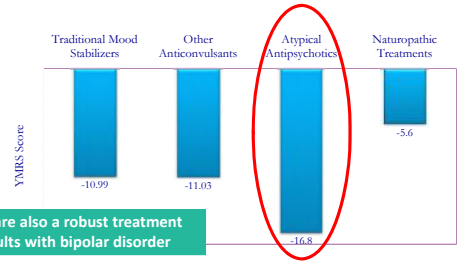
23

There are many FDA Approved Treatments for Children and Adolescents with Emotional Dysregulation

- Lithium: manic or mixed states, patients aged 13-17 years
- Risperidone: manic or mixed states, age 10-17 years
- Aripiprazole: manic or mixed states, age 10-17 years
- Olanzapine: manic or mixed states, age 13-17 years
- Quetiapine: monotherapy or adjunct to lithium or divalproex sodium, manic states, age 10-17 years
- Saphris manic or mixed episodes in BPD I, age 10-17
- Lurasidone: bipolar depression, age 10-17
- Fluoxetine: depression and OCD age 8+
- Escitalopram: depression age 12+
- Sertraline,fluvoxamine, anfranil: pediatric OCD
- Aripiprazole: irritability associated with autistic disorder ages 6-17
- Risperidone: irritability associated with autism ages 5-16

24

The mean decrease in YMRS in pediatric studies is much greater for the SGAs than for other agents



SGAs are also a robust treatment for adults with bipolar disorder

Liu JAACAP 2011; Perlis J Clin Psychiatry 2006

25

The result of omega-3s for bipolar disorder in children is about 50% what we see with SGAs, but without the side effects. NAC also promising.

Omega-3 fatty acid monotherapy for pediatric bipolar disorder: A prospective open-label trial

One of the concerns about increasing the diagnosis of bipolar disorder is that it will lead to exposure to medications with unknown effects on the developing brain

Advancing natural treatments for pediatric bipolar disorder may encourage earlier diagnosis.....and agents with minimal effect on the adult brain might play a major role in the developing brain

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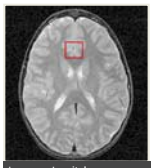
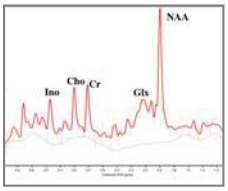
Unique Markers/ Biomarkers external to clinician diagnosis?

27

Proton Spectrum acquired from the anterior cingulate cortex of a child with bipolar disorder





Ino: myo-Inositol
Cho: choline
Cr: creatine
Glx: glutamate and glutamine
NAA: N-acetyl aspartate

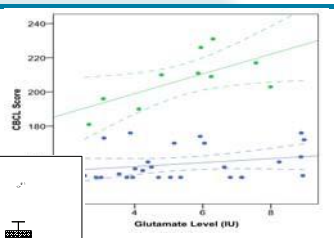
Moore Am J Psychiatry 2006

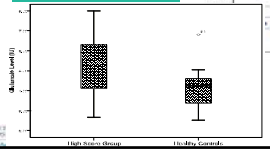
28

Elevated glutamate in the anterior cingulate cortex

Glutamatergic dysregulation in the ACC may represent a useful biomarker of emotional dysregulation in youth worthy of further investigation

The CBCL is a useful tool for providing a continuous measure of emotional dysregulation for correlation with biomarkers

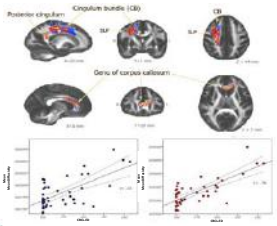




Wozniak 2011

29

Increased Mean and Axial Diffusivity Surrounding the Cingulum Bundle



- Track-Based Spatial Statistics (TBSS) using voxelwise analysis showed a significant positive correlation between the CBCL-ED score and median diffusivity (MD; $p < 0.05$) and axial diffusivity (AD; $p < .05$,) overlapping in cingulum bundle areas, the genu of the corpus callosum, and the superior longitudinal fasciculus (SLF).
- Findings indicate that greater severity the emotional dysregulation as indexed through the CBCL-ED profile is associated with more impaired matter abnormalities in the cingulum bundle areas as indexed through mean diffusivity and axial diffusivity values.

Uchida 2018

30

BPD with early age of onset shows genetic covariation with ADHD, suggesting different genetic mechanisms in early and later onset BPD

Archival Report

Genetic Overlap Between Attention-Deficit/ Hyperactivity Disorder and Bipolar Disorder: Evidence From Genome-wide Association Study Meta-analysis

Kimm J.E. van Hulzen, Claus J. Scholz, Barbara Franke, Stephan Ripke, Marieke Klein, Andrew McQuillin, Edmund J. Sonuga-Barke, PGC ADHD Working Group, John R. Kelsoe, Mikael Landén, Ole A. Andreassen, PGC Bipolar Disorder Working Group, Klaus-Peter Lesch, Heike Weber, Stephen V. Faraone, Alejandro Arias Vasquez, and Andreas Reif

BACKGROUND: Attention-deficit/hyperactivity disorder (ADHD) and bipolar disorder (BPD) are highly heritable mental health conditions. We hypothesized that BPD cases with an early age of onset (≤21 years old) would be particularly likely to show genetic covariation with ADHD.

METHODS: Genome-wide association study data were available for 4609 individuals with ADHD, 9650 individuals with BPD (5167 thereof with early-onset BPD), and 21,360 typically developing controls. We conducted a cross-disorder genome-wide association study meta-analysis to identify whether the observed comorbidity between ADHD and BPD could be due to shared genetic risks.

CONCLUSIONS: The single nucleotide polymorphism–based genetic correlation between ADHD and BPD is substantial, significant, and consistent with the existence of genetic overlap between ADHD and BPD, with potential differential genetic mechanisms involved in early and later BPD onset.

We say 'bipolar' but mean many different things. Age of onset is one source of the variance

Van Hulzen Biol Psychiatry 2017

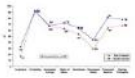
www.mphome.org

31

What questions would you like to ask?

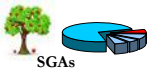
Overview: Pediatric Bipolar disorder is a highly morbid, valid condition that affects a significant minority of young children and is often comorbid with ADHD

Scope: Pediatric Bipolar Disorder is now in the differential diagnosis for moody children



Diagnostic description: Pediatric bipolar disorder can be reliably diagnosed and is often mixed and irritable and comorbid with ADHD

Persistence, Familiality, Treatment: Pediatric onset of bipolar disorder is familial, persists over time and responds to mood stabilizers



SGAs

Biomarkers: We have progress towards objective identification with biomarkers

www.mphome.org

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Comorbidity with ADHD and course in a Spanish sample of children & adolescents with Bipolar disorder

César Soutullo MD, PhD;
María Ribeiro, MD; Karol Machiñena RN,
Azucena Díez-Suárez, MD, PhD.
Child & Adolescent Psychiatry Unit, University of Navarra, Spain

CUN-Madrid
2017-

CUN-Pamplona
1962-

APSARD Meeting, Washington, DC, 17-20 Jan 2019
Bipolar disorder as it relates to ADHD.
Wozniak J, Biederman J, Merikangas K

1

Cesar A. Soutullo, MD, PhD
Disclosure (4 years: 2015 - Jan 2019)

Fulltime contract: University of Navarra, Associate Professor

Active
Past

Source	Consultant Advisory Board	Royalties (Books)	Stock >$10,000 €	Research (Departament)	Speaker (Education)	This talk
Lilly 2000-2015	X			X	X	
Shire 2005-	X			X	X	
Lundbeck 2016- (Vortioxetine MDD)	X			X		
NeuroTech Solutions 2016-	X					
Medice Group 2009-	X				X	
Janssen 2018- (Esketamine)				X		
TEVA 2019- (Deutetrabenazine Tourette)				X		
Fundación CAN 2014-2016				X		
F. A. Koplowitz 2003-2016	X			X	X	
Ministry Health (ESP) 2008-2015	X					
Ed. Médica Panamericana 2004-	X	X				
Mayo Eds 2014-		X				

2

Thanks

APSARD Scientific Committee

Drs. Janet Wozniak and Joseph Biederman
MGH, Boston, MA

Azucena Díez-Suárez MD PhD

María Ribeiro MD
PhD Candidate

Karol Machiñena RN

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Outline

Comorbidity with ADHD and course in a Spanish sample of children & adolescents with Bipolar disorder

Introduction: Controversy vs. Data on Pediatric Bipolar disorder

University of Navarra Sample of Children & Adolescents with Bipolar Disorder (2000-2018)

