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APSARD
The American Professional Society of ADHD and Related Disorders

ADHD and the Wandering Mind: a new perspective on Inattention in ADHD

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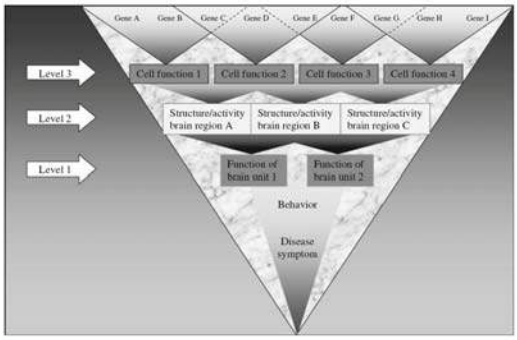
MRC Social Genetic and Developmental Psychiatry

Disclosures

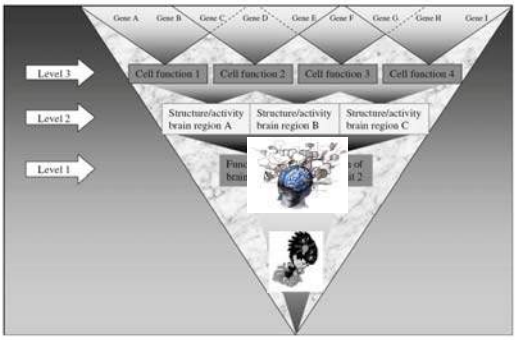
Company Name	Honoraria/ Expenses	Consulting/ Advisory Board	Funded Research	Royalties/ Patent	Stock Options	Ownership/ Equity Position	Employee	Other (please specify)
Jannssen-Cilag	X	X						
Shire	X	X	X					
Lilly	X	X						
Novartis	X	X						
Medice	X	X						
Lundbeck		X						
Vifor Pharma			X					
GW Pharma			X					

All payments to King's College London

Endophenotype concept



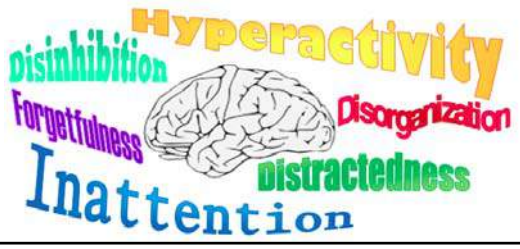
Endophenotype concept



ADHD and the wandering mind

What is ADHD?

A persistent pattern of inattention or hyperactivity/impulsivity that interferes with or reduces the quality of functioning in daily life



Symptom 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

Hyperactivity
- ❑ Fidgetiness b(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

Problems related to ADHD

1. **Work**
2. **Education**
3. **Social**
4. **Coping**
5. **Accidents**
6. **Distress**
7. **Self-esteem**
8. **Irritability**
9. **Sleep**

Psychosocial function

Mental health symptoms

NICE Clinical Guideline 72. 2008. http://guidance.nice.org.uk/cg72;
Asherson P, Expert Rev Neurotherapeutics. 2005 Jul;5(4):525-39.

8

Increasing the specificity of ADHD symptoms

Attention Dysregulation Hyperactivity Disorder

- Ability to hyper-focus
- Ability to focus on salient/rewarding activities
- Bored quickly and then lose focus
- Impatience when waiting

10

Increasing the specificity of ADHD symptoms

Attention Dysregulation Hyperactivity Disorder

- Ability to hyper focus
- Ability to focus on salient/rewarding activities
- Bored quickly and then lose focus
- Impatience when waiting
- **Excessive uncontrolled mind wandering**

11

What is mind wandering?

Mind wandering occurs when one's mind drifts away from a task and focuses on internal thoughts and images that are unrelated to the task or situation at hand

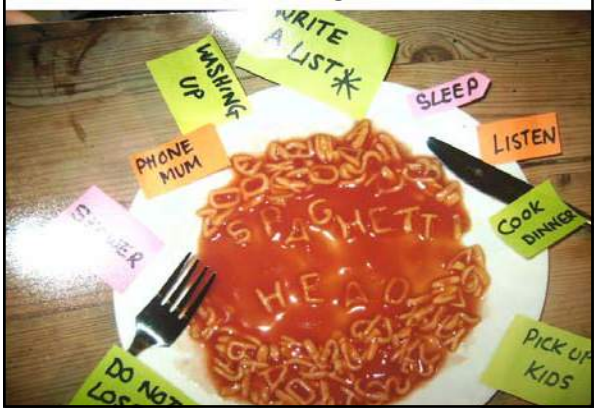
Mind wandering is a universal human experience, representing 20-50% of our daily thinking time

Words used to describe mind wandering by adults with ADHD

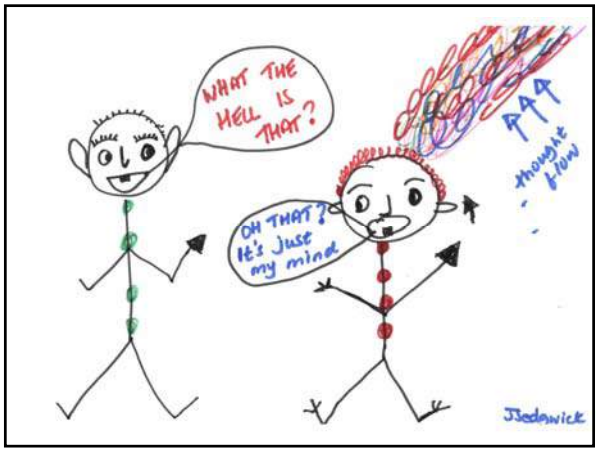
Constant daydreaming
In a fog
A whirlwind of thoughts
Hamster on a wheel
Jack in the box
Waves in a storm
Popping corn

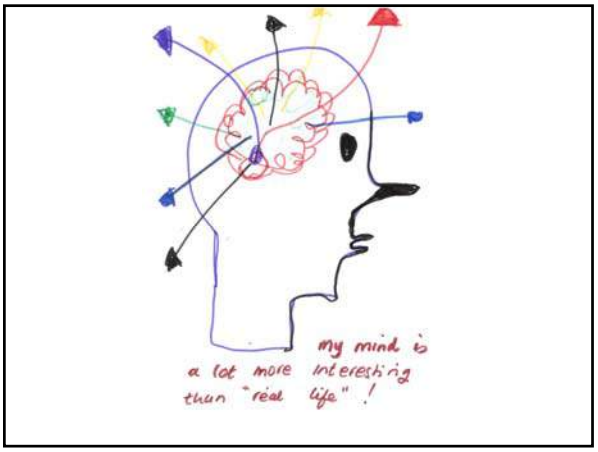
Asherson, Expert Review, 2005

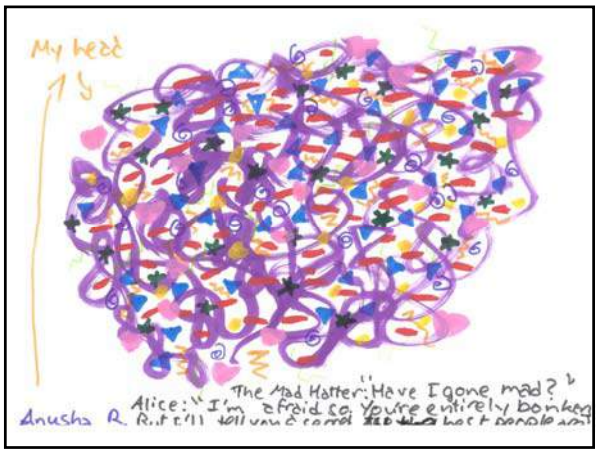
Mind Wandering in ADHD



"People with ADHD often struggle with filtering out"







Components of Excessive Mind Wandering in ADHD

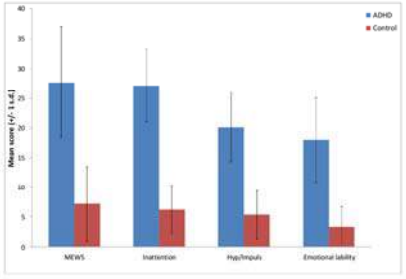
- Thoughts on the go all the time
- Thoughts jumping of flitting from one topic to another
- Multiple lines of thoughts at the same time

	The Excessively Mind Wandering Scale (MEWS)
1.	I have difficulty controlling my thoughts
2.	I find it hard to switch my thoughts off
3.	I have two or more different thoughts going on at the same time
4.	My thoughts are disorganised and 'all over the place'
5.	My thoughts are 'on the go' all the time
6.	I experience ceaseless mental activity
7.	I find it difficult to think about one thing without another thought entering my mind
8.	I find my thoughts are distracting and prevent me from focusing on what I am doing
9.	I have difficulty slowing my thoughts down and focusing on one thing at a time
10	I find it difficult to think clearly, as if my mind is in a fog
11	I find myself flitting back and forth between different thoughts
12	I can only focus my thoughts on one thing at a time with considerable effort

0 = Not at all / rarely; 1 = Some of the time;
2 = Most of the time; 3 = Nearly all of the time/constantly

Mowlem, et al., JAD, 2016

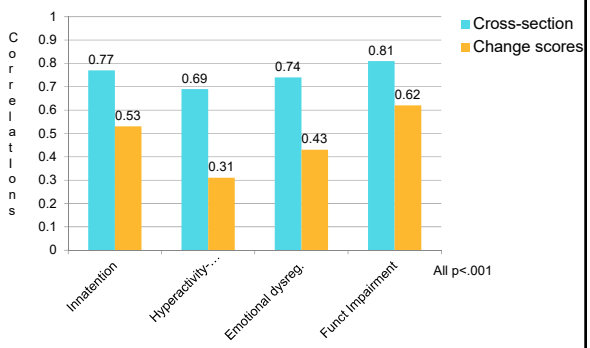
Case-control differences



d = 2.59 p < .001 | d = 4.05 p < .001 | d = 2.94 p < .001 | d = 2.63 p < .001

ROC (cut-off=15)	AUC	Sensitivity	Specificity
MEWS	.96	.90	.90

Polyserial Correlations between MEWS scores and ADHD symptoms and impairments scales



Mowlem, et al., JAD, 2016

Predictors of impairment (overall impairment score)

Predictors	R^2	$R^2\Delta$
Inattention + hyperactivity-impulsivity	.63**	
Inattention + hyperactivity-impulsivity + MW	.74**	0.11**

* p<.01
** p<.0001

Mowlem, et al., JAD, 2016

Predictors of impairment (overall impairment score)

Predictors	R^2	$R^2\Delta$
Inattention + hyperactivity-impulsivity	.63**	
Inattention + hyperactivity-impulsivity + MW	.74**	0.11**
Inattention alone	.25*	
MW alone	.58**	
Hyperactivity-impulsivity alone	.08	

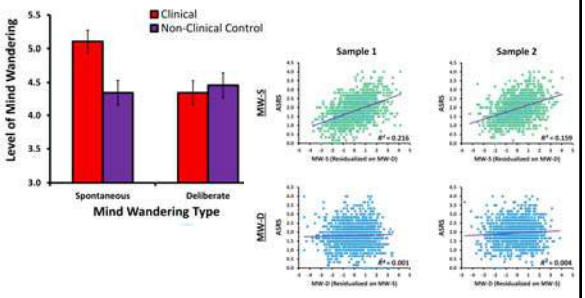
* p<.01
** p<.0001

Mowlem, et al., JAD, 2016

Problems linked to excessive mind wandering in ADHD

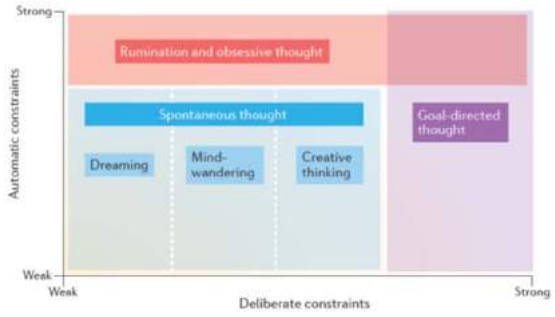
- Distracted from current tasks by internal thoughts
  - Difficulty following conversations
  - Reading difficulties
  - Sustaining attention
- Holding thoughts in mind
- Strategic thinking - planning/problem solving
- Fatigue secondary to constant mental activity
- Disrupted sleep

Spontaneous MW associated with ADHD diagnosis and ASRS scores



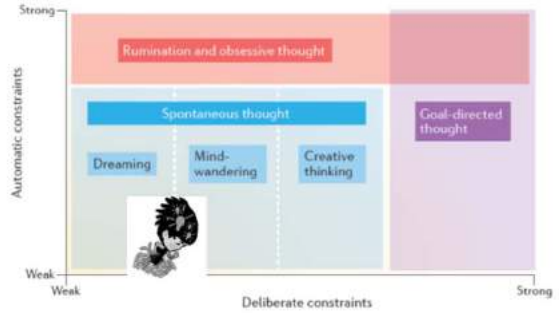
Seli, Smallwood, Cheyne, Smilek 2015, Psychonomic Bulletin and review

Mind wandering as spontaneous thought: a dynamic framework model



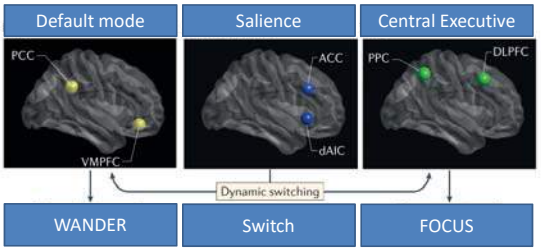
Christoff et al., Nature Reviews Neuroscience, 2016

Mind wandering as spontaneous thought: a dynamic framework model



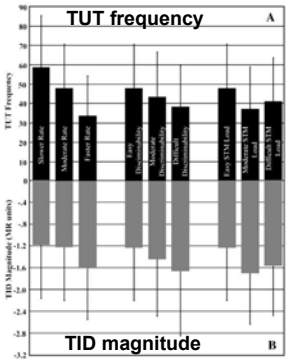
Christoff et al., Nature Reviews Neuroscience, 2016

Dynamic switching Focus - Wander



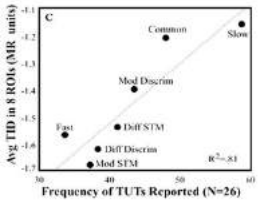
Uddin L.Q. 2014, Nature Reviews Neuroscience
McDonald et al., bioRxiv, 2016

Average Task Unrelated Thoughts (TUTs) and Task Induced Deactivations (TIDs)



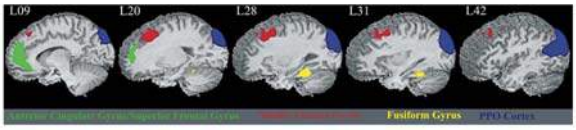
Auditory Detection Task:

Manipulated task conditions
- Presentation rate
- Target discriminability
- Short term memory load



McKiernan et al., Neuroimage, 2006

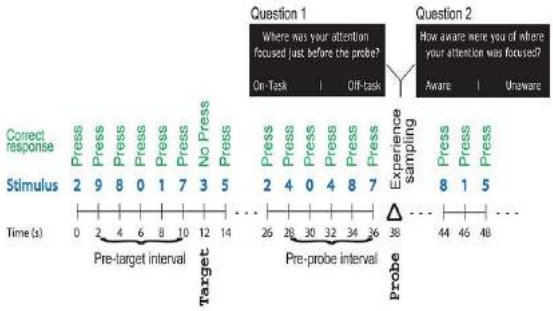
Regions where frequency of Task Unrelated Thoughts correlates with Task Induced Deactivation



Anterior Cingulate gyrus / superior frontal gyrus
Middle frontal gyrus,
Fusiform gyrus
Posterior Parietal-Occipital cortex

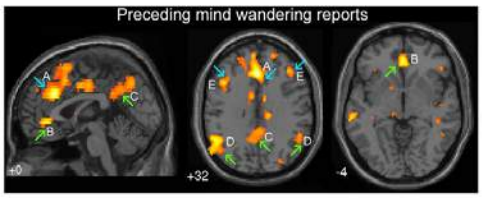
McKiernan et al., Neuroimage, 2006

DMN activity related to TUTs measured using experience sampling in the scanner



Christoff, Gordon, Smallwood et al., PNAS, 2009

Contrasting periods of Task Unrelated Thoughts versus periods of Task Related Thoughts



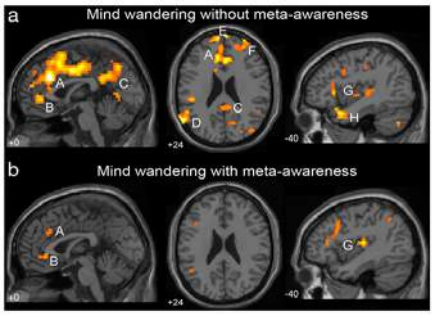
DMN
B: Ventral anterior cingulate gyrus
C: Precuneus
D: Bilateral tempero-parietal junction

ECN
A: Dorsal anterior cingulate gyrus
E: Bilateral dorsolateral prefrontal cortex

Both DMN and EC networks recruited during MW.

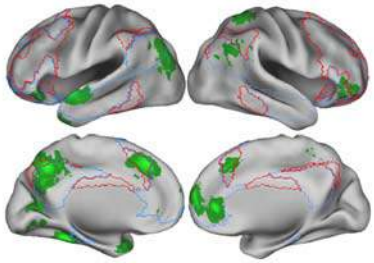
Christoff, Gordon, Smallwood et al., PNAS, 2009

- Greater activation during periods of being unaware that the mind had wandered



Christoff, Gordon, Smallwood et al., PNAS, 2009

Meta-analysis of functional neuroimaging studies of mind-wandering and related spontaneous thought processes (Fox et al., 2015)



Fronto-parietal control network

Default Mode Network

Does mind wandering reflect executive control or executive failure

Deliberate Mind Wandering

Executive Control

- Increased strategic thinking in low cognitive demand (e.g. driving)
- MW increases in low cognitive demand with increasing executive resources (e.g. working memory capacity)

Spontaneous Mind Wandering

Executive Failure

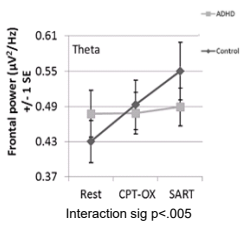
- Reduced suppression of internally generated thoughts
- Higher MW in high cognitive demand (performance deficits)

Adaptation from McVay and Kane, Psychol Bull, 2010 & Smallwood and Schooler 2006: Bozhilova in preparation

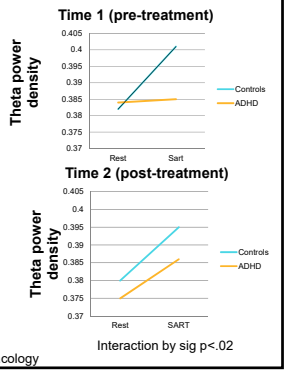
Characteristics of behavioural and neural regulation in ADHD and MW

- ❑ Context regulation
- ❑ Salience and reward
- ❑ Sensory decoupling

Normalisation of frontal theta activity following methylphenidate treatment in ADHD



Interaction sig p<.005

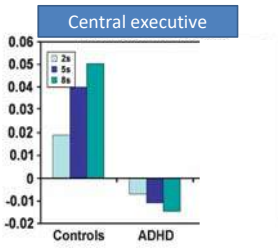


Interaction by sig p<.02

Midline frontal theta is strongly anti-correlated with DMN activity
(e.g. White et al., 2012, Michels et al., 2012

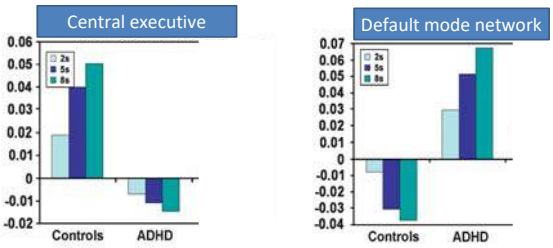
Skirrow et al., 2014, European Neuropsychopharmacology

SLOW and BORING!



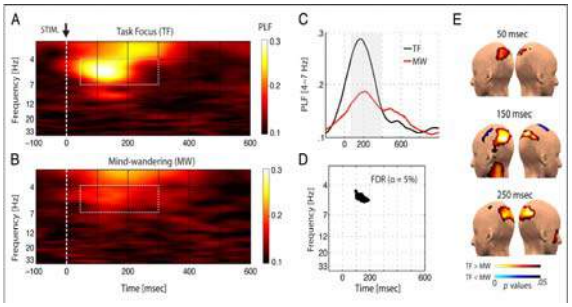
Chistakou et al., 2013

SLOW and BORING!



Chistakou et al., 2013

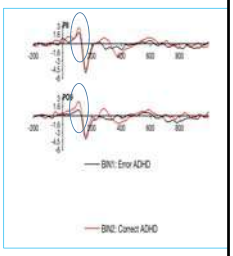
MW and sensory decoupling



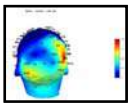
Baird et al (2014). *Journal of Cognitive Neuroscience*.

Early visual processing of no-go stimuli preceding a correctly withheld response or a response (error) in ADHD cases

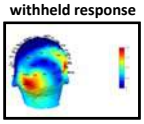
- Peak amplitude P1 were larger at PO9 for the correct condition compared to the error condition, p=0.001, p=0.008



Error response
100 ms post no-go stimuli preceding an erroneous response

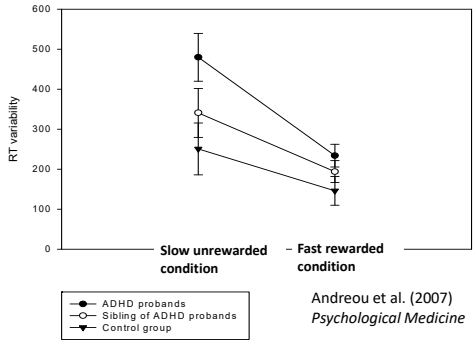


Correct response
100 ms post no-go stimuli preceding a correctly withheld response



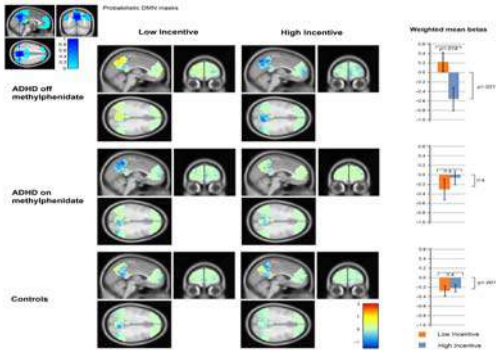
Bozhilova & Asherson, unpublished data

Incentives improve Reaction Time Variability (RTV) in ADHD



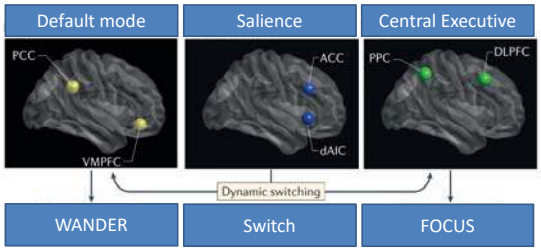
Andreou et al. (2007)
Psychological Medicine

Effects of methylphenidate and motivation on default mode network deactivation



Liddle et al., JCCP, 2011

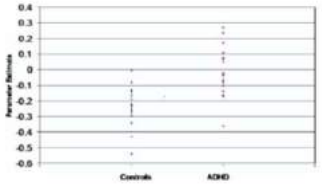
Dynamic switching Focus - Wander



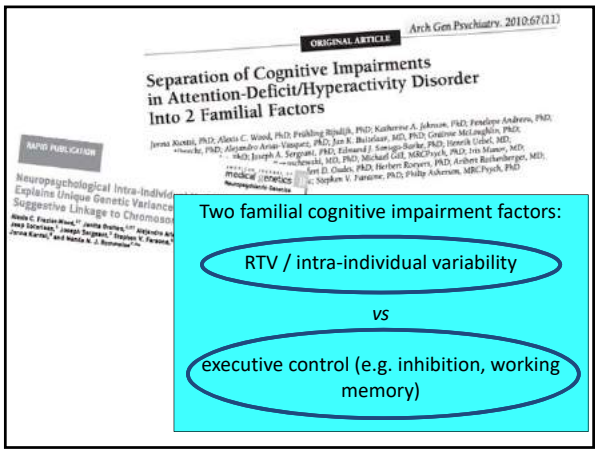
Uddin L.Q. 2014, Nature Reviews Neuroscience
McDonald et al., bioRxiv, 2016

Cingulate-Precuneus Interactions: A New Locus of Dysfunction in Adult Attention-Deficit/ Hyperactivity Disorder

F. Xavier Castellanos, Daniel S. Margulies, Clare Kelly, Lucina Q. Uddin, Manely Ghaffari, Andrew Kirsch, David Shaw, Zarrar Shehzad, Adriana Di Martino, Bharat Biswal, Edmund J. S. Sonuga-Barke, John Rotrosen, Lenard A. Adler, and Michael P. Milham

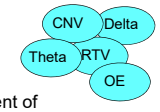


Decreased anterior cingulate cortex (salience) to precuneus (DMN) connectivity in ADHD



Key findings from ADHD follow-up study

- **Preparation-vigilance** measures were markers of remission, improving concurrently with ADHD symptoms
  - The strongest candidates for the development of non-pharmacological interventions involving cognitive training and neurofeedback



- **Executive control** measures of inhibition and working memory were not sensitive to ADHD persistence / remission

Cheung et al. (2015)
British Journal of Psychiatry

Default mode network: marker of remission

Reduced positive posterior cingulate – medial prefrontal cortex connectivity in persistent ADHD only:

- Indicates default mode network (DMN*) dysfunction as a marker of remission
- DMN dysfunction has been associated with high RTV (e.g. Kelly et al. 2008); *both* are markers of remission

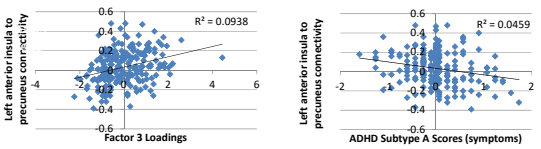
* DMN – comprised of brain regions typically more activated during rest than task performance

Resting-state fMRI: enduring deficit

Reduced medial-dorsolateral prefrontal cortex anti-correlation in both ADHD persisters and remitters:

- Such reduced anti-correlation has been linked to executive dysfunction (e.g. poor working memory)
- In this study: performance measures similarly showed EF impairments in both ADHD groups
- The findings "support the partial dissociation between ADHD and EF"

Salience – DMN Connectivity (left Insula – precuneus) anti-correlated with ADHD and dimension of deliberate-spontaneous mind wandering



Bozhilova, Vatansever, Asherson & Smallwood, preliminary (unpublished) data

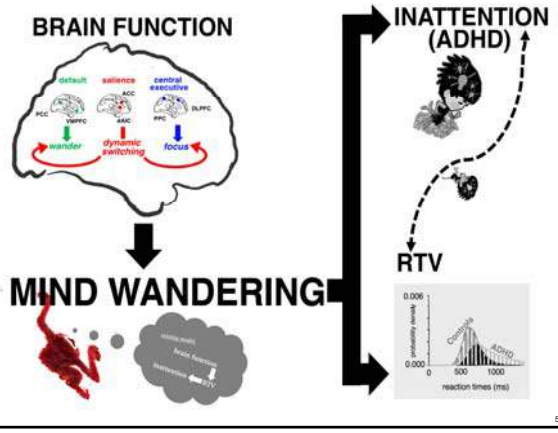


Table 2. Differences Between Groups at the End of Treatment, Controlling for Baseline Levels.

	Baseline		End of treatment		End of treatment	
	MBCT	WL	MBCT	WL	Group difference [95% CI]ª	Cohen's d type
ADHD symptoms, *CAARS*						
Investigator (n = 68)						
Inattention	16.3 (4.7)	17.0 (4.5)	12.4 (4.6)	16.5 (4.2)	−3.6 [−5.5, −1.8]***	0.78
Hyperactive-impulsive	13.0 (5.6)	12.0 (4.8)	9.0 (4.6)	11.5 (5.3)	−3.2 [−5.0, −1.4]***	0.62
Total score	29.3 (8.7)	29.0 (7.1)	21.5 (7.7)	28.0 (7.5)	−6.7 [−9.8, −3.6]***	0.85
Self report (n = 74)						
Inattention	15.4 (3.9)	16.6 (4.5)	12.8 (4.2)	16.1 (3.8)	−2.7 [−4.3, −1.2]***	0.64
Hyperactive-impulsive	12.8 (4.8)	13.6 (4.5)	10.3 (4.2)	12.6 (5.0)	−1.8 [−3.4, −0.2]**	0.39
Total score	28.2 (7.0)	30.2 (6.5)	23.0 (7.3)	28.8 (6.9)	−4.5 [−7.3, −1.8]***	0.67
EF, *BRIEF-ASR* (n = 74)						
Inhibit	17.2 (3.3)	18.2 (2.6)	14.7 (3.1)	17.4 (3.2)	−2.1 [−3.3, −0.9]***	0.71
Shift (n = 62)	12.6 (2.9)	12.5 (2.5)	11.1 (3.0)	12.3 (3.0)	−1.3 [−2.2, −0.3]**	0.48
Emotional control	19.5 (5.1)	19.1 (5.1)	17.1 (4.7)	18.8 (4.9)	−2.2 [−3.8, −0.6]**	0.43
Self-monitor	11.4 (2.7)	11.4 (2.8)	10.1 (2.5)	11.3 (2.8)	−1.3 [−2.3, −0.3]**	0.47
Initiate	17.4 (3.9)	18.4 (3.2)	15.7 (4.4)	18.1 (2.9)	−1.6 [−2.8, −0.4]**	0.45
Working memory	19.4 (3.0)	19.8 (2.2)	17.2 (3.4)	19.2 (2.6)	−1.7 [−2.9, −0.5]**	0.65
Plan/organize	23.0 (4.0)	24.5 (3.6)	19.8 (4.9)	24.1 (3.5)	−3.1 [−4.7, −1.5]***	0.82
Task monitor	13.1 (2.6)	13.7 (2.3)	11.6 (2.4)	13.5 (2.6)	−1.5 [−2.4, −0.6]**	0.61
Organization of materials	17.6 (4.2)	19.1 (3.6)	15.1 (4.2)	18.8 (4.1)	−2.4 [−3.5, −1.2]***	0.62
Total score	150.3 (22.2)	156.7 (17.2)	132.2 (26.4)	153.8 (18.8)	−18.4 [−26.6, −10.1]***	0.93

Hepark et al., J Attention Disorders, 2015

56

Why investigate MW in ADHD

❑ **Multiple methods of measurement:**
- Rating scales
- Experience sampling in daily life
- Experience sampling during experimental paradigms

❑ **Biomarker development**
- Diagnosis
- Treatment response
- Intermediate endophenotype (causal modelling required)

❑ **Drug/treatment development**
- Real time monitoring of treatment effects
- Treatment mechanisms (mediating effects)
- Target for treatment (drugs, mindfulness training, neurofeedback, other)

Thanks!

Natali Bozhilova
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Peter Reid
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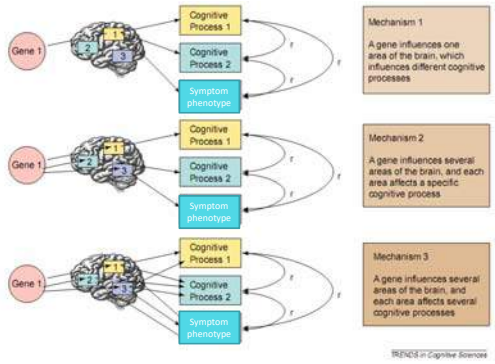
Celine Ryckaert
Ruth Cooper
Grainne McLoughlin
Stefanos Maltezos and the SLAM Maudsley ADHD clinic team
Jonna Kuntsi

Funders
National Institute of Health Research
Medical Research Council
Action Medical Research

60

Outline of talk

- ❑ What is mind wandering and how is it described by people with ADHD
- ❑ Neural correlates of mind wandering in control populations and ADHD
- ❑ Implications for clinical practice and research



Pleiotropy: **Individual genes effect multiple processes**

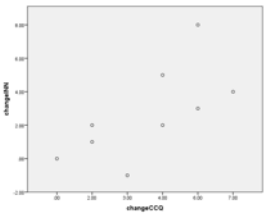
Polygenicity: **Multiple genes effect one process**

Kovas and Plomin, Trends in Cognitive Neuroscience, 2006

Mindfulness In ADHD (MIA) – feasibility study

10 participants:

- Change in Inattention: $p < .02$
- Change in MEWS: $p < .01$
- Change in Hyperactivity: ns



Changes score correlations:

- MEWS-Inattention: $r = .75$, $p < .02$
- MEWS-Hyper: ns

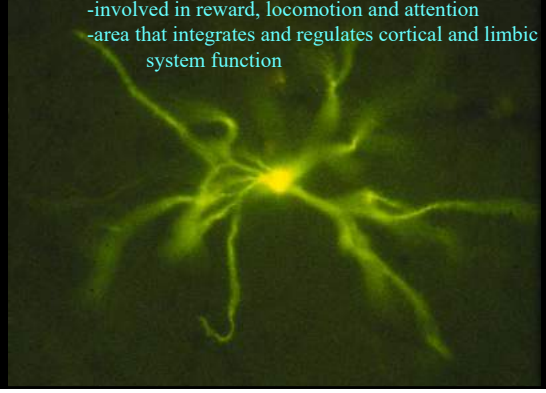
Asherson et al: feasibility study

Tonic-Phasic Dopamine Regulation of Limbic System Integration in the Pathophysiology and Treatment of ADHD

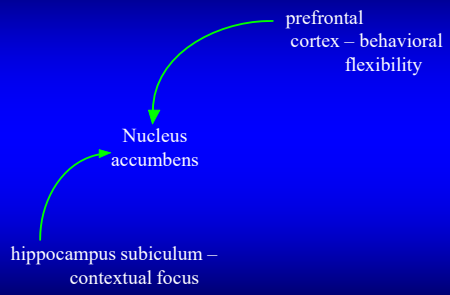
Anthony A. Grace, Ph.D.
Departments of Neuroscience, Psychiatry and Psychology
University of Pittsburgh

Disclosures: Johnson & Johnson, Lundbeck, Pfizer, GSK, Merck, Takeda, Dainippon Sumitomo, Otsuka, Lilly, Roche, Asubio, Akerrmes, Abbott

Nucleus Accumbens
-involved in reward, locomotion and attention
-area that integrates and regulates cortical and limbic system function



NUCLEUS ACCUMBENS CIRCUITS

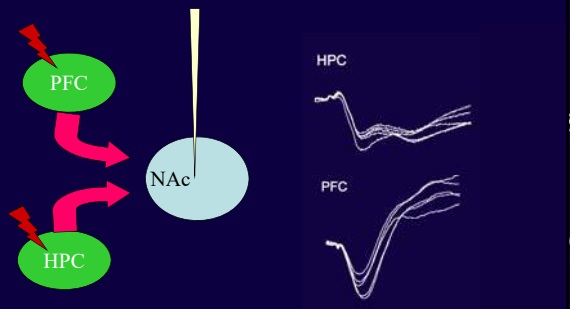


In ADHD, patients exhibit disruption in focused attention, instead shifting focus and interrupting their ability to achieve a goal.