4

Received: 5 April 2017 | Accepted: 14 August 2017
DOI: 10.1111/bdi.12556

TASK FORCE PAPERS

WILEY BIPOLAR DISORDERS

The International Society for Bipolar Disorders Task Force report on pediatric bipolar disorder: Knowledge to date and directions for future research

Benjamin I Goldstein[1,2] | Boris Birmaher[3] | Gabrielle A Carlson[4] | Melissa P DelBello[5] | Robert L Findling[6] | Mary Fristad[7] | Robert A Kowatch[7] | David J Miklowitz[8] | Fabiano G Nery[5] | Guillermo Perez-Algorta[9] | Anna Van Meter[10] | Cristian P Zeni[11] | Christoph U Correll[12,13] | Hyo-Won Kim[14] | Janet Wozniak[15] | Kiki D Chang[16] | Manon Hillegers[17] | Eric A Youngstrom[18]

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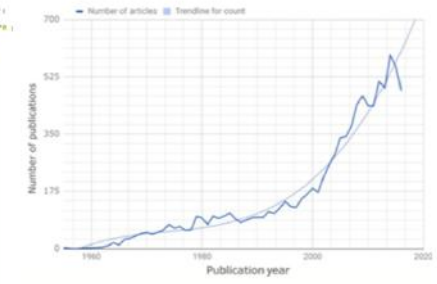

FIGURE 1 Articles about pediatric bipolar disorder indexed in PubMed each year. Search terms were ("bipolar disorder" or mania or manic) and (child or adole* or pediatric or juvenile) [Colour figure can be viewed at wileyonlinelibrary.com]

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Source of Discussion on Pediatric Bipolar Disorder. Adapted from Goldstein et al., 2017

International Soc. Bipolar Disorder Task Force on Pediatric Bipolar Disorder

- Does it exist?: Epidemiology: 1.8% (1.1-3.0) Van Meter, 2011
  - ¿Overdiagnosis?: DSM-5: DMDM
- Diagnostic Criteria (DSM?)
  - Type of symptoms
    - Grandiosity, Elation a MUST?, vs. Irritability or Elation (DSM), increased activity/energy
  - Duration of episodes:
    - Episodic vs. Cronic course.
      - Chronic irritability without other episodic symptoms is not mania
  - Leibenluft´s Narrow, Intermediate or Broad Phenotype 7

(Leibenluft et al., Defining clinical phenotypes of juvenile mania. Am J Psychiatry 2003)

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Language clarification

- Pediatric bipolar disorder, juvenile BD.
  - Usually refers to BP in <18, not just in children (0 to 12)
- Elation/Euphoria – Mania – Bipolar
  - Sometimes used as if they were interchangable
  - Elation (or Irritability) is NOT enough to diagnose BP, you need other symptoms
- ICD vs. DSM definitions of BP.
  - ICD-11 definition is now similar to DSM-5,
  - only 1 episode of mania required (no Depression required).

8

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Irritability

Birmaher, Godstein, Axelson & Pavuluri. Lewis´s Child and adolescent Psychiatry . Martin, Bloch & Volkmar, 2018

- "Low threshold for experiencing anger in response to negative emotional events"
  - Lower threshold
  - Faster increase of anger
  - Higher "peak"
  - Longer duration
- Present in nearly all children & adolescents with mania (sensitive marker), BUT also present in ODD-CD, MDD, GAD, PTSD, ASD (low specificity)
- Only 10% of BP youth had irritability or elation alone

(Hunt…/Birmaher et al, 2009, 2013)

9

9

EPIDEMIOLOGY

10

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J Clin Psychiatry 2011;72(9):1250-1256

The article you requested is

Meta-Analysis of Epidemiologic Studies of Pediatric Bipolar Disorder

Anna R. Van Meter, MA; Ana Lúcia R. Moreira, MD; and Eric A. Youngstrom, PhD

1.8% (95% CI: 1.1% - 3.0%)

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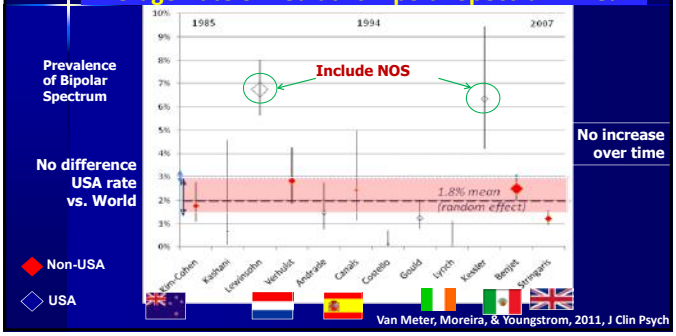
Slide: Eric Youngstrom

Meta-Analysis of Epidemiologic Studies of Pediatric Bipolar Disorder

Anna R. Van Meter, MA; Ana Lúcia R. Moreira, MD; and Eric A. Youngstrom, PhD

Average Rate of Pediatric Bipolar Spectrum: 1.8%



Van Meter, Moreira, & Youngstrom, 2011, J Clin Psych

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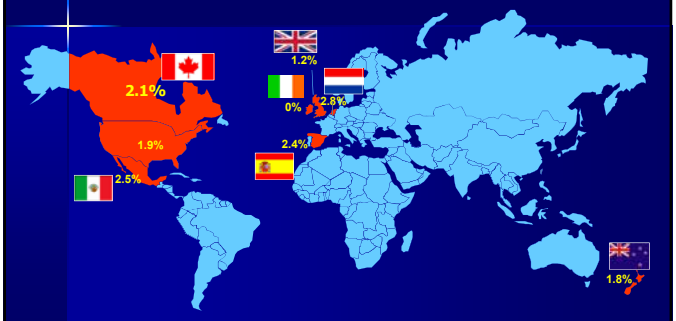
Slide: Eric Youngstrom

USA not driving increase of PBD-1



Van Meter, Moreira, & Youngstrom, 2011, May

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PHENOMENOLOGY
CLINICAL CHARACTERISTICS
EARLY DETECTION

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BIPOLAR DISORDERS

Bipolar Disorders 2016: 18: 19–32

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Published by John Wiley & Sons Ltd
BIPOLAR DISORDERS

Original Article

Ten-year updated meta-analysis of the clinical characteristics of pediatric mania and hypomania

Anna R Van Meter[a], Coty Burke[b], Robert A Kowatch[c], Robert L Findling[d] and Eric A Youngstrom[b]

Van Meter AR, Burke C, Kowatch RA, Findling RL, Youngstrom EA. Ten-year updated meta-analysis of the clinical characteristics of pediatric mania and hypomania. Bipolar Disord 2016; 18: 19–32. © 2016 John Wiley & Sons A/S.

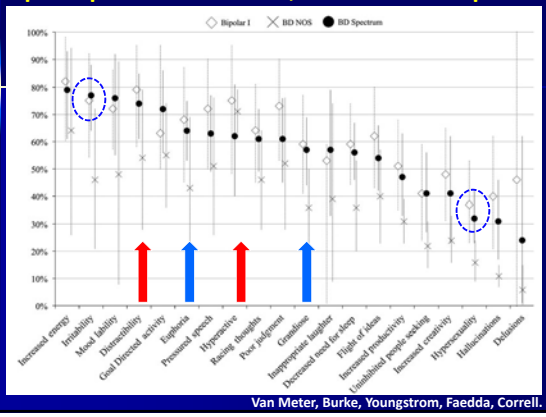
N=20 Studies
2,226 youths

15

Van Meter et al., 2016

15

Symptom prevalence in BD-I, BD-NOS & BD-Spectrum



Van Meter, Burke, Youngstrom, Faedda, Correll. 2016

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Van Meter, Burke, Youngstrom, Faedda, Correll. 2016

REVIEW

The Bipolar Prodrome: Meta-Analysis of Symptom Prevalence Prior to Initial or Recurrent Mood Episodes

Anna R. Van Meter, PhD, Coty Burke, BA, Eric A. Youngstrom, PhD, Gianni L. Faedda, MD, Christoph U. Correll, MD

N=11 studies
1,078 patients

Objective: The aim of this study was to meta-analyze the prevalence of symptoms before an initial mood episode of bipolar disorder (BD) and the prevalence of subthreshold symptoms before a BD mood episode recurrence, to facilitate early identification and prevention.

Method: Systematic literature reviews were conducted in PsycINFO and PubMed for prospective or retrospective

Prevalence & duration of symptoms before initial or recurrent BD episode

individuals, and study quality moderated the overall prevalence.