It may be that in this condition, the prefrontal cortex, which should only be shifting attention when a strategy is ineffective, is now inappropriately shifting strategies before the goal can be achieved. This could happen via a disruption of hippocampal-accumbens contextual focus on a task.

How do the prefrontal cortex and hippocampus compete for the control of goal-directed behavior?

PFC- and HPC-evoked Field Potential Responses in the NAcc

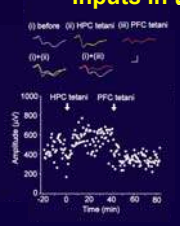


Tetanic stimulation: 100 pulses @ 50 Hz, 1.0 mA

Goto, Y. and Grace, A.A. (2005) Neuron 47: 255-266.

Associative LTP/LTD Induction at HPC and PFC Inputs in the NAcc

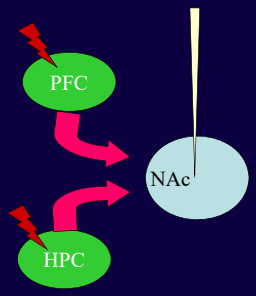
Hippocampal Input



Therefore, the HPC and PFC compete for control of information flow in the NAcc

Goto, Y. and Grace, A.A. (2005) Neuron 47: 255-266.

PFC- and HPC-evoked Field Potential Responses in the NAcc

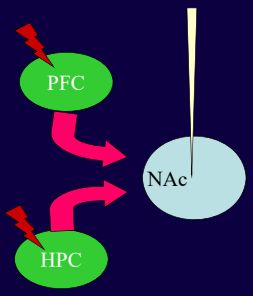


High-frequency activation of HPC inputs

Repeated HPC stimulation potentiates HPC input and attenuates PFC input

This will result in increased focus on task (contextual predominance)

PFC- and HPC-evoked Field Potential Responses in the NAcc



High-frequency activation of PFC inputs

Repeated PFC stimulation potentiates PFC input and attenuates HPC input

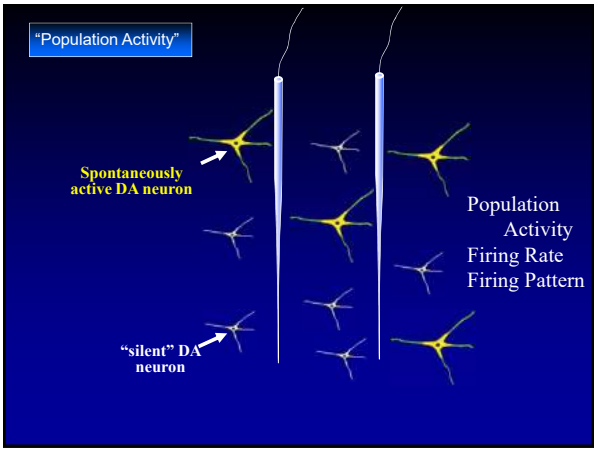
This will cause a shift from the current task to explore more effective response strategies

Therefore, these systems compete, with the HPC maintaining focus on task, and the mPFC shifting focus

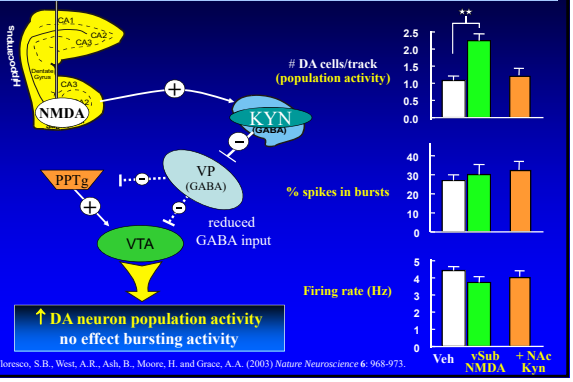
The ventral hippocampus drives context-dependent phenomena to enable focus on tasks, with the PFC allowing the system to break out of the context when the strategy is ineffective

In ADHD, there is a disruption in the ability to focus on a task to achieve a goal; one possibility is that the PFC is inappropriately shifting behavioral strategies before a goal is achieved

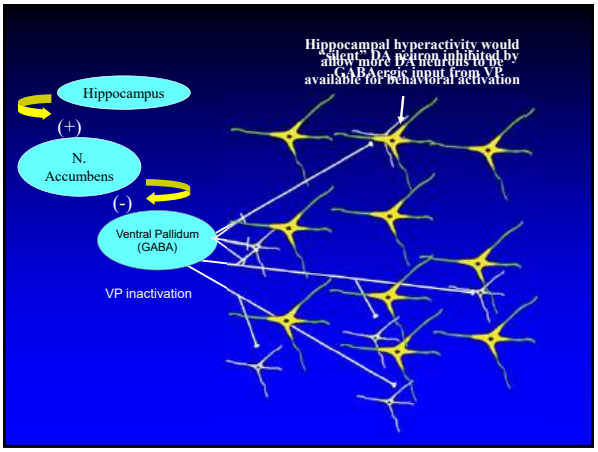
Hypothesis: psychostimulants enable maintenance of focus by shifting this balance via modulation of tonic/phasic dopamine

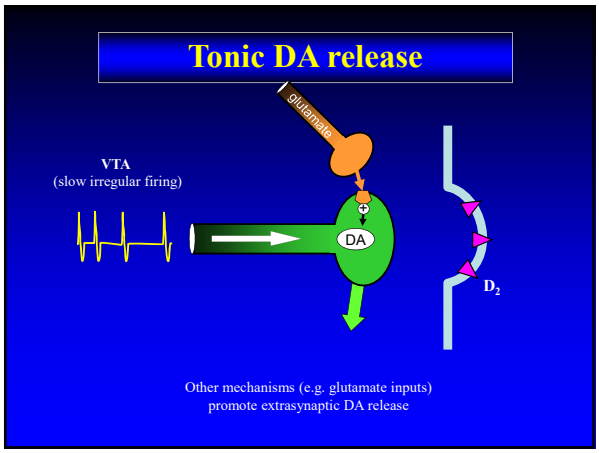


Activation of the *hippocampal-NAc pathway* increases TONIC DA neuron population activity, but does not affect burst firing



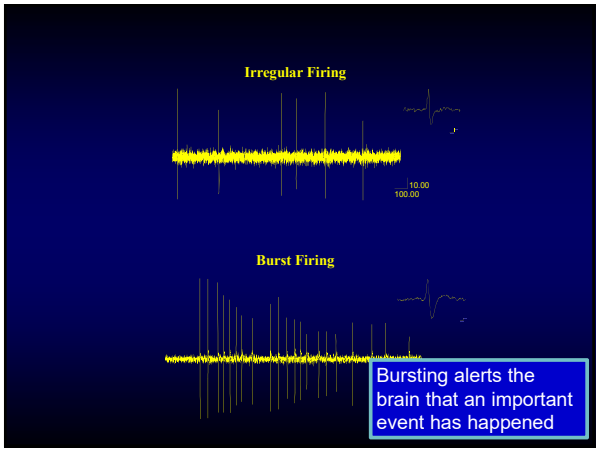
Floresco, S.B., West, A.R., Ash, B., Moore, H. and Grace, A.A. (2003) *Nature Neuroscience* 6: 968-973.

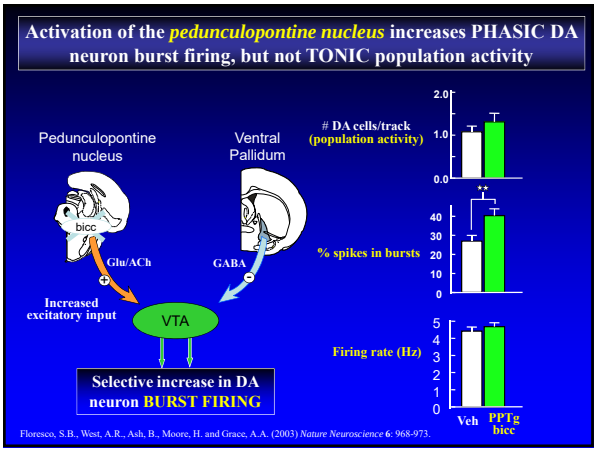


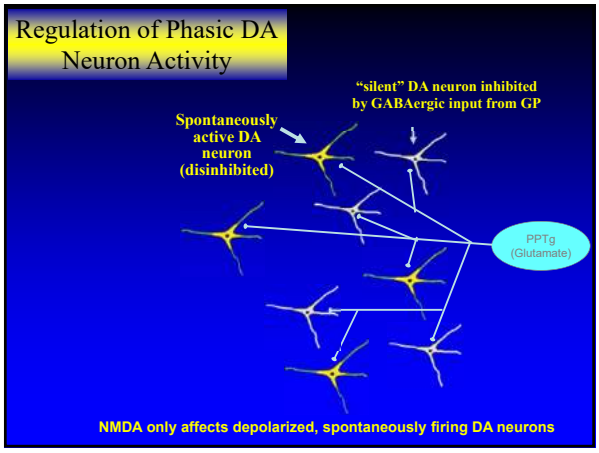


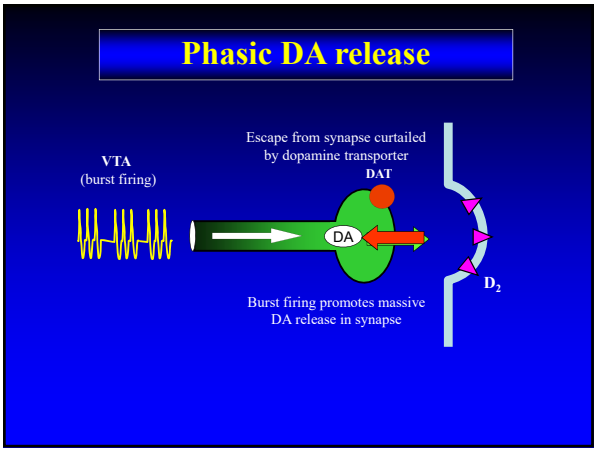
Regulation of DA neuron activity:

- Modulation of firing rate
  - Avg 4.6 Hz; range 2-8 Hz
- Modulation of Activity States
  - Can be activated by DA antagonists, etc.
  - Approx. 50% not firing spontaneously
- Modulation of firing pattern
  - Single spike firing – idling state
  - Burst firing – when activated by demand

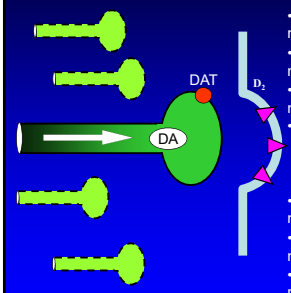








The DA system is compartmentalized



Synaptic (Phasic) DA

- Massive DA release within the synapse, mediated by burst firing
- Fast acting: escape of DA from synapse restricted by dopamine transporter
- Cannot be detected with conventional neurochemical measures (ie: microdialysis)
- Detected by raclopride displacement

Modulated by PPTg Glutamate

Extrasynaptic (Tonic) DA

- Would influence large ensemble of striatal neurons (volume transmission)
- Longer lasting: mediated by increased DA neuron population activity (and GLU inputs)
- Detectable with microdialysis but not by raclopride displacement
- Not heavily influenced by reuptake

Modulated by VP afferents

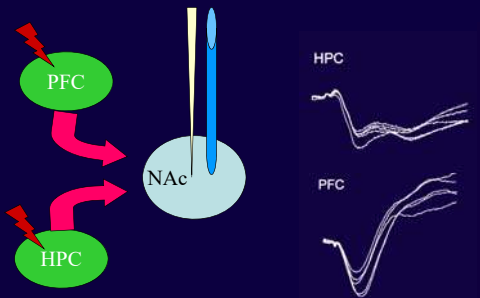
Summary

- Baseline DA neuron population activity determines low level TONIC DA release in the nucleus accumbens
- Activation of DA neuron burst firing leads to the behaviorally salient PHASIC DA response associated with reward

What is the Role of Tonic and Phasic DA Transmission In Regulating Synaptic Inputs to Accumbens Neurons?

-Differentially activate tonic and phasic DA while recording field potentials evoked by afferent stimulation

PFC- and HPC-evoked Field Potential Responses in the NAcc

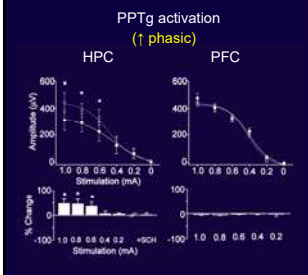


Drugs are infused locally into the NAc via reverse dialysis

Goto, Y, & Grace, A.A. (2005) Nature-Neuroscience 8: 805-812.

Effects of PPTg (phasic DA) Manipulation on Hippocampal and Prefrontal Cortical Evoked Field Potentials

PPTg activation
(↑ phasic)

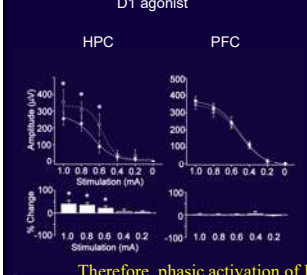


Phasic must be activated by behaviorally salient stimuli

Goto, Y, & Grace, A.A. (2005) Nature-Neuroscience 8: 805-812.

Effects of D1 Drug Infusion into the Nucleus Accumbens on Hippocampal and Prefrontal Cortical Evoked Field Potentials

D1 agonist



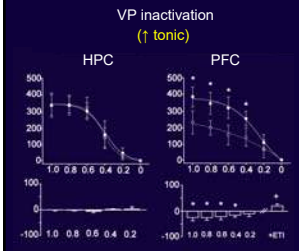
Therefore, phasic activation of D1 receptors selectively facilitates hippocampal input to the accumbens

Goto, Y, & Grace, A.A. (2005) Nature-Neuroscience 8: 805-812.

Summary

PPTg-mediated increases in phasic DA stimulates D1 receptors and shifts balance toward limbic inputs

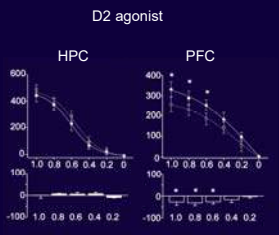
Effects of VP (tonic DA) Stimulation on Hippocampal and Prefrontal Cortical Evoked Field Potentials



Tonic DA is always active at a baseline level

Goto, Y, & Grace, A.A. (2005) Nature-Neuroscience 8: 805-812.

Effects of D2 Drug Infusion into the Nucleus Accumbens on Hippocampal and Prefrontal Cortical Evoked Field Potentials



Therefore, tonic activation of the DA system selectively attenuates PFC input via D2 receptor stimulation

Goto, Y, & Grace, A.A. (2005) Nature-Neuroscience 8: 805-812.

Summary

VP inactivation-induced increases in tonic DA stimulates D2 receptors and shifts the balance away from cortical inputs

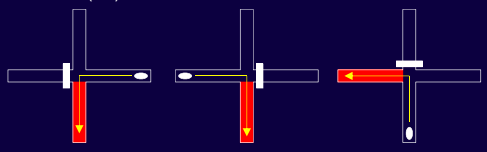
D1 Selectively Increases HPC drive
D2 Selectively Attenuates PFC drive

This should preferentially facilitate focus on task while attenuating shifts of attention

How Does D1/D2 DA Receptor Regulation of Limbic and Cortical Information Processing Mediate Goal-directed Behavior?

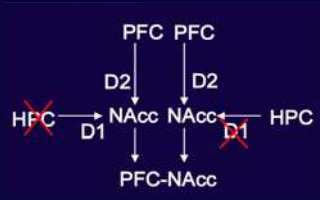
Behavioral Tests

Visual Cue Task (VCT)



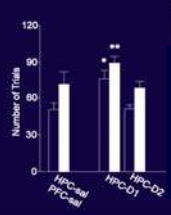
Goto, Y, & Grace, A.A. (2005) Nature-Neuroscience 8: 805-812.

Disconnection of Limbic Inputs into the NAcc



Goto, Y, & Grace, A.A. (2005) Nature-Neuroscience 8: 805-812.

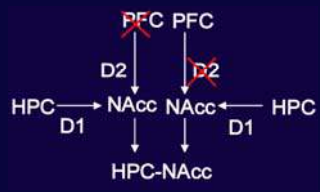
Selective Disruption of Cognitive Functions



Therefore, when hippocampal inputs are not potentiated by DA, there is a disruption in the ability to learn each type of task

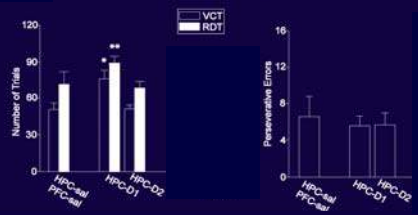
Goto, Y, & Grace, A.A. (2005) Nature-Neuroscience 8: 805-812.

Disconnection of PFC Inputs into the NAcc



Goto, Y, & Grace, A.A. (2005) Nature-Neuroscience

Selective Disruption of Cognitive Functions



Therefore, when D2 stimulation interferes with PFC function, there is a disruption in the ability to switch tasks

Goto, Y, & Grace, A.A. (2005) Nature-Neuroscience 8: 805-812.

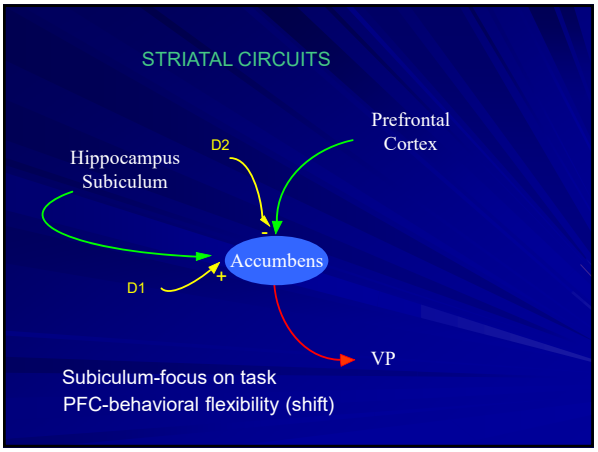
Summary of Results

Phasic D1-dependent limbic-NAcc information processing mediates learning and maintaining a response strategy in goal-directed behavior.

Tonic D2-dependent PFC-NAcc information processing mediates a shifting away from a current response strategy in goal-directed behavior.

Under a normal tonic/phasic balance, this would enable the systems to maintain an effective response strategy (HPC), but to shift the strategy if it is ineffective (PFC).

However, if tonic DA is disrupted, this would cause more rapid PFC-mediated shifts in strategy even when not appropriate; this could also occur via decreased baseline D2 receptor levels (Robbins)

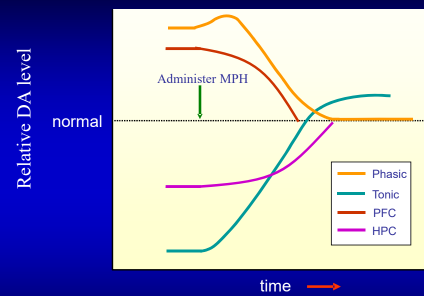


This normal function would depend on an adequate balance of tonic-phasic dopamine, and normal levels of activity within the HPC-PFC afferents

However, if the PFC is hyperactive, or if there is inadequate tonic down-modulation of the PFC via decreased D2 receptors, then there would be an inability to focus on task, instead replaced by rapid shifts in contextual, attentional focus

In either case, increasing tonic DA would restore balance to the system

The mechanism of action of MPH for ADHD



By preferentially increasing tonic DA, oral methylphenidate will restore balance to the system and dopaminergic control over PFC-HPC interactions

Proposal:

In ADHD, the PFC is overly active (either endogenously or via inadequate tonic attenuation of PFC input to the accumbens) in switching response strategies, preventing contextual focus on the task by the hippocampus until the task is completed

By increasing tonic DA levels, psychostimulants given orally in a continuous maintenance dose, it should attenuate the abnormal PFC-driven switching behavior and potentiate the ability of the hippocampus subiculum to maintain focus on task

Increasing tonic DA will also decrease phasic DA release, restoring balance to activity levels and reward systems

Plenary Lecture

The Translational Neuropsychopharmacology of Attention Deficit/Hyperactivity Disorder

T.W. Robbins

Department of Psychology and

Supported by a joint award from the Medical Research Council and the Wellcome Trust

UNIVERSITY OF CAMBRIDGE

wellcome trust

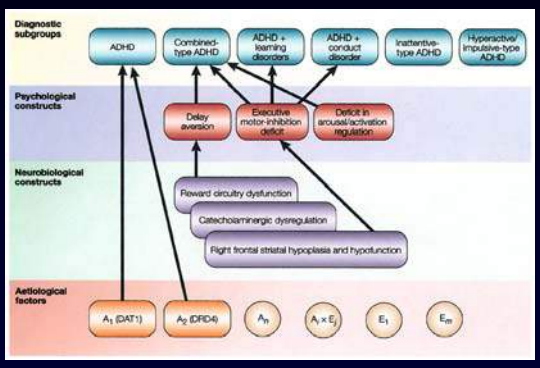
MRC Medical Research Council

Clinical Psychology Unit BCNI Behavioural & Clinical Neuroscience Institute

The University of Cambridge Behavioural and Clinical Neurosciences Institute

Disclosure; Cambridge Cognition: Lundbeck, Otsuka, Shionogi, Mundipharma

ADHD: A causal-developmental model

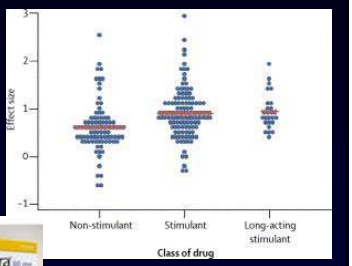


Castellanos & Tannock 2002 ,Nature Rev Neurosci.

Evidence-based pharmacological treatment of ADHD

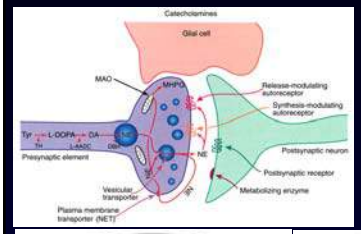
Drugs

- Methylphenidate
- D-Amphetamine
- Atomoxetine



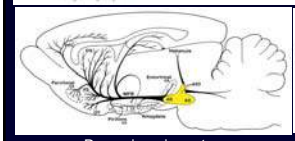
Biederman & Faraone, Lancet 2005; Peterson et al., Psychopharmacology 2008

Ritalin's effects in ADHD are mediated at the catecholaminergic (dopamine and noradrenaline) synapses

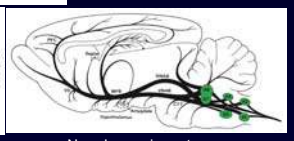


But which one, and where!?

Zigmond M et al
Fundamental Neuroscience

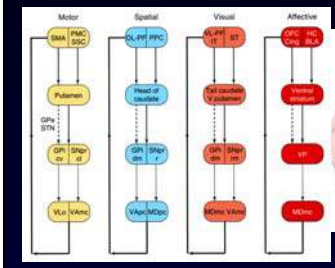


Dopaminergic systems



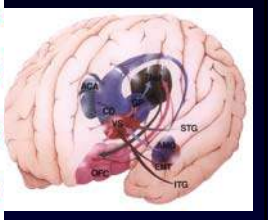
Noradrenergic systems

Cortico-striatal circuits, chemical neuromodulation, executive function and neuropsychiatric disorders



Alexander et al

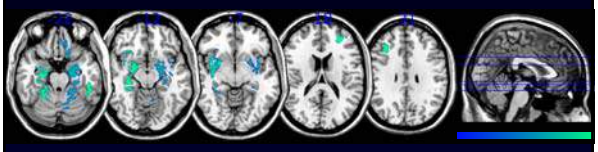
Human reward system



Zald

Serotonin ↑ Dopamine ↑ Noradrenaline ↑

Reduced grey matter density in adult ADHD patients

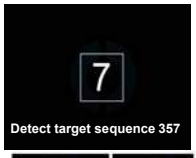


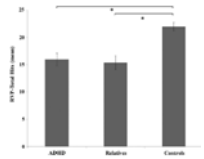
- R mid/inferior frontal gyrus
- L mid frontal gyrus

Bilaterally:
- posterior putamen
- hippocampus & amygdala
- cerebellum (vermis+hemispheres)

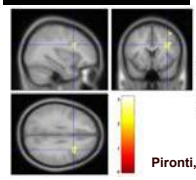
Del Campo, Fryer, Aigbirhio, Robbins, Sahakian, Muller et al
Brain 2013

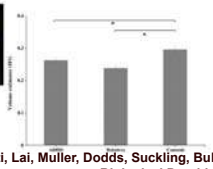
Patients with attention deficit hyperactivity disorder and their unaffected first-degree relatives had impaired sustained attention associated with decreased grey matter volume in the right inferior frontal gyrus compared to healthy control subjects





Sustained attention (CANTAB RVP) score according to group. ADHD and relatives did not differ from each other, and both performed significantly worse than control subjects

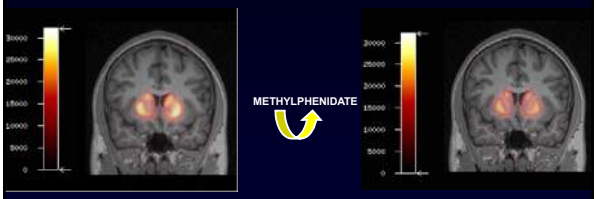




Significant cluster of decreased gray matter volume in the right inferior frontal gyrus (rIFG) in ADHD and first-degree relatives compared to control subjects.

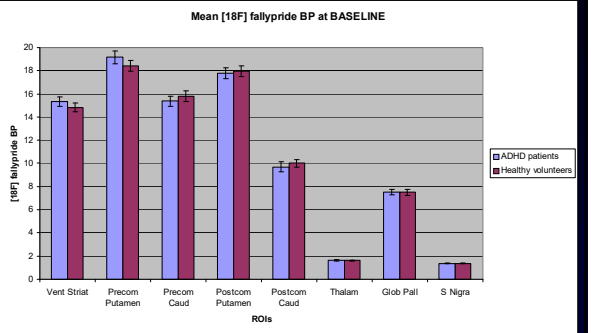
Pironti, Lai, Muller, Dodds, Suckling, Bullmore & Sahakian (2013), Biological Psychiatry

In vivo displacement of [18F] fallypride BP in a healthy volunteer

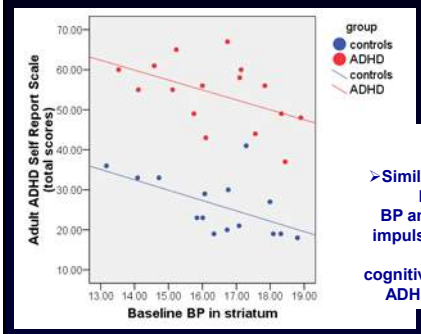


Del Campo, Fryer, Aigbirhio, Robbins, Sahakian, Muller et al
Brain 2013

No differences between ADHD and controls in baseline D2/D3 R availability (Del Campo et al *Brain* 2013)



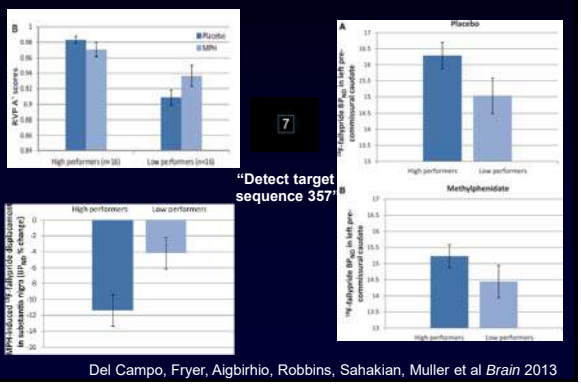
Negative relationship between striatal [18F]fallypride BP and ASRS scores in adult ADHD patients and controls



Del Campo, Fryer, Aigbirhio, Robbins, Sahakian, Muller et al *Brain* 2013

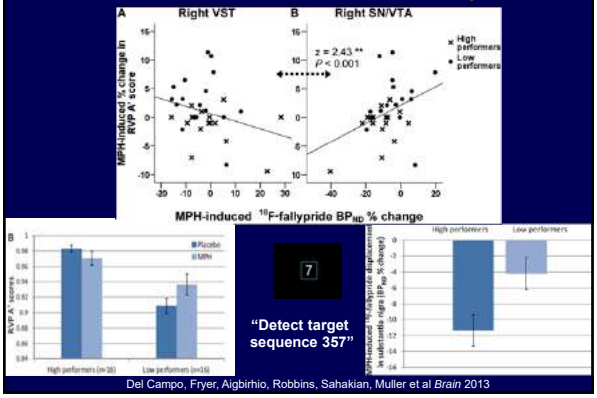
- **Similar correlations between BP and self-reported impulsivity, inattention and cognitive performance in ADHD and controls**

Low vs high performers on RVIP task and methylphenidate: Relationship to midbrain and striatal D2-R receptor changes



Del Campo, Fryer, Aigbirhio, Robbins, Sahakian, Muller et al *Brain* 2013

Significant relationship between D2-R availability change in midbrain and RVIP performance after oral methylphenidate



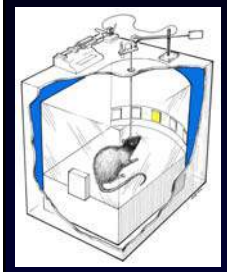
Del Campo, Fryer, Aigbirhio, Robbins, Sahakian, Muller et al *Brain* 2013

Building aetiological models of ADHD

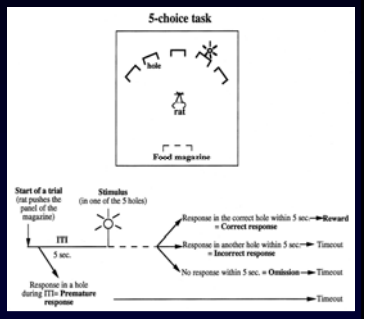
See Bari & Robbins 2011, Gainetdinov 2010 ; Sagvolden et al 2005; Sontag et al 2010; van der Kooij & Glennon 2007

- **Genetic mutants; k.d.** etc *DAT1;* 'functional hyperdopaminergia'; *DRD4;DRD5*; *5HTT*; *5HTR1B;* DA beta hydroxylase. Coloboma mutant mouse (SNAP-25 protein);beta subunit nicotinic-R; thyroid hormone receptor (TR beta 1)
- **Rodent strains** SHR-Wistar Kyoto rat (Sagvolden); Genetic hypertensive (GH) rat; Naples high excitability (NHE) rat; acallosal mouse I/LnJ
- **Traits in normal population**: 'Poor performers' & 'High impulsives'
- **Lesions** Catecholamine depletion (neonatal 6-OHDA); PFC damage
- **Early stress/trauma** Isolation-rearing (from 21 days); maternal drug exposure; heavy metal exposure (Pb, Cd, Mg); hypoxia; X-irradiation

The 5 choice serial reaction time task for rats: Test of sustained attention and executive response control

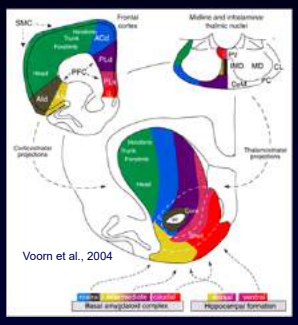


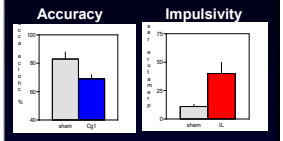
Dalley et al 2001

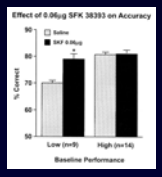


Robbins 2002

Dissociable effects of PFC lesions on 5-CSRTT performance and effects of D1-R agonists

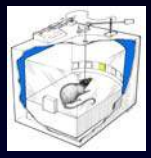


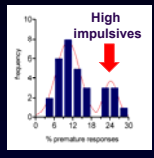




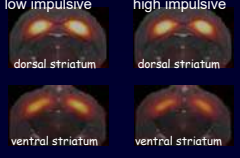
Chudasama et al., 2003 Behav Brain Res; Granon et al 2000 J. Neurroscience

Trait impulsivity in rats linked to low striatal dopamine D2 receptors and altered response to cocaine





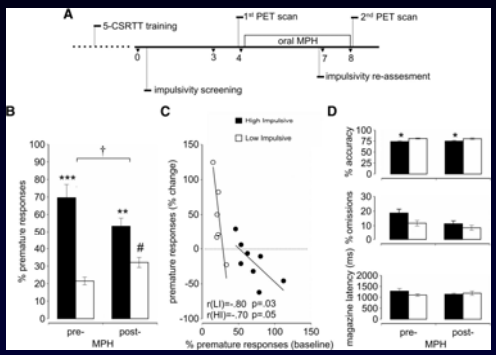
'Zippy'



Cocaine iv Self-admin

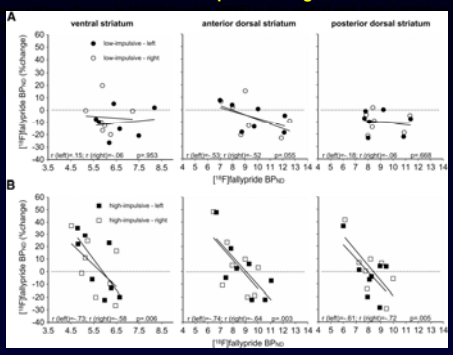
Dalley et al Science 2007

Baseline-dependent effects of methylphenidate on impulsive responding



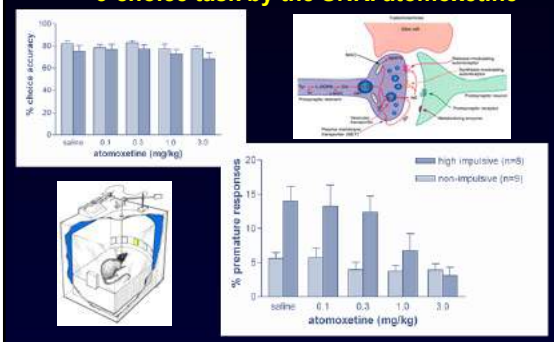
Caprioli et al. J. Neurosci. 2015;35:3747-3755

Baseline-dependent effects of methylphenidate on striatal D2/3 receptor binding in rats