Results: In 11 studies (n = 1,078), the prodrome preced-

Prodrome 27.1 ± 23.1 months (4.6-130)

Subthreshold 1.0 ± 0.9 months (0.5-1.3)

The most common symptoms were largely consistent with diagnostic criteria symptoms associated with the subsequent mood polarity for both the initial prodrome and the period prior to a recurrent mood episode. Few moderators of symptom prevalences emerged, and significant heterogeneity remained.

Conclusion: The initial prodromal period is sufficiently long and characterized by symptoms of the subsequent mood episode to make early identification and intervention programs feasible. Conversely, the period of subthreshold symptoms before a recurrent mood episode is short, mandating adequate psychoeducation of patients and families, monitoring of changes in sleep and activity, plus sufficiently frequent follow-up visits to identify patients before a mood episode recurrence. Future prospective investigations, designed to address the identified shortcomings in the extant literature, are needed to identify more clinically applicable information.

Key words: bipolar disorder, prodrome, subthreshold, first episode, early identification

J Am Acad Child Adolesc Psychiatry 2016;55(7):543–555.

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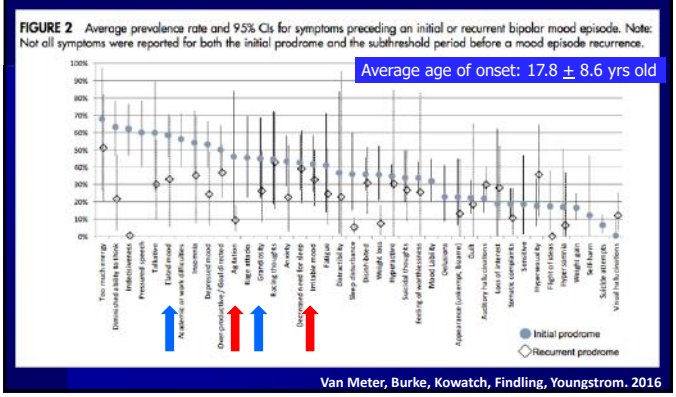
Prevalence of Symptoms in BD Prodromes



Average age of onset: 17.8 ± 8.6 yrs old

Van Meter, Burke, Kowatch, Findling, Youngstrom. 2016

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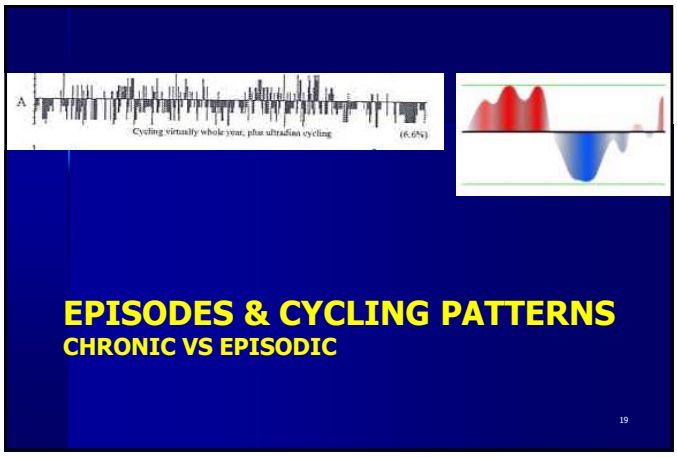

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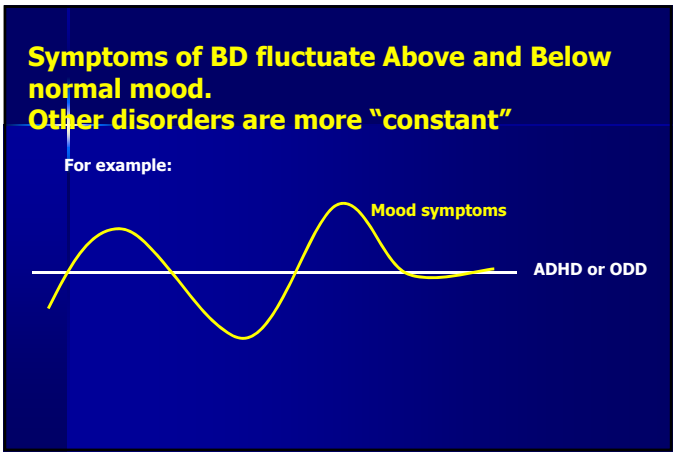

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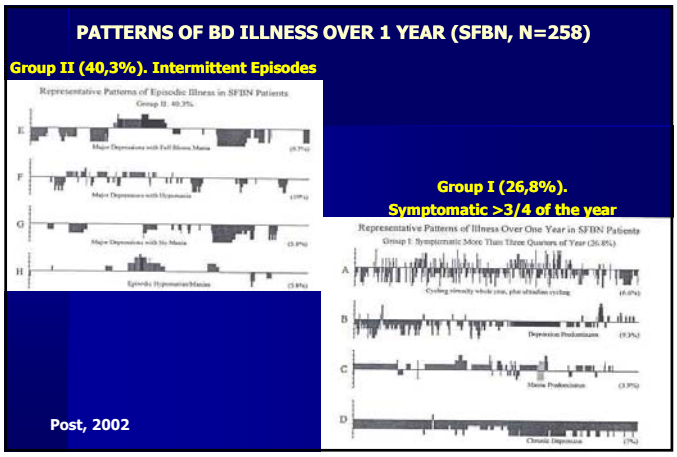

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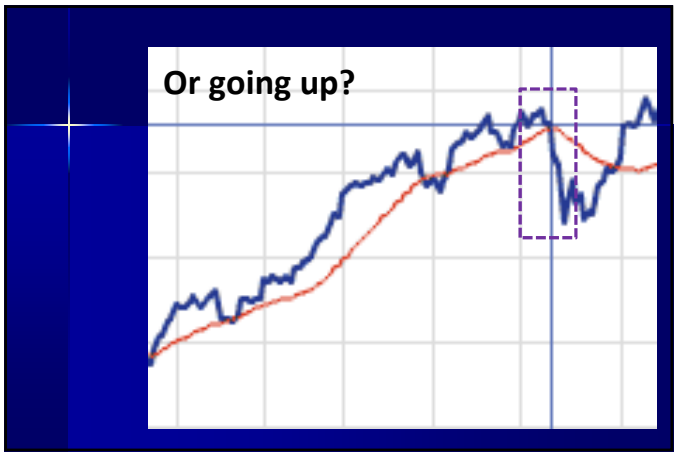

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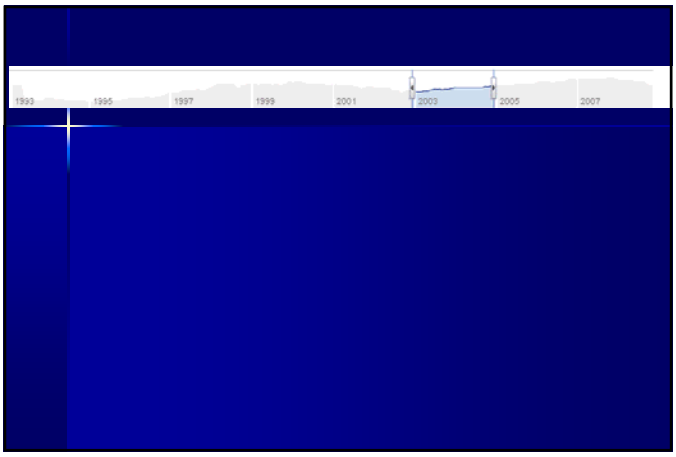

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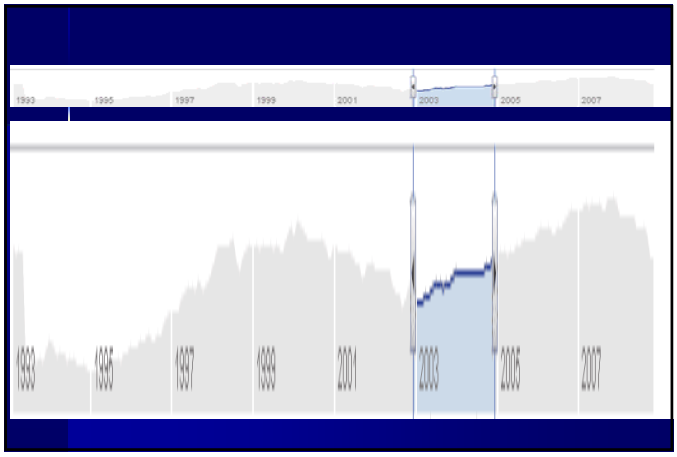

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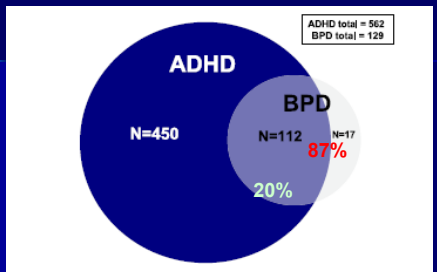
87% of BPD had TDAH
20% of ADHD had BPD



87% (112 of 129) of the BPD children met criteria for ADHD;
20% (112 of 562) of ADHD children met criteria for BPD.