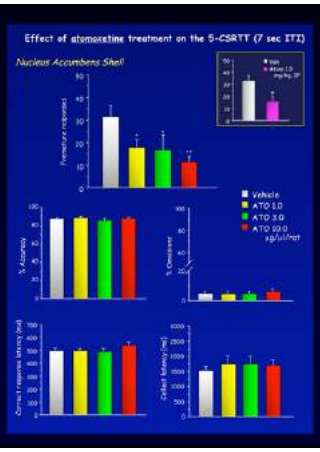
Caprioli et al. J. Neurosci. 2015;35:3747-3755

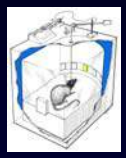
Dose-dependent reduction in trait impulsivity on the 5-choice task by the SNRI atomoxetine



Fernando et al 2014

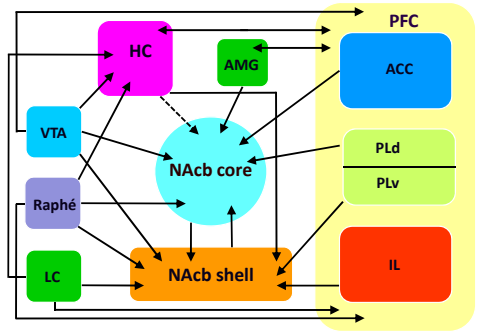
Intra-accumbens shell atomoxetine dose-dependently reduces 5CSRTT impulsivity





Economidou et al Neuropsychopharmacology 2012

Defining brain networks associated with 'waiting' impulsivity

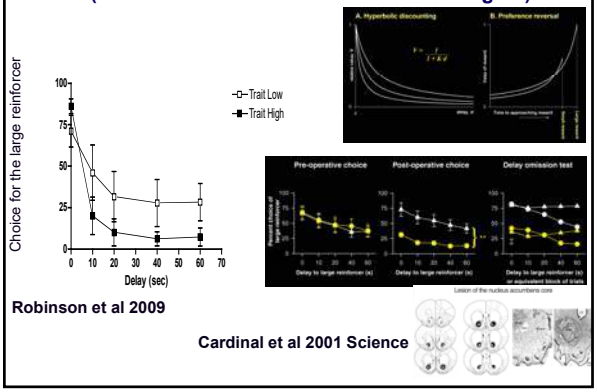


Bottom-up Dysregulation'

Dalley, Everitt, Robbins Neuron 2011

'Top-down Dyscontrol

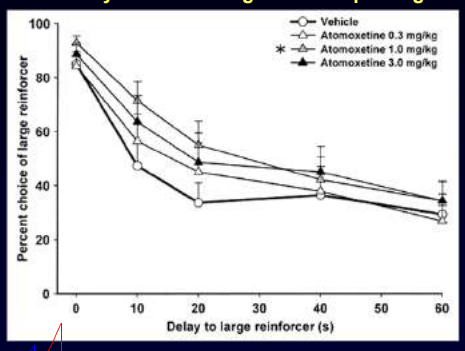
High impulsive rats also show steep reward discounting (like effects of lesions of N. Acc. Core region)



Robinson et al 2009

Cardinal et al 2001 Science

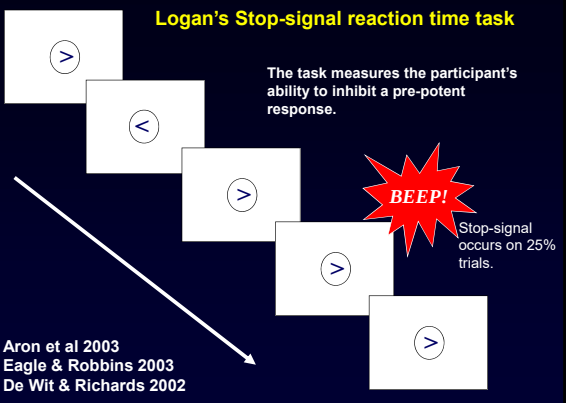
Atomoxetine reduces impulsive choice in rats in delayed discounting of reward paradigm



Robinson et al 2008

Logan's Stop-signal reaction time task

The task measures the participant's ability to inhibit a pre-potent response.



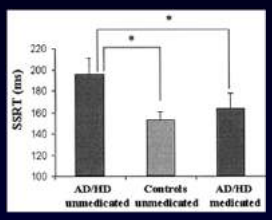
Stop-signal occurs on 25% trials.

Aron et al 2003
Eagle & Robbins 2003
De Wit & Richards 2002

Methylphenidate and Atomoxetine improve stop-signal inhibition in adult ADHD

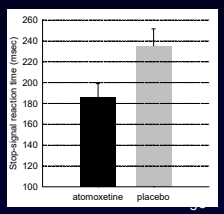
Better Performance

Methylphenidate



Aron et al. 2003

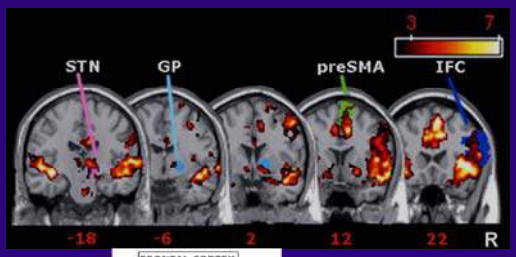
Atomoxetine

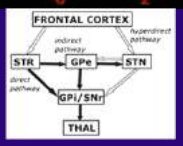


Chamberlain et al 2007

Biological Psychiatry

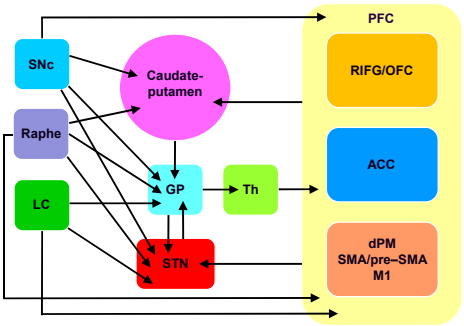
fMRI study of stop-signal reaction time





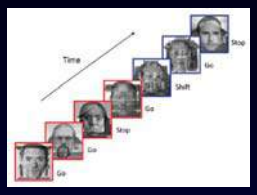
Aron and Poldrack 2006

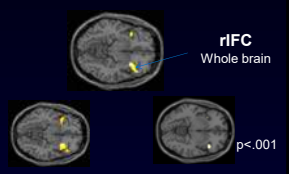
Defining neural networks associated with 'Stopping' impulsivity



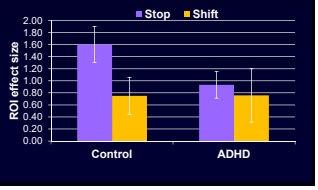
Dalley, Everitt, Robbins, Neuron 2011

Functional neuromaging of stopping vs shifting: Adult ADHD patients exhibit reduced activation for stopping in Right Inferior PFC





- Significantly more activation in the right IFC in stopping compared to shifting, in both groups
- ADHD patients have significantly lower activation than controls



A Longitudinal Assessment of Healthy Adolescents

PI: Gunter Schumann (Institute of Psychiatry, London)

An EU-funded project to assess 2,000 fourteen year olds recruited from mainstream schools. Assessment, with follow-up in three years, includes:

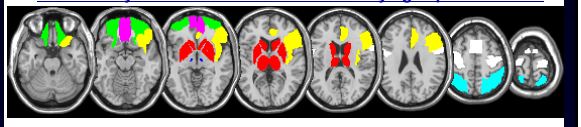
- Clinical Assessments;
- Neuropsychology;
- Cognitive Abilities;
- Whole Genome Analysis;
- Brain structure;
- Brain function including inhibitory control, error detection, reward processing, emotion processing and general cognitive abilities.

Whelan, Conrod, Buehler, Robbins,Schumann, Garavan Nature Neuroscience 2012

IMAGEN: Individual Differences in Impulse Control

1,252 fourteen year olds (52.1% female) performed a STOP task.

Factor analysis identified 7 networks underlying impulse control.



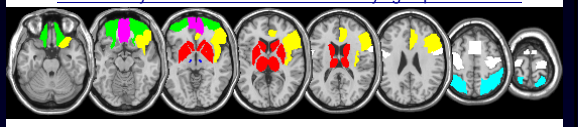
- Different networks were associated with different aspects of impulse control:
- Those reporting ADHD symptoms had reduced activity in a bilateral right frontal error-monitoring network (ACC/Insula/IFG) and the basal ganglia (but on STOP Fail trials only)
- Thus, drug use and ADHD symptoms were related to different networks underlying impulse control, but with some overlap.

Whelan, Robbins, Garavan, IMAGEN consortium 2012 Nature Neurosci.

IMAGEN: Individual Differences in Impulse Control: A NA transporter polymorphism linked to RIFG function & executive control

1,252 fourteen year olds (52.1% female) performed a STOP task.

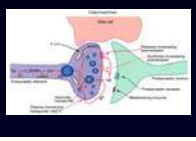
Factor analysis identified 7 networks underlying impulse control.

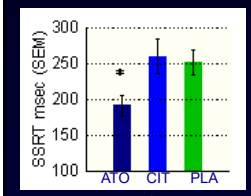


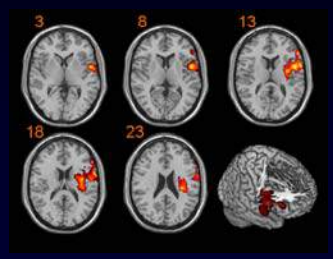
- **Different networks were associated with different aspects of impulse control:**
- **A right prefrontal network (right IFG, insula and ACC) was associated with better inhibitory abilities and with alleles of a polymorphism of NET (noradrenaline transporter) (SLC6A2; rs36024, intron 4).**

Whelan, Robbins, Garavan, IMAGEN consortium 2012 Nature Neuroscience

The SNRI atomoxetine speeds SSRT and enhances task-dependent SSRT activity in right inferior frontal gyrus in healthy volunteers

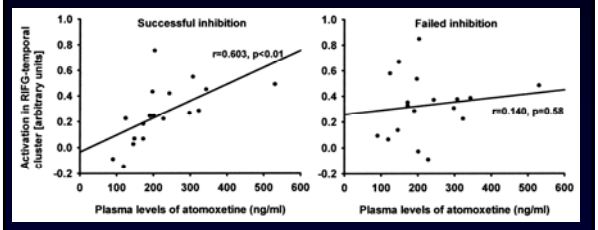






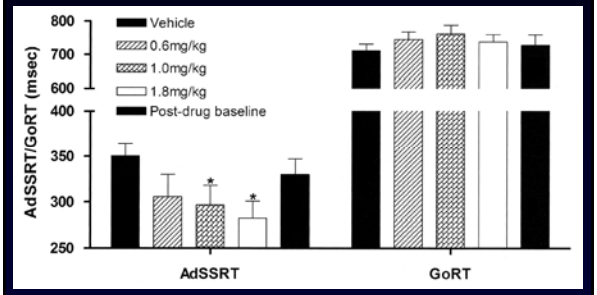
Chamberlain et al 2009 Biological Psychiatry
Chamberlain, Sahakian et al Science 2006

Plasma atomoxetine linked to activation in RIFG during successful stopping



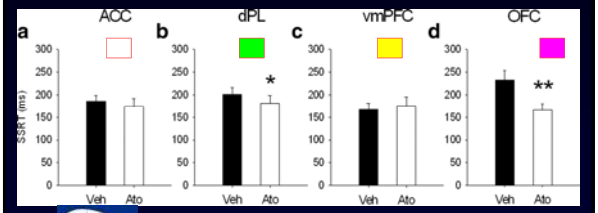
Chamberlain et al 2009 Biological Psychiatry

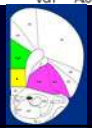
Atomoxetine dose-dependently improves SSRT in the rat, while not affecting Go-RT



Robinson et al Neuropsychopharmacology 2008

Atomoxetine the NA reuptake blocker also speeds the stop signal reaction time in rat when infused into certain regions of the prefrontal cortex

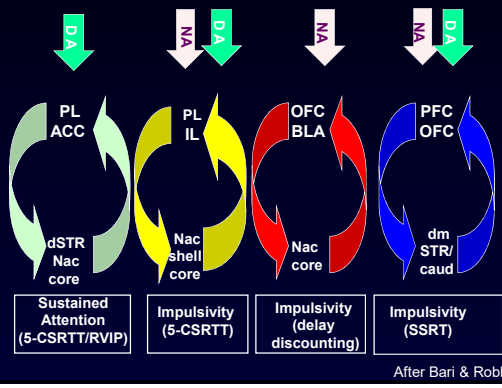




Effects of 0.1 µg/0.5 µl per side of atomoxetine in ACC (a), dPL (b), vmPFC (c), and OFC (d) on SSRT.

Bari A et al. J. Neurosci. 2011;31:9254-9263

Cortico-striatal loops, attention, response control and its neuromodulation Relevance to 'Spectrum' models of ADHD (re Sonuga-Barke, Solanto et al)



After Bari & Robbins 2011

Collaborators

- BJ Everitt
- D Economidou +
- D Eagle
- J Dalley
- A Bari
- A Mar
- E Robinson
- D Theobald
- BJ Sahakian
- U Muller
- S Morein-Zamir
- N Del Campo
- V Pironti
- C Dodds
- S Chamberlain
- K Ersche
- D Turner
- A Aron
- JH Dowson
- ET Bullmore

The ADHD "Head-to-Head" study

- Delay aversion versus stop signal performance in a multi-site centre study of juvenile ADHD
- Large deficits in both tasks, unrelated to co-morbid conduct disorder or anxiety
- Performance on the two tasks was uncorrelated
- But the two tasks together effectively diagnosed 90% of the sample
- Suggestion that "impulsivity" is a valid construct for ADHD, but that it might be fractionated into sub-types, possibly associated with distinct neural pathology
- Solanto, Sonuga-Barke et al (2001) J Abnorm Child Psychol 29, 215-228

High impulsive rats have a 'waiting' not a 'stopping' problem

'Waiting'

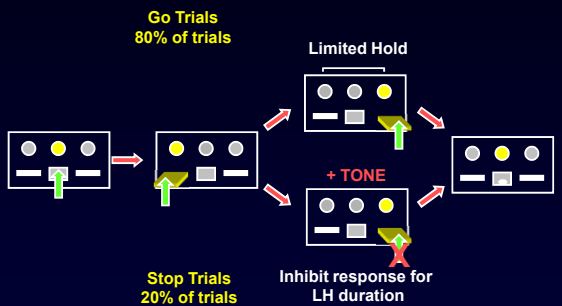
Robinson et al 2009
Behav. Brain Res

"Stopping"

Intra-PFC atomoxetine fails to affect 5CSRTT impulsivity

Economidou et al
Unpublished observations

Stop-Signal Reaction Time Task for Rats



Ritalin improves self-ordered spatial working memory & increases 'efficiency' of DL-PFC cortical network in normals

Elliott et al 1997

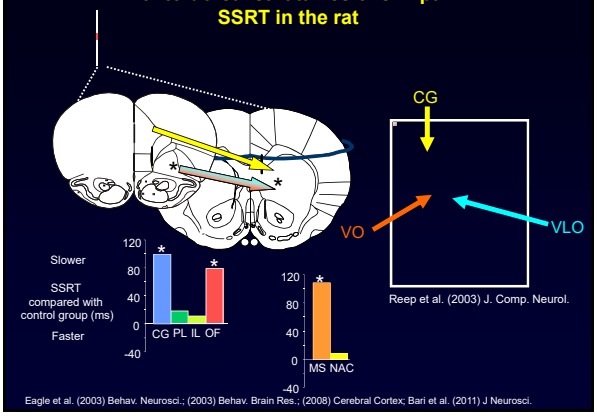
Mehta et al 2000

DSM-IV Criteria/behavioral symptoms for Attention-Deficit/Hyperactivity Disorder

- EITHER Inattention
  - Impaired sustained attention
  - Fails to complete
  - Difficulties in organization
  - Distractible, forgetful
- OR Hyperactivity-Impulsivity
  - Fidgeting, running about, noisy, 'on-the-go'
  - Difficulty in awaiting turn
  - Interrupts, blurts out answers
  - 'Behavioural disinhibition'

Nb Other cognitive deficits include timing, working memory, attentional set-shifting, recognition memory

Fronto-dorsal striatal lesions impair SSRT in the rat

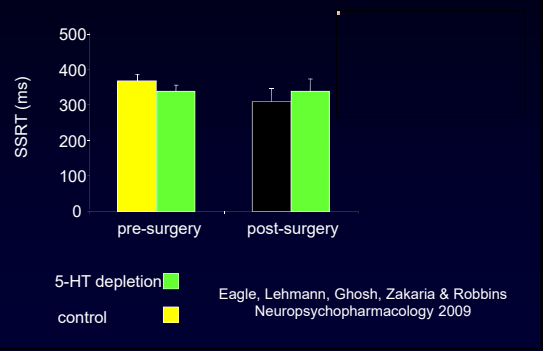


Eagle et al. (2003) Behav. Neurosci.; (2003) Behav. Brain Res.; (2008) Cerebral Cortex; Bari et al. (2011) J Neurosci.

No effect of citalopram (SSRI) on SSRT performance

Bari et al 2009 Psychopharm

Global 5-HT Depletion has no effect on SSRT in rats



Eagle, Lehmann, Ghosh, Zakaria & Robbins Neuropsychopharmacology 2009

Opposite behavioral effects of infusions of DRD1 antagonist SCH 23390 or DRD2 antagonist sulpiride into DMStr or NAcbC.

Eagle D M et al. J. Neurosci. 2011;31:7349-7356

The Impact of Treating ADHD on Later Substance Use Disorders

Timothy E. Wilens, M.D.