Fig. 1. Diagnostic overlap of BDP and ADHD (2nd cohort).

J. Biederman et al. / Journal of Affective Disorders 82S (2004) S45–S58

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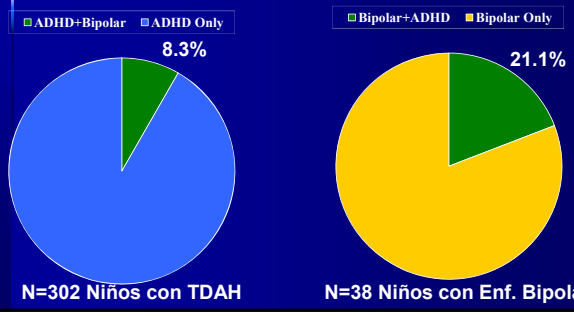
Comorbilidad: BP en niños con TDAH y TDAH en niños con BP

Child & Adolescent Psychiatry Unit, University of Navarra, Spain.
Soutullo et al., 2005 Bipolar Disorders



N=302 Niños con TDAH

N=38 Niños con Enf. Bipolar

32

Comorbidity in BP

Joshi & Willems, 2009. Child Adolesc Psychiatric Clin N Am 18 (2009) 291–319

Adapted from: **Biederman J, Petty C, Faraone SV, et al.** Moderating effects of major depression on patterns of comorbidity in referred adults with panic disorder: a controlled study. Psychiatry Res 2004

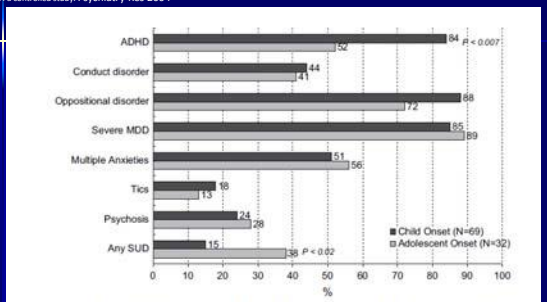


Fig. 1. Rates of psychiatric comorbidity in bipolar youth stratified by age at onset of BPD. (*Adapted from* Biederman J, Petty C, Faraone SV, et al. Moderating effects of major depression on patterns of comorbidity in referred adults with panic disorder: a controlled study. Psychiatry Res 2004;126:143.)

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Pediatric bipolar disorder in a Spanish sample: Features before and at the time of diagnosis

Cesar A. Soutullo [a,*], Inmaculada Escamilla-Canales [b], Janet Wozniak [c], Pilar Gamazo-Garrán [b], Ana Figueroa-Quintana [a], Joseph Biederman [c]

N=38

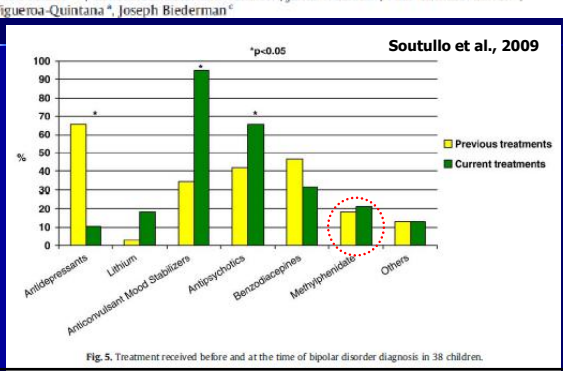

Fig. 5. Treatment received before and at the time of bipolar disorder diagnosis in 38 children.

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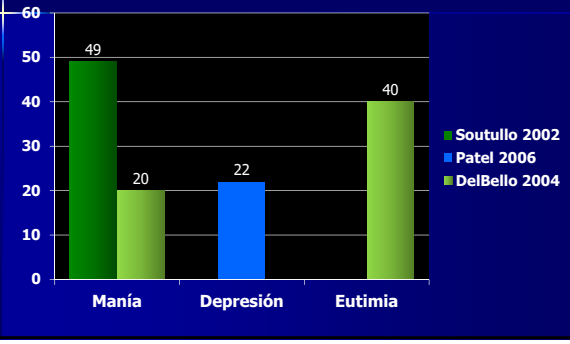
% Tasa de Comorbilidad con TDAH según polaridad del episodio



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JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume 10, Number 3, 2000
Mary Ann Liebert, Inc.
Pp. 157–164

Diagnostic Characteristics of 93 Cases of a Prepubertal and Early Adolescent Bipolar Disorder Phenotype by Gender, Puberty and Comorbid Attention Deficit Hyperactivity Disorder

BARBARA GELLER, M.D., BETSY ZIMERMAN, M.A., MARLENE WILLIAMS, R.N., KRISTINE BOLHOFNER, B.S., JAMES L. CRANEY, M.S., M.P.H., MELISSA P. DELBELLO, M.D., and CESAR A. SOUTULLO, M.D.

Geller et al, 2000

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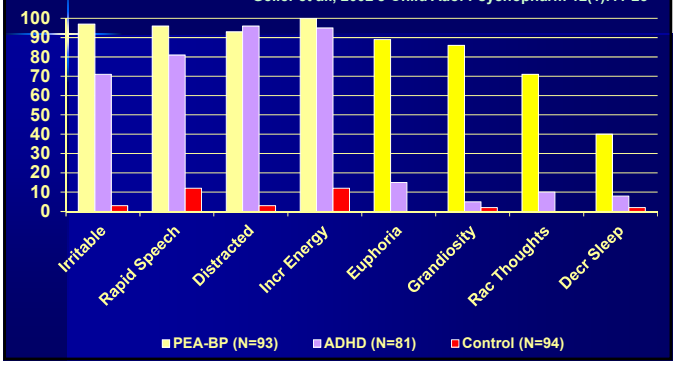
DSM-IV MANIA-SPECIFIC & NON-SPECIFIC SYMPTOMS

in 93 PEA-BP, 81 ADHD & 94 Controls

Washington University in St.Louis

Geller et al., 2002 J Child Adol Psychopharm 12(1):11-25



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Reliability of the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) Mania and Rapid Cycling Sections

BARBARA GELLER, M.D., BETSY ZIMERMAN, M.A., MARLENE WILLIAMS, R.N., KRISTINE BOLHOFNER, B.S., JAMES L. CRANEY, M.PH., MELISSA P. DELBELLO, M.D., AND CESAR SOUTULLO, M.D.

J. AM. ACAD. CHILD ADOLESC. PSYCHIATRY, 40:4, APRIL 2001

38

Bipolaridad Pediátrica y TDAH

Singh, DelBello et al., 2006 Bipolar Bisorders;8:710-720

- **3. Factores asociados al TDAH (Tratamiento con Estimulantes) induce BP**
- Estimulantes mejoran BP
  (Clower, 1998; Carlson et al., 2000; Biederman et al., 2004)
- Estimulantes empeoran BP
  (Koehler-Troy et al., 1986; Clower, 1998; DelBello et al., 2001; Soutullo et al., 2002)
- Usar estimulantes pero PRIMERO estabilizar humor (Findling et al., 2003; Biederman et al., 2004)

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Bipolaridad Pediátrica y TDAH

Singh, DelBello et al., 2006 Bipolar Bisorders;8:710-720

- **4. TDAH y BP comparten etiología biológica**
- Transmisión familiar. TDAH+BP pueden ser otra enfermedad (Faraone et al., 1997; 1998)
- Genética
  - TDAH: DAT1 & DRD4
  - BP: hSERT, MAOA
- Hallazgos de Neuroimagen

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Clínica Universidad de Navarra

University of Navarra Sample: Children & Adolescents with Bipolar Disorder

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Clínica Universidad de Navarra

Method

- Chart Review, Retrospective & Prospective
- Included all patients (<18 yr old) with DSM-IV BP
- Univ. of Navarra Child & Adolesc Psychiatry Unit
- Semistructured interview based on DSM-IV & K-SADS-PL template
- Originally 1999-2005 (N=38) (Soutullo 2009; Escamilla 2011)
  - Updated original sample (1999-2012)
- Included more patients (2005 to 2014)
  - LOCF, Preliminary results

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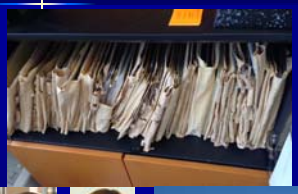
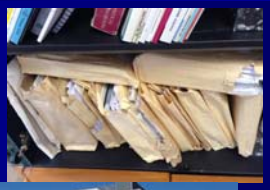
Method: Highly Sophisticated Technology





Dra. Azucena Díez-Suárez

Dra. María Ribeiro

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Clínica Universidad de Navarra

Objective

- Phenomenology, Clinical Characteristics of Bipolar disorder in Children & Adolescents
- Comorbidity
- Longitudinal course of BP (including BP-NOS)
  - Diagnostic Stability
  - Treatment Response

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Journal of Affective Disorders

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

Soutullo, Escamilla, Wozniak, et al., 2009, J Affective Disord

Research report

Pediatric bipolar disorder in a Spanish sample: Features before and at the time of diagnosis

Cesar A. Soutullo[a,*], Inmaculada Escamilla-Canales[b], Janet Wozniak[c], Pilar Gamazo-Garrán[b], Ana Figueroa-Quintana[a], Joseph Biederman[c]

Baseline & Before Diagnosis

N=38

Follow-up

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Escamilla, Wozniak, Soutullo, et al., 2011, J Affective Disord

Brief report

Pediatric bipolar disorder in a Spanish sample: Results after 2.6 years of follow-up

Inmaculada Escamilla[a,*], Janet Wozniak[b], Cesar A. Soutullo[c], Pilar Gamazo-Garrán[a], Ana Figueroa-Quintana[d], Joseph Biederman[b]

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Journal of Affective Disorders 242 (2019) 224–233

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Phenomenology and diagnostic stability of paediatric bipolar disorder in a Spanish sample

María Ribeiro-Fernández[a,b,c], Azucena Díez-Suárez[a,c,*], César Soutullo[b,c]

Ribeiro-Fernández M, Díez-Suárez A, Soutullo C, 2019 Jan J Affect Disord

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Clínica Universidad de Navarra

Sample Characteristics

(Median IQR p25p75)

- N=72 (38+34) Children and Adolescents
- 76.1% Males
- Median Age of 1st symptoms: 10.5 (6.5 – 13.7)
- Media Age of 1st consultation: 13.6 (9.6 – 15.6)
- Median Age of Diagnosis of BD: 14.5 (10.5-16.0)
- Follow up: 3.86 (1.8 – 5.9 years) (prior sample 2.6)

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Clínica Universidad de Navarra

Clinical Characteristics

Comorbidity with ADHD and course in a Spanish sample of children & adolescents with Bipolar disorder

Type of Bipolar Disorder

Diagnostic Stability: 3,9 yrs Follow-up

Rate of Psychosis, ADHD & Hospitalization

48

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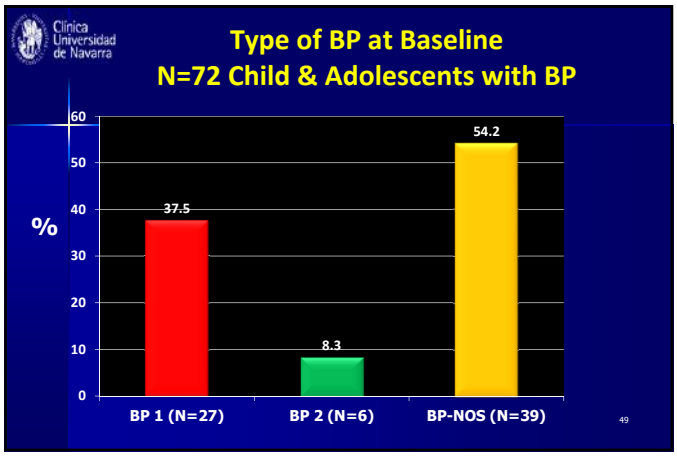

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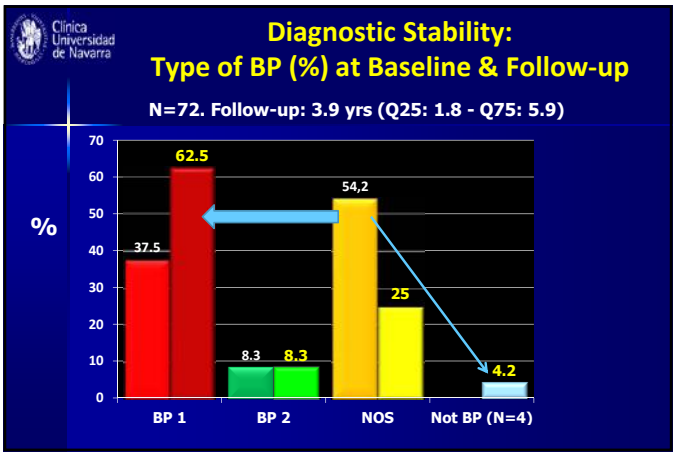

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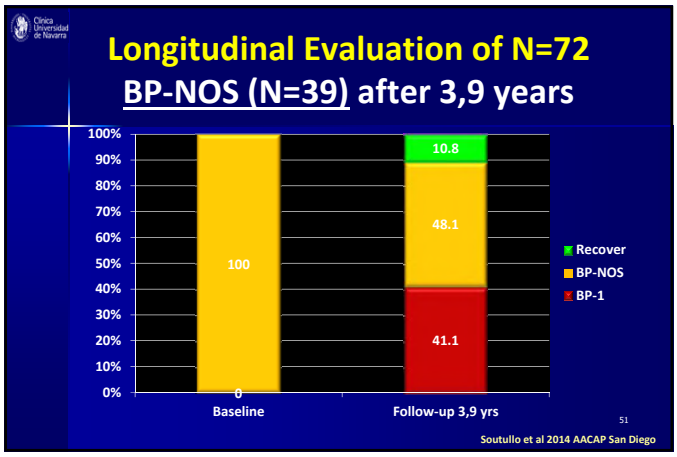

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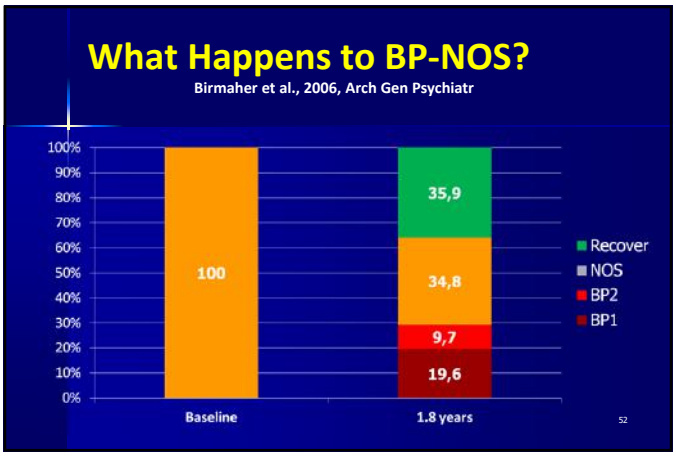

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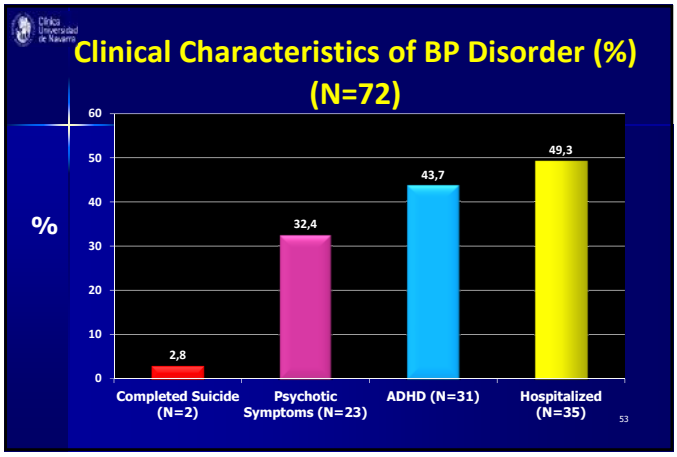