Chief, Division of Child & Adolescent Psychiatry
Director, Center for Addiction Medicine

Massachusetts General Hospital
Harvard Medical School

Disclosures*

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

- NIH (National Institute on Drug Abuse)
- Alcobra, Ironshore, Neurovance/Otsuka
- National Football League (ERM), Minor/Major League Baseball
- Bay Cove Human Services, Phoenix House (Clinical Services)
- (Co)Edited Straight Talk About Psychiatric Medications for Kids (Guilford Press); ADHD Across the Lifespan (Cambridge Univ Press); Comprehensive Clinical Psychiatry; Psychopharmacology & Neurotherapeutics (Elsevier)
- Some of the medications discussed may not be FDA approved in the manner in which they are discussed

* Past 2 years

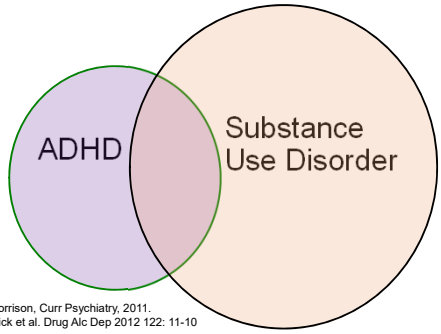
Learning Objectives

- Examine the risk for SUD in ADHD youth growing up
- Evaluate the literature on the impact of treatment of ADHD on later SUD

"I hate to advocate drugs, alcohol, violence, or insanity to anyone, but they've always worked for me."

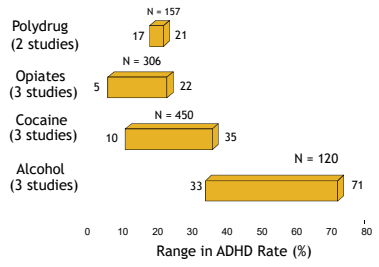
Hunter S. Thompson

Overlap between ADHD and Substance Use Disorders(SUD)



Wilens & Morrison, Curr Psychiatry, 2011.
van Emmerick et al. Drug Alc Dep 2012 122: 11-10

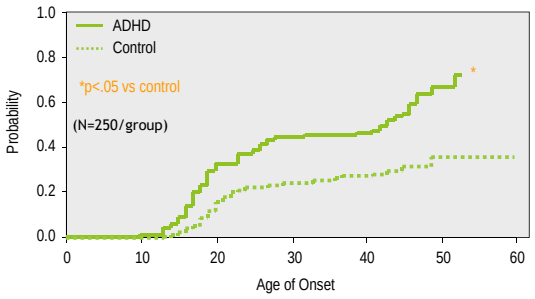
SUD is a Risk Factor for ADHD: Illustrative Overlap of ADHD in Adults With SUD



Overall, 23% of adults with substance abuse have ADHD (N=29 studies)*.

Wilens T. *Psychiatr Clin N Am.* 2004;27:283-301; *van Emmerick et al. Drug Alc Dep 2012 122: 11-10

Onset of Substance Abuse in Untreated ADHD Adults (Retrospectively Derived)



Wilens TE, et al. *J Nerv Ment Dis.* 1997;185(8):475-482.

Childhood ADHD is Related to Future Cigarette and SUD

Likelihood (Odds Ratio; OR) to Develop SUD

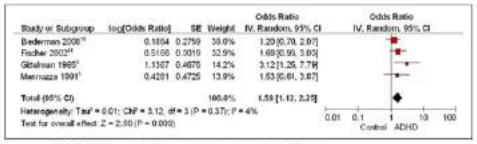


FIGURE 4 Meta-analysis of attention-deficit/hyperactivity disorder (ADHD) and psychoactive substance use disorder. Note: Results from a meta-analysis comparing ADHD versus control subjects for psychoactive substance use disorder. CI = confidence interval.

Likelihood (Odds Ratio; OR) to develop Cigarette Smoking

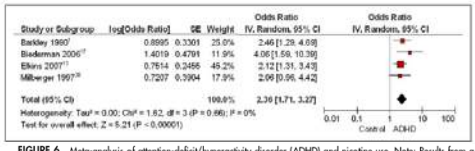
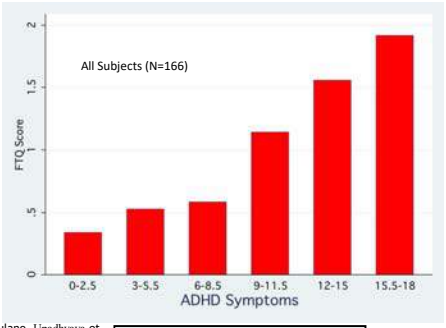


FIGURE 6 Meta-analysis of attention-deficit/hyperactivity disorder (ADHD) and nicotine use. Note: Results from a meta-analysis comparing ADHD versus control subjects for nicotine use. CI = confidence interval.

Charach et al. JAACAP 2011 50(1)9-21

ADHD Symptoms are Directly Related to Higher Smoking Scores



(Wilens, Vitulano, Upadhyaya et al. *Journal of Pediatrics* 2008; 153: 414-419)

t=5.00, p<0.001

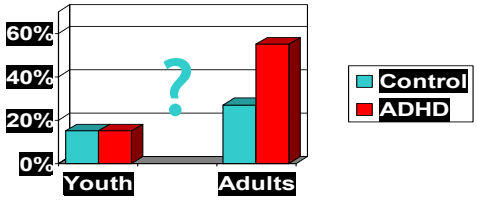
A More Complicated Course of SUD Is Associated with ADHD

- More severe SUD
- Lower retention in SUD treatment
- Longer course of SUD
- Less remission from SUD
- Higher rates of other psychiatric comorbidities (e.g. conduct/antisocial disorders)

(Carroll and Rounsaville, Comp Psych 1993: 34:75-82; Schubiner et al J Clin Psych:2000:61:244-251 Levin et al. Drug Alc Dep 1998; 52:15-25; Levin et al. 2004; Wilens et al. Am J Add 1998, 2004)

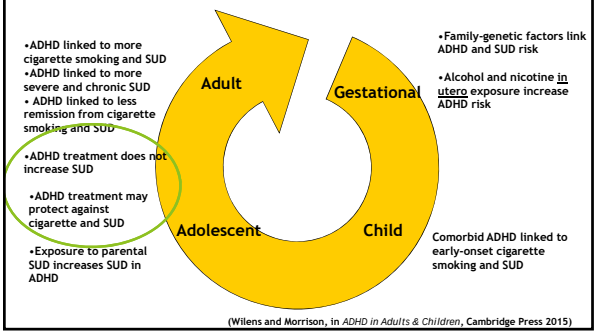
ADHD: Risk of Substance Use Disorders

Sharp rise in SUD between mid-adolescence and adulthood



Biederman et al. *JAACAP* 1997;36:21.
Wilens et al., J Nerv Ment Disor, 1997.

Developmental Relationship between ADHD & Substance Abuse



(Wilens and Morrison, in *ADHD in Adults & Children*, Cambridge Press 2015)

Does the Pharmacotherapy of ADHD Beget Later Substance Use Disorders?

Baseline Severity Issue

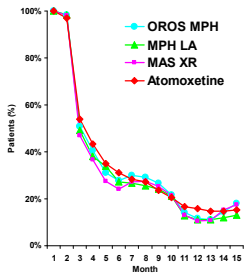
More Severe Illness → More Treatment

Poorer Outcome

(confounded association with more treatment)

(Wilens et al., Pediatrics:2003)

ADHD Adherence is Generally Poor



- Within 2 to 3 months, a majority of patients with ADHD have stopped taking medication consistently[1,2]
- Adherence rates tend to be better for long-acting medications for ADHD[3]
- One study has shown similar adherence for the long-acting agents OROS MPH, MPH LA, MAS XR, and atomoxetine[1]
- Patients renewed their monthly prescriptions about 2 to 3 times per year[1]

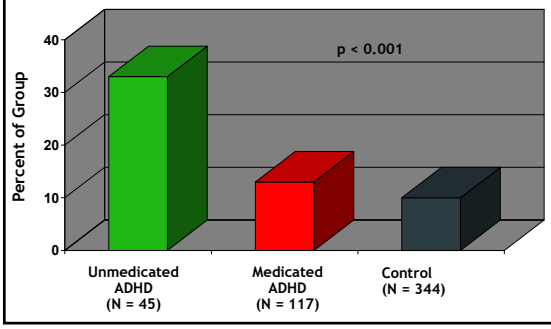
1. Capone. Presented at CHADD Annual International Conference, Dallas, Texas; October 27, 2005.
2. Perwien et al. *J Manag Care Pharm.* 2004;10(2):122-129.
3. Sanchez et al. *Pharmacotherapy.* 2005;25(7):909-917.

Effect of Monitoring?

Prevention of SUD in ADHD Youths

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

(Biederman, Wilens, Mick et al., Pediatrics, 1999)



Does the Pharmacotherapy of ADHD Beget Later Substance Use Disorders? A Meta-Analytic Review of the Literature

Methods

- **We identified the following studies:**

-Loney et al. 1998, 2001 also cited in Paternite et al. 1999 (tx=182, untx=37)
-Lambert et al. 1999 (tx=93, untx=81)
-Biederman et al. 1999& Wilens et al. 1999 (tx=145, untx=45, ctrls)
-Molina et al. 1999 (tx=53, untx=73)
-Huss et al. 1999 (tx=103, untx=103)
-Barkley et al. 2002 (tx=98, untx=21)
-Huss et al., 2003 (tx =92, untx = 69)

Total sample = 766 Tx with stimulants and 429 unTx with stimulants (N = 1195)

(Wilens et al., Pediatrics 2003, 111:179-185; Faraone & Wilens, J Clin Psych:In press)

Is ADHD Pharmacotherapy in Youths a Risk Factor for Subsequent SUD?

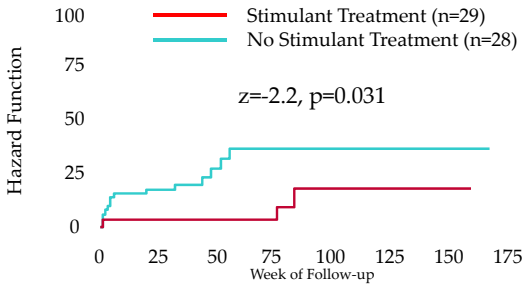
Evaluation of 766 medicated and 429 unmedicated patients with ADHD followed into adolescence (2 studies) or adulthood (5 studies)

- **Majority of studies (4/7) indicate reduced risk for SUD in treated vs. untreated ADHD individuals**
- **Meta-analysis suggests treatment of ADHD associated with a 2-fold reduction in the risk for SUD**

Kollins SH, et al. *Pharmacol Biochem Behav.* 2001;68(3):611-627.; Garasimov, et al. *J Clin Pharm Ther.* 2001.; Biederman J, et al. *Pediatrics.* 1999;104(2):20.; Lambert NM, Hartsough CS. *J Learn Disabil.* 1998;31(6):533-544.; Wilens TE, et al. *Pediatrics.* 2003;111:179-185; Barkley, et al. *Pediatrics.* 2003:111.; Wilens TE, et al. *Pediatrics.* 2003;111:179-185.; Faraone, Wilens. *J Clin Psych.* 2004.

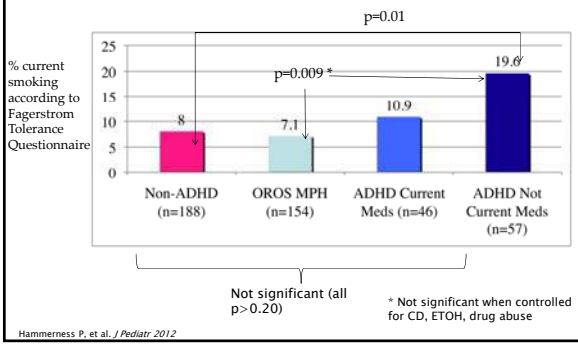
Concurrent Stimulant Treatment Reduces Smoking Initiation in ADHD Youth

(Monuteaux et al. J Clin Psych: 2007)



74% reduced risk for smoking initiation over the course of the follow-up period for stimulant treatment, relative to no stimulant treatment

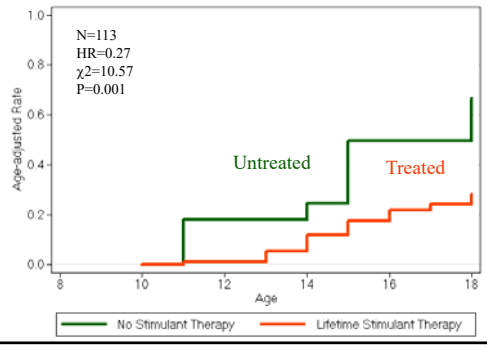
Treating Adolescents with OROS MPH Improves Smoking Outcomes Up to 2 years (mean 10 mo)



Hammerness P, et al. *J Pediatr 2012*

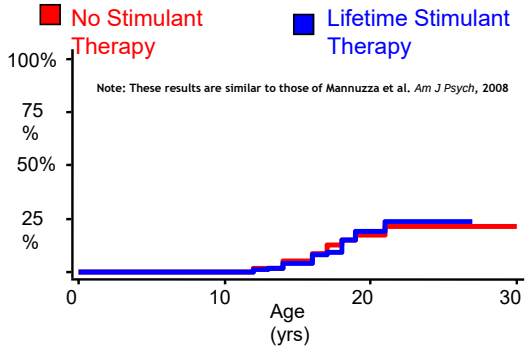
MGH Study of Adolescent Girls with ADHD: Stimulant Treatment Protects Against Subsequent SUD

(Wilens et al. Arch Ped Adoles Med, 2008)

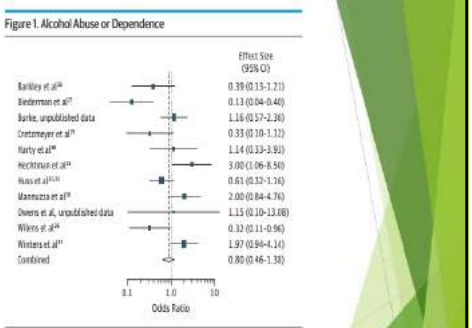


Treatment of ADHD Does Not Impact Later Alcohol Dependence in Young Adults

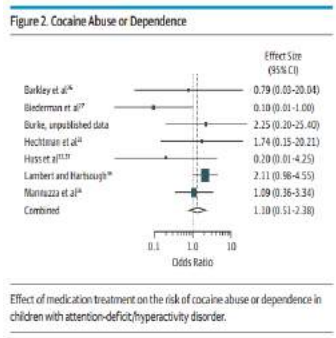
(Biederman, Monateaux, Wilens et al, *Am J Psych*, 2008)



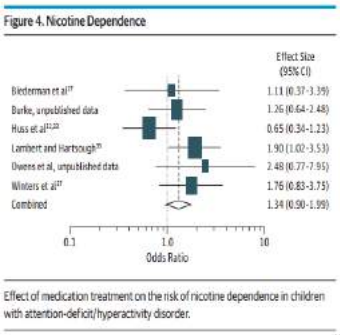

Stimulant Medication and Substance Use Outcomes
A Meta-analysis



Humphreys KL, Eng T, Lee SS. Stimulant Medication and Substance Use Outcomes: A Meta-analysis. JAMA Psychiatry. 2013;70(7):740-749



Humphreys KL, Eng T, Lee SS. Stimulant Medication and Substance Use Outcomes: A Meta-analysis. JAMA Psychiatry. 2013;70(7):740-749



Humphreys KL, Eng T, Lee SS. Stimulant Medication and Substance Use Outcomes: A Meta-analysis. JAMA Psychiatry. 2013;70(7):740-749

Groenman et al. *Br J Psychiatry* 2013; 203:112-119

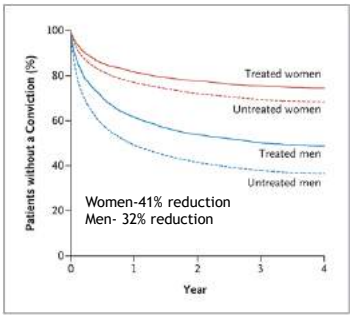
Stimulant ADHD medication and risk for SUD

Zheng Chang, MSc, Paul Lichtenstein, PhD, Linda Halldner, MD, PhD, Brian D'Onofrio, PhD, Eva Serlachius, MD, PhD, Seena Fazel, MD, Niklas Långström, MD, PhD, and Henrik Larsson, PhD

Chang Z, et al. Stimulant ADHD medication and risk for substance abuse. J Child Psychol Psychiatry. 2014;55(8):878-85.

Medication for ADHD Reduces Criminality (including Drug Offenses)

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



Swedish national registers (N= 25,656 with ADHD-about 50% on medications Approx. 40% of convictions related to drug offenses (Tx OR=0.6). No difference in type of ADHD medication (stimulants, nonstimulants) or level of crime.

Methods

- Data collected from Swedish national registers
- Studied individuals were born 1960-1998 and diagnosed with ADHD (N= 38,753; 26,249 males & 12,504 females)
- Authors examined the association between stimulant ADHD medication in 2006 and SUD during 2009
- 49% of males and 53% of females received stimulant medication
- SUD→ indexed by substance-related crime, hospital visits or death
  - 6.2% with SUD "entry" with ADHD vs 0.5% in general population

Chang Z et al.. J Child Psychol Psychiatry. 2014;55(8):878-85

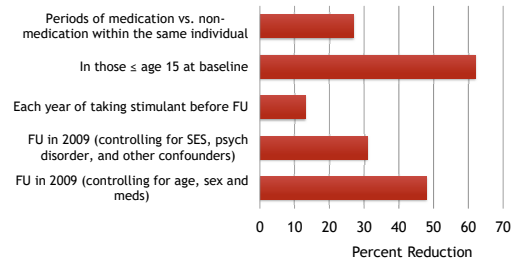
Results

- ADHD medication was not associated with increased rates of substance abuse
- In fact, significant reductions in substance use were observed among those treated with stimulant medication for ADHD
- These reductions remained significant after controlling for age, sex, SES, psychiatric disorders, and other confounding factors
- Additionally, the longer the duration of medication intervention, the lower the rate of substance abuse

Chang Z et al.. J Child Psychol Psychiatry. 2014;55(8):878-85

Among those subjects treated with stimulant ADHD medication, there was a significant reduction in rates of substance use disorders

(Chang Z et al. Stimulant ADHD medication and risk for substance abuse. J Child Psychol Psychiatry. 2014;55(8):878-85).



Individuals were born 1960-1998 and diagnosed with ADHD (26,249 men and 12,504 women; circa 50% on stimulant medication in 2006); Authors examined the association between stimulant ADHD medication in 2006 and substance abuse during 2009 (e.g. substance-related crime, hospital visits or death; outcomes ca 6% vs 0.5% ADHD vs gen pop)

Age of Onset, Duration, and Type of Medication Therapy for ADHD and Substance Use During Adolescence: A US National Study

- Study of U.S. Survey Data from 2004-2013
- Monitoring the Future (MTF) is a yearly, cross sectional study of representative High School seniors in 127 public and private schools
- Cohorts in this study were N=10 (senior year 2005-2014)
- N=40,358 overall
  - 3,539 treated ever with stimulants
  - 1,332 only treated w nonstimulants
  - Controls never on ADHD medications (could include untreated ADHD)

McCabe, West, Dickinson, Wilens. *Age of Onset, Duration, and Type of Medication Therapy for ADHD and Substance Use During Adolescence: A Multi-Cohort National Study.* J Am Acad Child Adoles Psych 2016;55(6):479-486

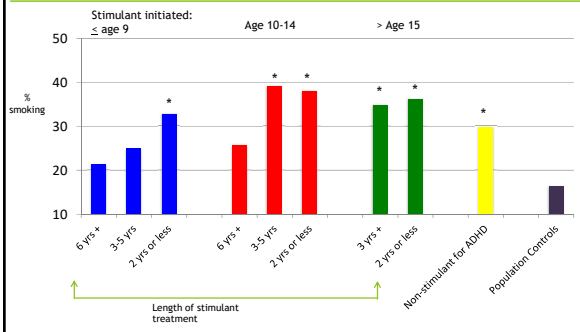
Age of Onset, Duration, and Type of Medication Therapy for ADHD and Substance Use During Adolescence: A US National Study

- Examination: ADHD (stimulant treated, nonstimulant treated), age at onset of stimulant, duration of stimulant treatment (N's evenly distributed amongst duration/onset)
- Main outcomes: Cigarette, marijuana, alcohol and other substance use (past month, 12 months)

McCabe, West, Dickinson, Wilens. *Age of Onset, Duration, and Type of Medication Therapy for ADHD and Substance Use During Adolescence: A Multi-Cohort National Study.* J Am Acad Child Adoles Psych 2016;55(6):479-486

ADHD Treatment and Past-Month Cigarette Smoking

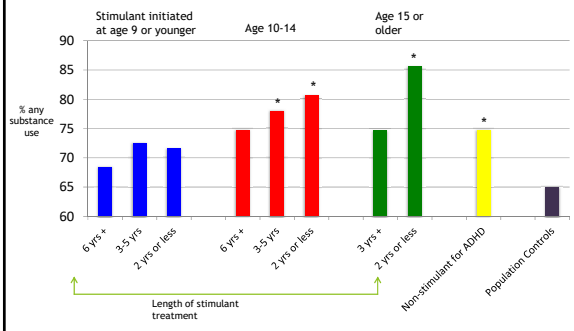
(N=40,358: Monitoring the Future Survey, 10 Cohorts of senior years 2005 to 2014)



McCabe, West, Dickinson, Wilens. *Age of Onset, Duration, and Type of Medication Therapy for ADHD and Substance Use During Adolescence: A Multi-Cohort National Study.* J Am Acad Child Adoles Psych 2016;55(6):479-486.

ADHD Treatment and Past-Year Any Substance Use

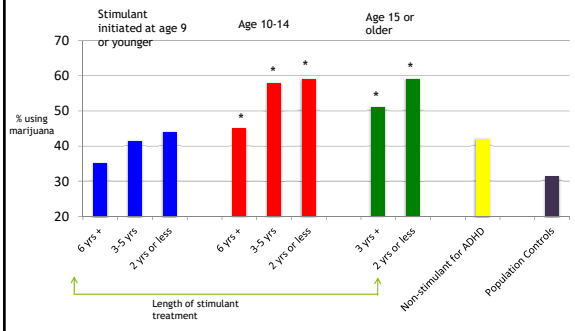
(N=40,358: Monitoring the Future Survey, 10 Cohorts of senior years 2005 to 2014)



McCabe, West, Dickinson, Wilens. *Age of Onset, Duration, and Type of Medication Therapy for ADHD and Substance Use During Adolescence: A Multi-Cohort National Study.* J Am Acad Child Adoles Psych 2016;55(6):479-486.

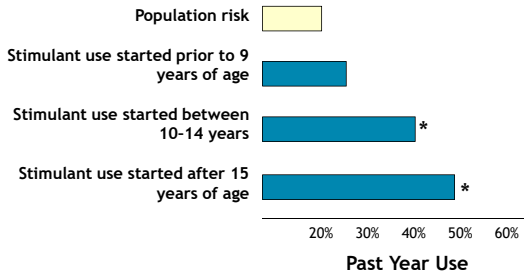
ADHD Treatment and Past-Year Marijuana Use

(N=40,358: Monitoring the Future Survey, 10 Cohorts of senior years 2005 to 2014)



McCabe, West, Dickinson, Wilens. *Age of Onset, Duration, and Type of Medication Therapy for ADHD and Substance Use During Adolescence: A Multi-Cohort National Study.* J Am Acad Child Adoles Psych 2016;55(6):479-486.

MTF Study: Early ADHD Treatment Reduces Marijuana Use in High School



10 Cohorts of high school seniors 2005 to 2014 (N = 40,358; ~10% with ADHD).

*P < .001 vs controls. Data shown are for those with longer duration treatment (e.g. > 3-6 years/group)

McCabe SE, et al. *J Am Acad Child Adolesc Psychiatry*. 2016;55(6):479-486.

Monitoring the Future: ADHD Meds & Substance Use Summary

- 12% of HS Seniors used stimulants/nonstimulants for ADHD
- No differences in cigarette/substance use between early-onset and long duration stimulant use and population controls
- Higher substance use was noted with *later onsets* and *shorter duration* stimulant use- especially in adolescents >15 years of age
- Nonstimulants did not appear to provide a protective effect on substance use

ADHD Medication Reduces SUD: Within Subjects Analyses

- Study of U.S. Claims Data from 2004-2013
- Follow-up of from 1 to 120 months (median 15.5 months)
- N = 2,993,887 ADHD > 13 years old (47% female)
- Stimulants and atomoxetine (no other [adjunct use])
- Age at follow-up (median 21 yrs [male], 28 yrs [female])
- Controls: Matched 1:1 on sex, enrollment
- Examination: Main outcome within subject changes based on medication periods vs nonperiods, sex, age groups
- Data adjusted for confounds
- Secondary vs nonADHD controls
- Outcome: Substance related events

(Patrick et al. Am J Psych 2017: 877-885)

ADHD Medication and SUD Results

- Of almost 3 million individuals with ADHD, 85% were on ADHD medication >1 month.
- Approximately 2% (N=58,851) with SUD claims
- ADHD > Controls for SUD claims
  - OR 2.7 for males (e.g. 2.7 times the risk for SUD)
  - OR 3.3 for females (e.g. 3.3 times the risk for SUD)

(Patrick et al. Am J Psych 2017: 877-885)

ADHD Medication and SUD Results

- Comparison of Medicated ADHD vs Never Medicated ADHD
  - Treated males 24% lower than untreated males for SUD risk (3.1% vs 4%, OR=0.76, CI 0.75-0.78)
  - Treated females 6% lower than untreated females for SUD risk (2.6% vs 2.8%, OR=0.94, CI 0.91-0.97)

(Patrick et al. Am J Psych 2017: 877-885)

ADHD Medication and SUD Results

- Comparison of periods of medicated vs unmedicated ADHD individuals (*primary outcome*)
  - Males 35% lower risk: treated periods < untreated periods for SUD risk (OR=0.65, CI 0.64-0.67)
  - Females 31% lower risk: treated periods < untreated periods for SUD risk (OR=0.69, CI 0.67-0.71)

For first-only SUD incidents, medication was associated with 55% and 43% lower SUD events in male and females, respectively

(Patrick et al. Am J Psych 2017: 877-885)

ADHD Medication and SUD Results

- 2 year outcomes
  - Within individual models ADHD medication predicted a 19% and 14% reduction in SUD risk (ORs 0.81, 0.86; males/females)
  - Population models show 2-10% increase in risk for SUD after medication periods (Ors 1.02/1.1 male/female)

(Patrick et al. Am J Psych 2017: 877-885)

ADHD Medication and SUD Conclusions

- Largest US database examining ADHD medication treatment and later SUD
- Medicated ADHD was associated with lower SUD risk when compared to unmedicated ADHD groups
- Medication periods were generally associated with reduced risk of SUD events
- Most findings maintained long-term
- SUD reductions associated with ADHD medication similar to Scandinavian and some US Studies
- No evidence of worsened SUD

(Patrick et al. Am J Psych 2017: 877-885)

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

Sean Esteban McC… Schulenberg, PhD

Clinical Guidance

- About one in every six US high school seniors reported lifetime nonmedical use of prescription stimulants for ADHD. Especially noteworthy is that nonmedical use of prescription stimulants is highly prevalent (43%) among adolescent medical users of prescription stimulants.
- Nonmedical use of prescription stimulants (within or outside of stimulant medication therapy) during adolescence is associated with higher risk of SUD symptoms and lower educational attainment almost two decades later at age 35 years, controlling for adolescent sociodemographic, other drug use, and behavioral controls.
- In contrast, adolescents who use prescription stimulant therapy appropriately have risks of adult SUD symptoms and educational attainment in adulthood similar to those of population controls.

Objective: To assess the pro… between the medical and no… stimulants during adolescen… tional attainment and sub… symptoms in adulthood (age…

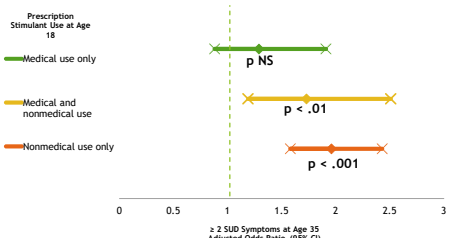
Method: A survey was sel… representative probability sa… niors from the Monitoring th… individuals were followed … ence (age 18, high school … adulthood (age 35, 1993–201…

Results: An estimated 8.1%… scription stimulants, and 16.… of prescription stimulants by … 43% of adolescent medical us… had also engaged in nonm… stimulants during adolescen… cent 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 …m population controls …ctivity disorder [ADHD] … ADHD during adoles… …and SUD symptoms in …nt nonmedical users of …without medical use) had …more SUD symptoms in …ion controls and medical …without nonmedical use …prescription stimulants is …cribed these medications. …d be carefully monitored …s behavior is associated …nt and more SUD symp…

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

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

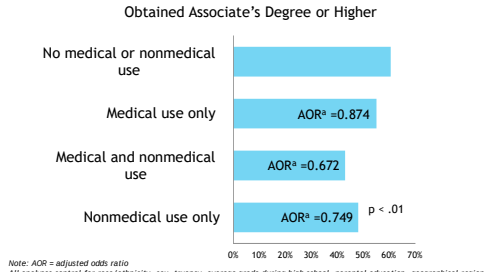
Medical and Nonmedical Use of Prescription Stimulants at Age 18 Years Is Linked to SUD at Age 35 Years (N=8362)



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.
Attrition weights applied and sample sizes vary due to missing data on the dependent measures.

McCabe SE, Veliz P, Wilens TE, Schulenberg JE. J Am Acad Child Adolesc Psychiatry. 2017 Mar;56(3):226-233.e4

Educational Attainment at Age 35 Years as a Function of Medical and Nonmedical Use of Prescription Stimulants at Age 18 Years (N=7813)



Note: AOR = adjusted odds ratio
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.
Attrition weights applied and sample sizes vary due to missing data on the dependent measures
**

McCabe SE, Veliz P, Wilens TE, Schulenberg JE. J Am Acad Child Adolesc Psychiatry. 2017 Mar;56(3):226-233.e4

Adolescents Prescription Stimulant Use and Adult Functional Outcomes: Conclusion

- This comprehensive, large-scale US investigation did not find different rates of SUD in medicated ADHD groups compared to controls
- Those misusing stimulants (±medical use) by age 18 years were at heightened risk for SUD at follow-up (age 35 years)

McCabe SE, Veliz P, Wilens TE, Schulenberg JE. J Am Acad Child Adolesc Psychiatry. 2017 Mar;56(3):226-233.e4

Is ADHD Pharmacotherapy a Risk Factor For Subsequent Substance Use Disorders?

Conclusions

Prospective clinical trials of treated children and adolescents with ADHD show improved cigarette smoking and SUD outcomes

Naturalistic studies appear to support improved cigarette smoking and SUD in treated-adolescents with ADHD.

However, naturalistic studies into adulthood are equivocal

Is ADHD Pharmacotherapy a Risk Factor For Subsequent Substance Use Disorders?

Conclusions

More recently, large registry and survey studies show substantial reductions in cigarette and substance use & disorders

Stimulant misuse by those with/without ADHD *IS* associated with significant functional impairments and later SUD in mid-adulthood

Comments or Questions?

Presenter Disclosure – Prior 12 Months

Speaker (Honoraria):

- University of Alabama Annual ADHD Conference
- Center for Pediatric Excellence 10th Annual ADHD Conference, Ottawa, Canada
- Patrick Beaver Learning Resource Center and Catawba Valley Memorial Hospital, Hickory, NC
- Butler University Conference on Neuroscience and Education, Indianapolis, IN
- Seminarer Denmark, Copenhagen
- South Dakota Counselors Association, Sioux Falls, SD
- Nova University, Ft. Lauderdale, FL
- International Dyslexia Association annual conference, Atlanta, GA
- Yachad, Union of Orthodox Jewish Associations, Brooklyn, NY

Royalties:

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

Industry Speaker/Consultant:

- Eli Lilly (Taiwan) - Speaker
- Ironshore Pharmaceutical & Development, Inc. – Consultant
- Takeda Pharmaceutical Company - Consultant
- AiCure - Consultant

Health Outcomes of ADHD: Impact on Life Expectancy?

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Websites:
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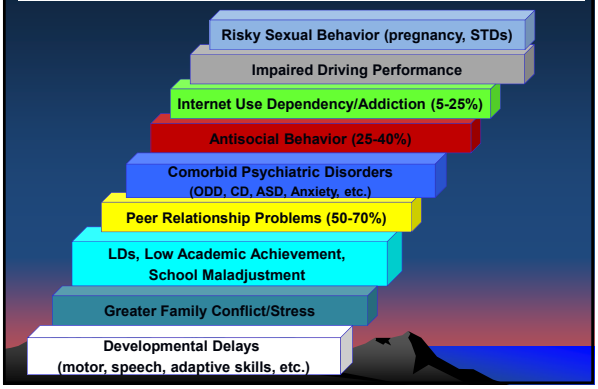
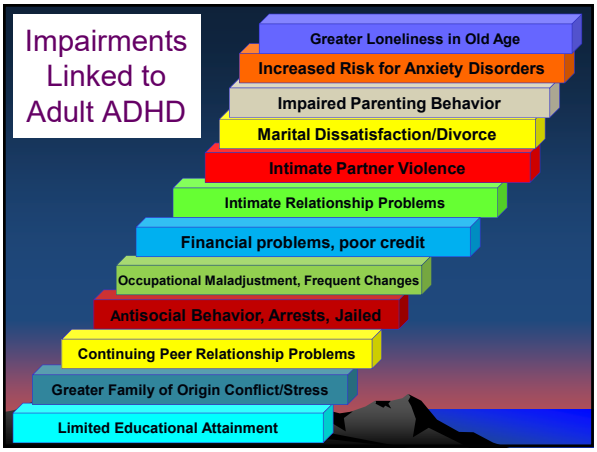
Adhdlectures.com

Impairments Associated with Child/Teen ADHD



Impairments Linked to Adult ADHD



Extant Evidence for Earlier Mortality

Increased Risk for Earlier Mortality

- ✓ Beginning in 2000 with the Freidman et al. follow-up study of the "Termites," studies and reviews continued to show that decreased child conscientiousness is associated with earlier death by all causes (<25th percentile = -7 years) Friedman (2000) *Journal of Personality, 68*, 1089-1107. Hampson (2008) *Current Directions in Psychological Science, 17*, 264-268.
- ✓ Given that ADHD is linked to very low conscientiousness, being the bottom 5-7% of the population, it should be linked to an even greater reduction in life expectancy.
- ✓ Greater child externalizing behavior has been linked to 1.5-2x greater risk of mortality by age 46 [Jokela et al. (2009) *Journal of the American Academy of Child and Adolescent Psychiatry, 48.]*

More evidence of earlier mortality

- ✓Barbaresi et al. noted an increased risk for suicide in their Mayo Clinic longitudinal study (SMR = 4.83) *[Pediatrics (2013), 131, 637-644]*
- ✓London & Landes found that adults with ADHD are 1.8x more likely to die within any 4 year period than the general population. [*Preventive Medicine (2016) 90*, 8-10.]
- ✓ Dalsgaard et al. observed that the risk for mortality increases with age from 1.86 in children with ADHD to 4.25 in adulthood. And those with ADHD are 3x more prone (13% vs. 4%) to death by accident. [Dalsgaard, S. et al. (2015). *Lancet, 385,* 2190-2196.]