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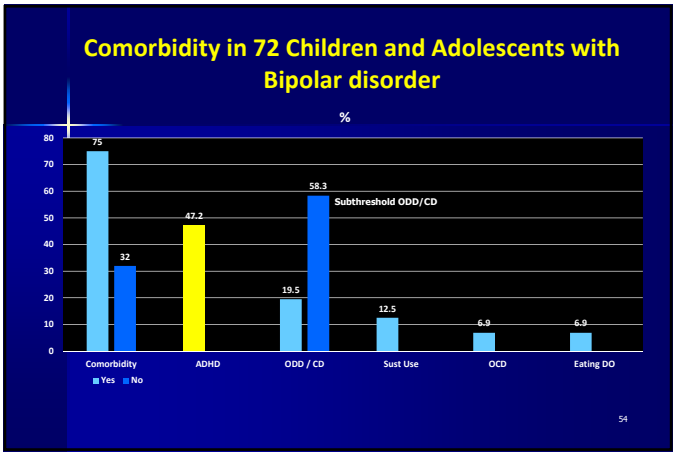

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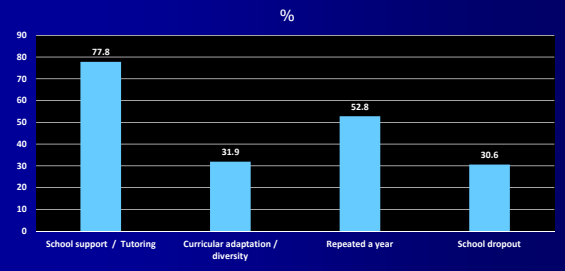
Academic characteristics of 72 children & adolescents with Bipolar disorder



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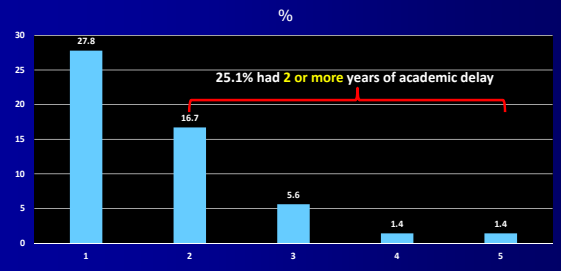
Years of Academic delay in 72 children & adolescents with Bipolar disorder

52% of Sample repeated at leats ONE year



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PHENOMENOLOGY

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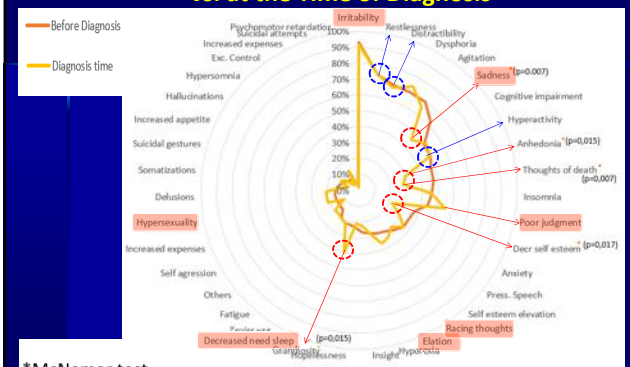
57

Frequency (%) of Symptoms Before Diagnosis (prodromal?) vs. at the Time of Diagnosis

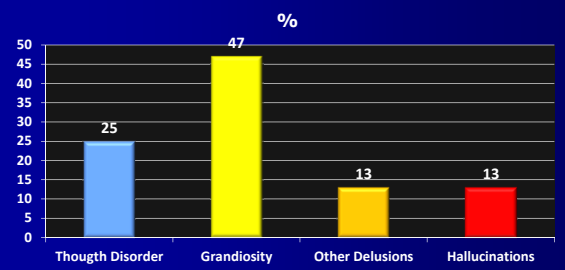


*McNemar test

Soutullo et al 2018 IACAPAP Prague

58

Type of Psychotic Symptom in Children & Adolescents with Bipolar Disorder (N=23, 32.4%, from a Total of 72)



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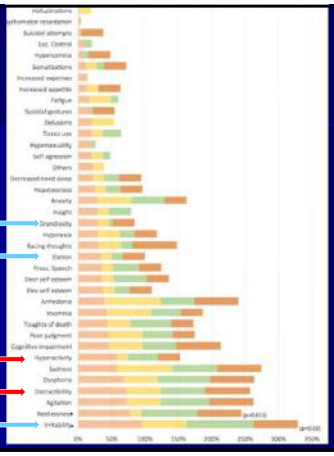
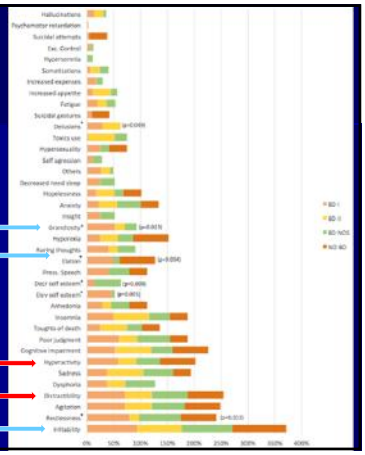
% Prodromal symptoms by Final diagnosis (N=72) (Sx prior to diagnosis)

BD-I
BD-II
BD-NOS
No BD



60

% Baseline symptoms by Final diagnosis (N=72) (Sx at the time of diagnosis)



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Agenda

Course and diagnostic stability in a Spanish sample of children & adolescents with Bipolar disorder

Treatment: Outcome & Response

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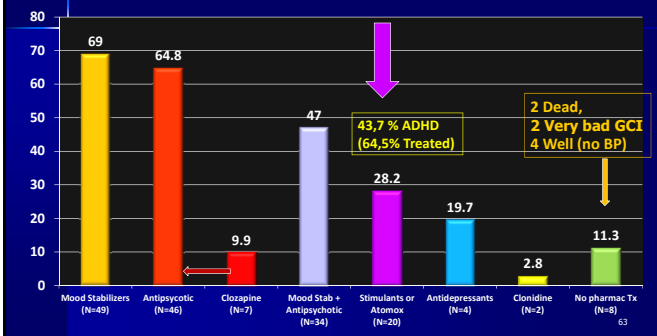
Treatment of Bipolar Disorder (%)

N=72 Children & Adolesc, 3.9 Yrs Follow-up



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CGI-Severity

1	Normal, not at all ill
2	Borderline mentally ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most severely ill subjects

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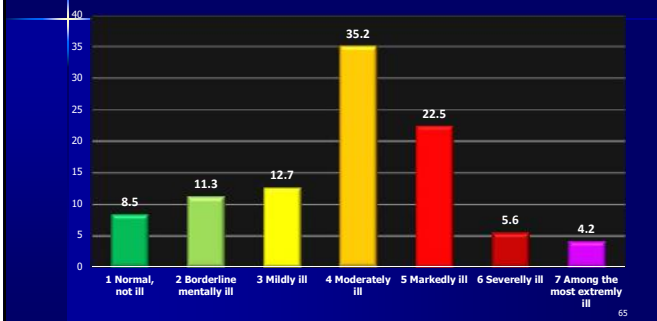
Outcome: CGI-Severity

Total Sample (N=72), After 3.9 yrs of Follow-up



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Soutullo, Díez & Ribeiro 2014 AACAP San Diego, USA

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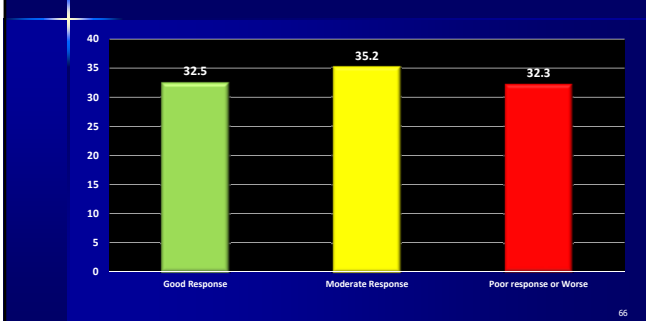
Outcome: Response

Total Sample (N=72), After 3.9 yrs of Follow-up



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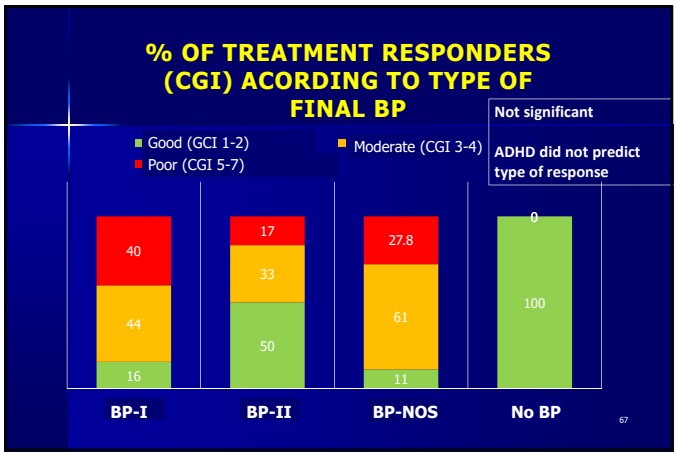
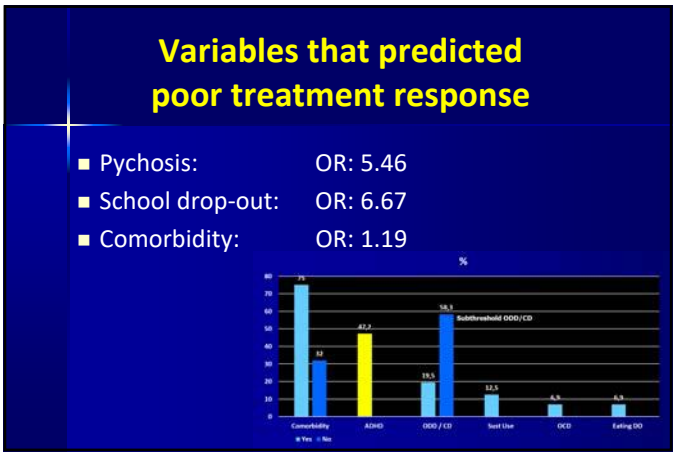
Soutullo, Díez & Ribeiro 2014 AACAP San Diego, USA

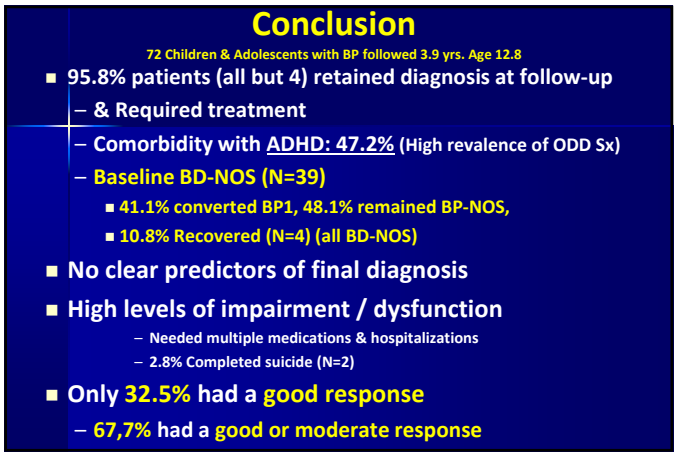
66


% OF TREATMENT RESPONDERS (CGI) ACORDING TO TYPE OF FINAL BP
Good (GCI 1-2)
Poor (CGI 5-7)
Moderate (CGI 3-4)
Not significant
ADHD did not predict type of response
40
44
16
17
33
50
27.8
61
11
0
100
BP-I
BP-II
BP-NOS
No BP
67

67


Variables that predicted poor treatment response
Pychosis: OR: 5.46
School drop-out: OR: 6.67
Comorbidity: OR: 1.19
%
Subthreshold ODD/CD
Comorbidity
ADHD
ODD / CD
Sust Use
OCD
Eating DD

68


Conclusion
72 Children & Adolescents with BP followed 3.9 yrs. Age 12.8
95.8% patients (all but 4) retained diagnosis at follow-up
– & Required treatment
– Comorbidity with ADHD: 47.2% (High revalence of ODD Sx)
– Baseline BD-NOS (N=39)
41.1% converted BP1, 48.1% remained BP-NOS,
10.8% Recovered (N=4) (all BD-NOS)
No clear predictors of final diagnosis
High levels of impairment / dysfunction
– Needed multiple medications & hospitalizations
– 2.8% Completed suicide (N=2)
Only 32.5% had a good response
– 67,7% had a good or moderate response

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Gracias!!
María Ribeiro MD PhD Candidate
P. Pries Psicóloga
C. Maestro Psicóloga
Karol Machiñena
Azucena Díez
Cesar Soutullo
Arancha Díez
María Vallejo
Maite Lasheras
Pilar de Castro
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APSARD
The American Professional Society of ADHD and Related Disorders

Comorbidity and co-aggregation of mood disorders and ADHD

Kathleen Ries Merikangas, Ph.D.
Senior Investigator
Intramural Research Program

1

Disclosure

- This work was supported by the National Institute of Mental Health Intramural Research Program.
- The views and opinions expressed in this article are those of the authors and should not be construed to represent the views of any of the U.S. Government.

2

Aims

- To describe patterns of comorbidity of mood disorder subtypes and ADHD in a community based family study
- To examine whether there are familial associations between ADHD and mood disorder subtypes
- To identify core domains that may underlie mania and mood disorders

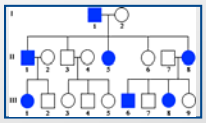
3

3

Approaches

General Population

Extended Families



Biobehavioral Measures

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Bipolar Disorder: Current DSM Conceptualization

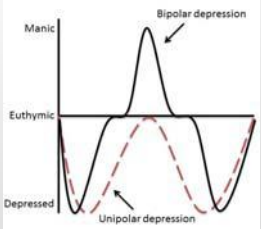
Severe Mania

Hypomania (mild to moderate mania)

Normal / balanced mood

Mild to moderate depression

Severe depression



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5

Explanations for Comorbidity: Family Studies

Common Risk Factors

Mania Depression

Mania

Depression

Probands Relatives

Common etiology

Mania Mania

MDD MDD

Causal association

6

6

Independence of Familial Transmission of Mania and Depression

Molecular Psychiatry (2013), 1–3

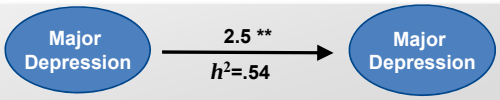
www.nature.com/mp

NEWS AND COMMENTARY

Independence of Mania and Depression

Evidence for separate inheritance of mania and depression challenges current concepts of bipolar mood disorder

IB Hickie



Merikangas et al, Molecular Psychiatry, 2014

7

7

Sample & Methods: NIMH Family Study

Aims:

- ✓ Core components, patterns of comorbidity, and biobehavioral markers associated with BPD to identify more homogenous groups and etiologic processes

Methods:

- ✓ Household screening of local area
- ✓ Enrichment of mood disorders (Dr. Zarate Branch)
- ✓ Collaborative with Lausanne Family Study (M. Preisig)
- ✓ Sample size = 525+ Adult Probands (150 Bipolar; 200 Major Depression; 150 Other/Controls)
- ✓ Relatives: N=1100 directly interviewed; N=2800 Fam Hx; 400 evaluated at NIH Clinical Center

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Measures: NIMH Family Study

- ✓ Phenomenologic diagnostic interview validated against the SCID
- ✓ Assessment of both mental and physical disorders
- ✓ Development of diagnostic tools for sleep patterns/ disorders and for headache syndromes
- ✓ Biologic measures in families (subset = 400)
- ✓ Mobile technologies to track activity and daily events

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Sample: N and Characteristics of Probands and Relatives with ADHD by Mood Disorder Subgroups

		Bipolar I	Bipolar II	Major Depression	Anxiety	Other/ Control
Probands Sex	% male	31.6	35.2	22.9	19.6	52.7
Age	mean	43.7	48.1	49.3	50.8	51.7
Relatives Sex	% male	35.8	33.8	39.4	42.6	37.2
Age	mean	35.8	33.8	39.4	42.6	37.2

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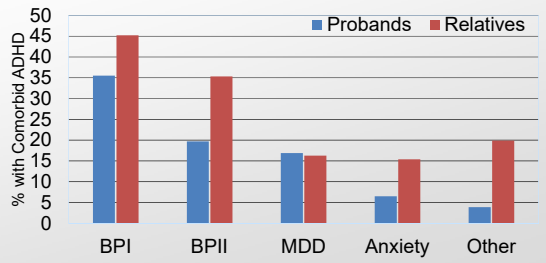
Rates of ADHD by Mood Disorder Subgroups



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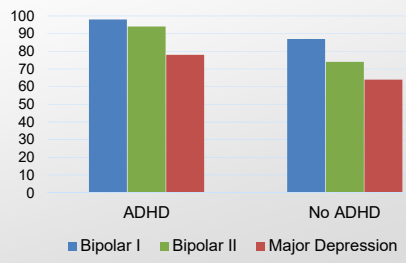
Lifetime rates of Anxiety Disorders among those with ADHD by Mood Disorder Subgroups



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Clinical Characteristics of Comorbid vs Non Comorbid Bipolar Disorder

- Greater functional impairment
- Greater severity of mood disorder
- More likely to have history of treatment
- Earlier age of onset of mood disorder
- More comorbidity with anxiety and substance use disorders
- Comorbid ADHD had greater influence on clinical correlates of those with MDD and BPII disorder than those with BPI

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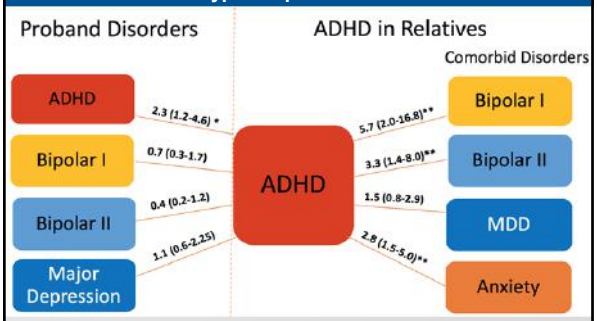
Is ADHD familial after controlling for comorbidity of mood disorder subtypes in probands and relatives?



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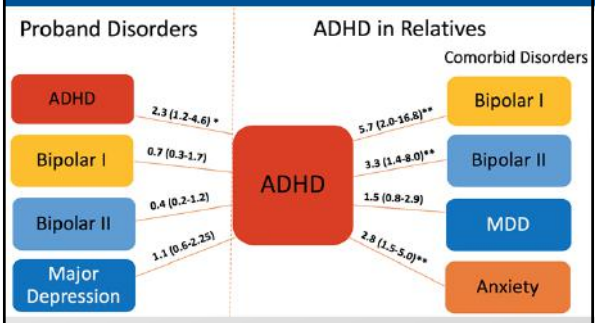
Do Mood Disorders in Probands predict ADHD in Relatives?



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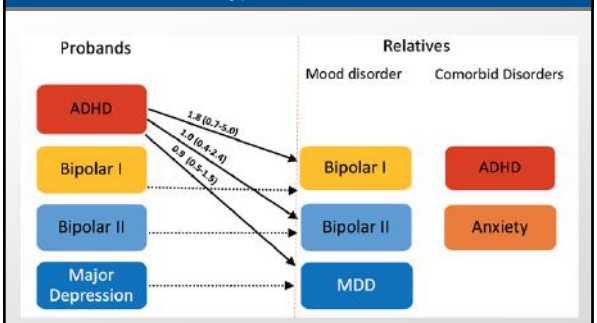
Is ADHD in Probands associated with Mood Disorder Subtypes in Relatives?



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Summary of Familial Patterns

- Bipolar disorder is highly familial and ADHD is moderately familial
- There was no familial overlap between any subtype of mood disorder with ADHD

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Limitations

- Heterogeneity of ADHD in this community based sample
- The majority of participants with ADHD had comorbid mood or anxiety disorders
- Under-representation of ADHD in older family members
- Assessments to date are cross-sectional

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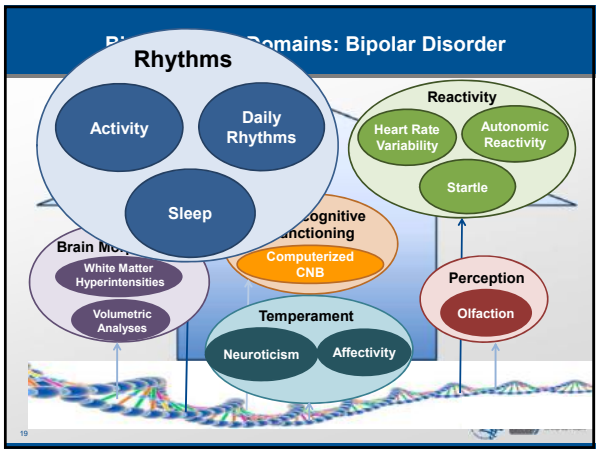

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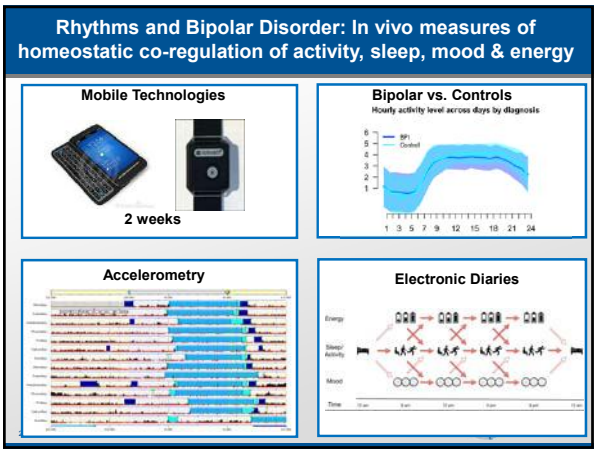

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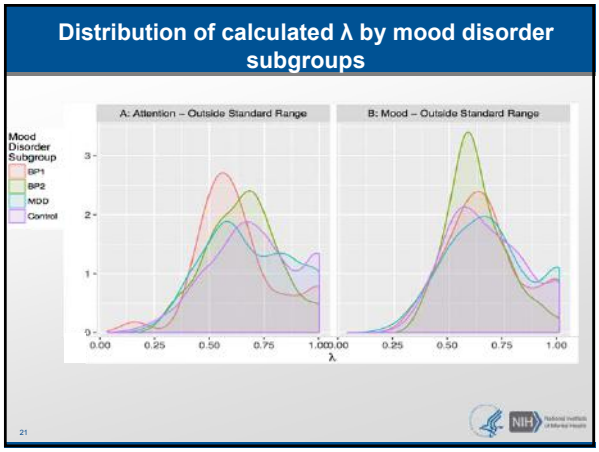

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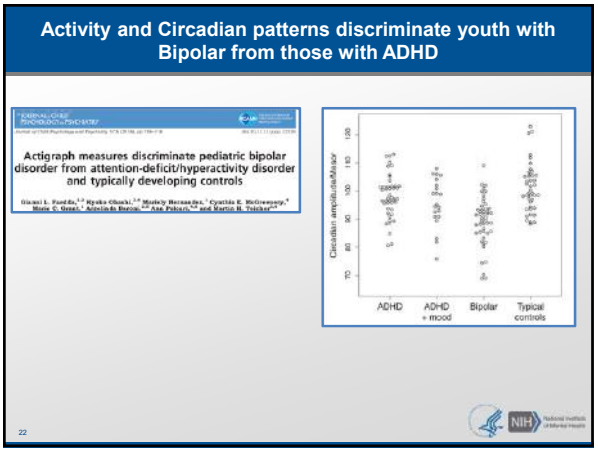

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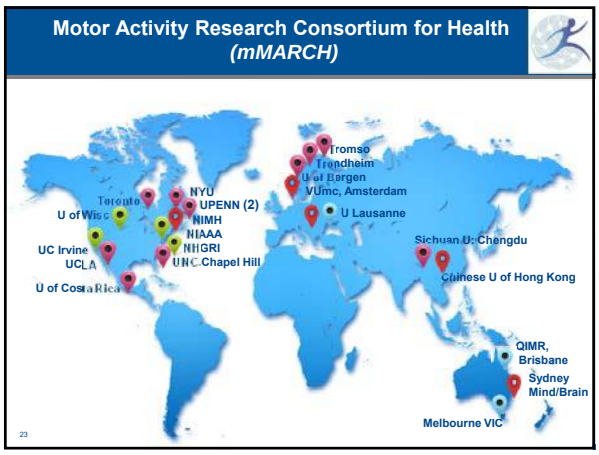

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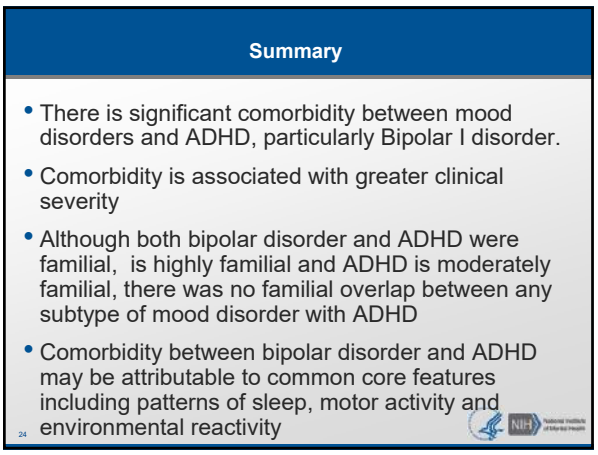

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Collaborators

External Collaborators

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Genetic Epidemiology Resarch Branch, NIMH

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Thank you!

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