Other Reasons to Expect ADHD to be Linked tp Shortened Longevity

ADHD Related Health Concerns

- Less healthy "Western style" diet
- More likely to be overweight and eat impulsively
  - Twice as likely to be obese by adulthood; risk increases with age
  - Conversely, ADHD is over-represented in patients treated for obesity at eating disorders clinics (32% vs. 4% population prevalence)**
- Higher risk in females for eating disorders (10-20% of ADHD females vs. 0-5% of controls)* & increased eating pathology***
  - EDs are 3.5 x more likely in females with ADHD by adolescence
  - Bulimia is most likely subtype, being 5.6x more likely by age 16
  - ED linked to earlier impulsivity, peer rejection & harsh parenting,** and concurrent MDD, anxiety disorders, & ODD/CD*

*Biederman et al. (2007). *Journal of Developmental and Behavioral Pediatrics, 28, 302-307.*
*Sobanski et al. (2008). *European Psychiatry, 23, 142-149.*
** *Journal of Obesity, 2009, March issue.*
***Mikami et al., (2008). *Journal of Abnormal Psychology, 117,* 225-235.

More Medical-Health Concerns

- Greater likelihood of using tobacco, marijuana, and alcohol and greater frequency of using these substances*
- Growing risk of cardiovascular disease (CHD)*
  - Greater body mass index (higher percent obese), especially in females
  - Lower HDL cholesterol and higher Total/HDL ratio
  - Higher atherosclerotic risk to coronary arteries
  - Higher Framingham CHD risk percent over next 5 and 10 years
- Greater risk for developing dementia (5.5%) which is 3.4 times higher when controlling for other factors***
- Possibly greater risk for mid-late life cancer ?

*BARKLEY, R. ET AL. (2008). *ADHD IN ADULTS: WHAT THE SCIENCE SAYS. NEW YORK: GUILFORD.*
**GOODWIN ET AL. (2009) *PSYCHOLOGICAL MEDICINE, 39(2), 301-311.*
***ZENG, N S. ET AL. (2017). *JOURNAL OF ATTENTION DISORDERS,* EPUB AHEAD OF PRINT.

Computing the Life Expectancy of Children with ADHD Followed to Young Adulthood

Milwaukee Study Collaborators

- Mariellen Fischer, Ph.D., Co-PI
  - Department of Neurology, Medical College of Wisconsin (MCOW), Milwaukee, WI
- Research Assistants:
  - Lori Smallish, Lori Bauer (MCOW)
- Health Screeners – Physician Assistants:
  - Hope Schrader, Kent Shiffert (MCOW)
- Data Entry Software Program
  - Kenneth Fletcher, Ph.D., University of Massachusetts Medical School
- Data Entry
  - Peter Leo

Milwaukee Study Methods

- 158 children ages 4-11 years diagnosed as hyperactive child syndrome in 1978-1980
  - Had significant symptoms of inattention, impulsiveness, and hyperactivity as reported by parents
  - Were +2SDs on Conners Hyperactivity Index & Werry-Weiss-Peters Activity Rating Scale, and +1SD (6 or more settings) on Home Situations Questionnaire
  - Onset of symptoms by 6 years of age
  - Excluded children with autism, psychosis, deafness, blindness, epilepsy, significant brain damage, etc.
- 81 control children from same schools and neighborhoods matched on age and obtained via a "snowball" sampling procedure
- Most children re-evaluated at mean ages of 15 (C=78% & H=81%), 21 (C=93 & H=90%), and now 27 years (C=93% & H=85%).
- To be currently ADHD (H+ADHD), participants had to have 4+ symptoms on either DSM-IV symptom list and 1+ domains of impairment (out of 8) by self report (N=55). Remainder (N=80) were grouped as H-ADHD.
- Groups were 83-94% males

Source: Barkley, R. A., Murphy, K. R., & Fischer, M. (2008). *ADHD in Adults: What the Science Says*. New York: Guilford Press.

Life Expectancy Calculator
Goldenson Center for Actuarial Research[1]

- Fixed variables – same entry for all participants, regardless of analysis
  - Male (83-94% of all groups were male)
  - Age 27 years (mean for all groups)
  - Mean height for group (5 ft. 10 in. for all 3 groups)
  - Mean income (always $25-50K categorization)
  - Type 2 diabetes (always No)
  - Current Health (Good; options Poor, Fair, Very Good, Excellent)
  - Driving accidents (always 0; options: 1/yr or 2+/yr)

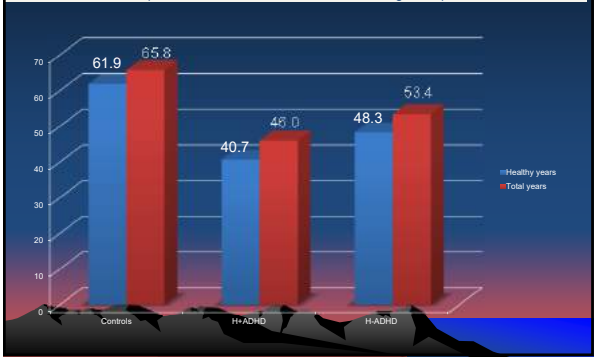
[1]https://apps.goldensoncenter.uconn.edu/HLEC/

More Calculator Entries

- Fixed variables adjusted for each group (C, H+, H-) in analysis of typical (average) group comparison:
  - Mean weight for group (194, 209, 205, respectively)
  - Diet (Good for controls, Fair for both ADHD groups)
  - Sleep (8+ hrs/night for controls, <5 for H+group, 5-8 for H– sleep concerns were 14%, 52%, 32%, respect.)
- Variables [binary] adjusted for analysis of Worst and Best case scenarios
  - Education (non-HS, HS, college, ot graduate school)
  - Current Smoker – No or Yes
  - Alcohol Use - (No [rarely] or Yes [used mean drinks per week for group]
  - Diet (Good for controls, Fair for both ADHD groups)
  - Regular Exercise (No [rarely] or Yes [3-4 days/wk]; other options: 1-2 days/wk, 5+ days/wk)

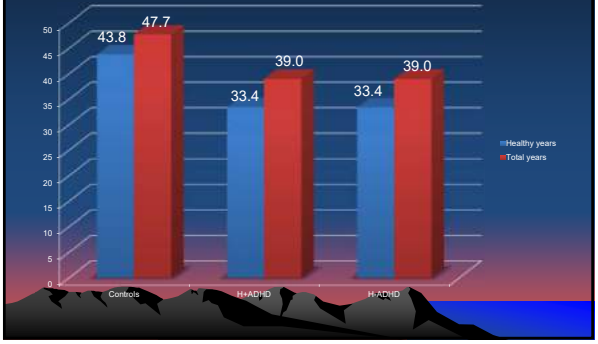
Life Expectancy (yrs. Left) – Typical

(Controls – College, Nonsmoker, 3-7 drinks/wk, Reg. Exer.)
(ADHD+H – HS, Smoker, 8+ drinks/wk, Rarely Exer.)
(ADHD-H – HS, Smoker, 3-7 drinks/wk, Reg. Exer.)

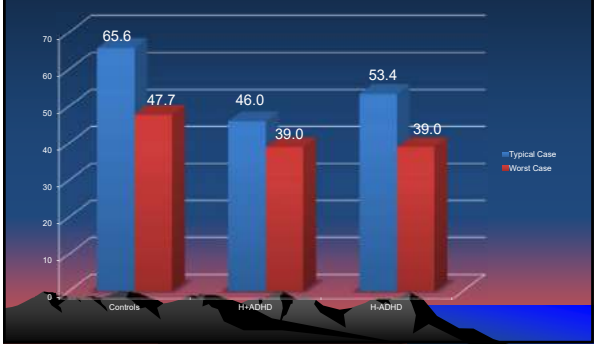


Life Expectancy – Worst Case (+/- 1 SD)

(Controls – Wgt = 245, College, Income 25-50K, Diet Fair, Sleep 5-8 hr, Smoker, 8+ drinks/wk, Rarely Exer.)
(ADHD+H – Wgt = 275, Not HS, Income <25K, Diet Poor, Sleep <5 hr., Smoker, 8+ drinks/wk, Rarely Exer.)
(ADHD-H – Wgt = 253, Not HS, Income <25K, Diet Poor, Sleep <8 hr., Smoker, 8+ drinks/wk, Rarely Exer.)



Life Expectancy (years left)
Typical vs. Worst Case



Limitations

- Group means or percentages served as data for entry into calculator; better to use calculator for each participants factors, then analyze life expectancy statistically
- Relatively small sample sizes for inferring risk to ADHD population
- Clinical samples of ADHD cases are more severe than community samples and so may exaggerate differences in life expectancy
- Severely limited number of females restricts results to male cases
- Lack of ethnic and regional diversity restricts results to mainly white populations and Midwest of US

Conclusions

- ADHD is a disorder of self-regulation
- The disorder is associated with more numerous and serious impairments in major life activities
- More recent research demonstrates an increased risk for earlier mortality in children and especially adults with ADHD, particularly related to accidents and suicide
- But ADHD is also linked to other health risks generally known to adversely impact life expectancy
- Evidence shown here indicates that childhood ADHD persisting to young adulthood may typically shorten life expectancy by nearly 20 years and by 12 years in nonpersistent cases compared to concurrently followed control children
- Thus ADHD is a serious public health problem
- Unrecognized and untreated ADHD may preclude successful management of the associated health impairments by primary care providers
- Yet ADHD is among the most treatable psychiatric disorders
- The greatest problems currently are under-recognition and treatment of adult ADHD and its health risks, access to evidence-based treatments, cost, and getting patients to remain in treatment through the critical adolescent and adult years.

The Risks and Benefits of ADHD Medication: A Pharmacoepidemiologic Perspective

Brian M. D'Onofrio, PhD
Indiana University & Karolinska Institutet

APSARD Conference
January 13, 2017

Collaborators & Funding

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University of Chicago
Robert Gibbons, Kwan Hur, & Benjamin Lahey

IU School of Medicine
David Dunn

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I have **NO** financial conflicts of interest.

Outline

- Introduction
  - Translational epidemiology
  - Importance of design features
- ADHD Medication
  - Substance use problems
  - Motor vehicle accidents
  - Quick review of other outcomes
- Summary
  - Review
  - Clinical implications

De Testimonio: on the evidence for decisions about the use of therapeutic interventions

Michael Rawlins

Table 1. A hierarchy of evidence. Reproduced with permission from the BMJ Publishing Group.[3]

Level	Criteria
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High-quality systematic reviews of case-control studies or cohort studies; or high-quality case-control or cohort studies with a very low risk of confounding, bias, or chance
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance.
2–	Case-control or cohort studies with a high risk of confounding, bias, or chance.
3	Non-analytic studies (eg case report, case studies)
4	Expert opinion

"The notion that evidence can be reliably or usefully placed in 'hierarchies' is illusory."

Major Limitations of RCTs

- Cannot study rare-but-serious events because of low statistical power (Shaw, 2016)
- Generalizability of findings (Surman, 2010)
  - Patients (e.g., severity of disease, comorbidity, SES)
  - Treatment (e.g., dose, timing of administration, duration of therapy)
  - Setting (e.g., treatment or monitoring by less specialists)

How Do We Proceed?


JAMA
Registries for Robust Evidence
Nancy A. Dreyer; Sarah Garner
JAMA. 2009;302(7):790-791 (doi:10.1001/jama.2009.1092)
http://jama.ama-assn.org/cgi/content/full/302/7/790
Online article and related content current as of August 19, 2009.

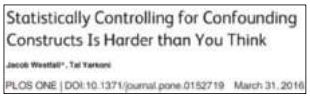
Building Trust in the Power of "Big Data" Research to Serve the Public Good
Eric B. Larson, MD, MPH
systems.[1] The report highlights the challenge of applying strict features of research oversight—much of which evolved

VIEWPOINT
Clinical Informatics
Prospects for a New Medical Subspecialty

Dreyer & Garner, 2009; Larson, 2013; Detmer & Shortliffe, 2014

How Do We Make Causal Inferences?

- Research needs to rule out plausible alternative hypotheses
- Importance of using design features
- Need converging evidence from multiple methods

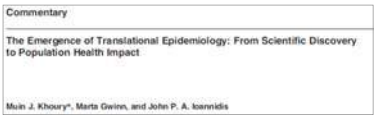

Statistically Controlling for Confounding Constructs Is Harder than You Think

Jacob Westfall*, Tal Yarkoni

PLOS ONE | DOI:10.1371/journal.pone.0152719 March 31, 2016

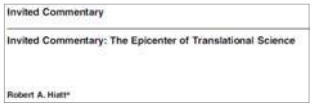
Kraemer et al., 1997; Rutter et al., 2001; Shadish, Cook, & Campbell, 2002

Translational Epidemiology


Commentary

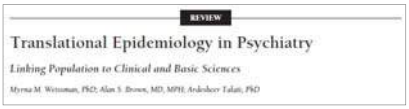
The Emergence of Translational Epidemiology: From Scientific Discovery to Population Health Impact

Muin J. Khoury*, Marta Gwinn, and John P. A. Ioannidis


Invited Commentary

Invited Commentary: The Epicenter of Translational Science

Robert A. Hiatt*


REVIEW

Translational Epidemiology in Psychiatry

Linking Population to Clinical and Basic Sciences

Myrna M. Weissman, PhD; Alan S. Brown, MD, MPH; Ardeshcer Talati, PhD

ADHD Medication

- RCTs have shown short-term effects
- Serious concerns about concomitant and long-term problems (e.g., substance use problems and suicidal behavior)


Drowned in a Stream of Prescriptions

Do Stimulants Prevent Substance Use and Misuse Among Youth With Attention-Deficit/Hyperactivity Disorder? The Answer Is Still Maybe

Benjamin I. Goldstein, M.D., Ph.D.

JOURNAL OF THE AMERICAN ACADEMY OF CHILD & ADOLESCENT PSYCHIATRY
VOLUME 52 NUMBER 3 MARCH 2013

JAMA Clinical Evidence Synopsis

Methylphenidate for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents

JAMA May 10, 2016 Volume 315, Number 18

ADHD Medication

- RCTs have shown short-term effects
- Serious concerns about concomitant and long-term problems (e.g., substance use problems and suicidal behavior)
- RCTs cannot explore rare/serious outcomes or long-term consequences
  - We don't know about serious consequences (Chan et al., 2016)
- Observation studies – Confounding by Indication
  - Patients who receive medication are different than those who do not!

Using United States Dataset

- ***MarketScan*** Commercial Claims and Encounters databases
  - Truven Health Analytics Inc. – IBM Watson Health
  - Inpatient, outpatient, and prescription claims
  - ***Large employers and health plans*** (private)
    - Employees, spouses, dependents, early retirees, COBRA
- 2005-2014 : ***~146 million*** individuals
  - In 2013: 51% female, 78% with drug coverage
  - Individuals covered for different amounts of time

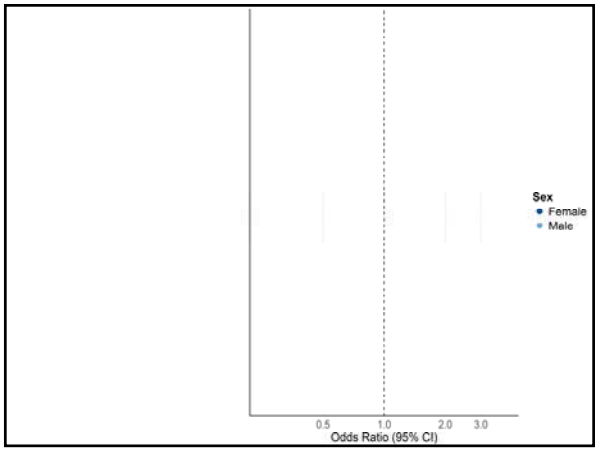
Within-Individual Analyses

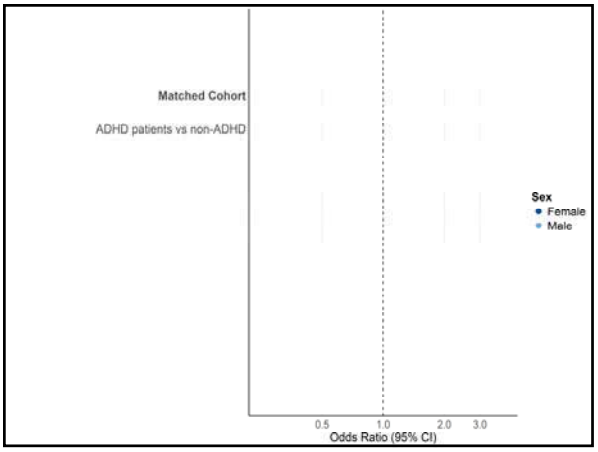
- Each person as his/her own control
- Compare risks when same individual is on versus off their medication
- Accounts for all stable factors
- Adjust for time-varying covariates to help rule out dynamic confounding

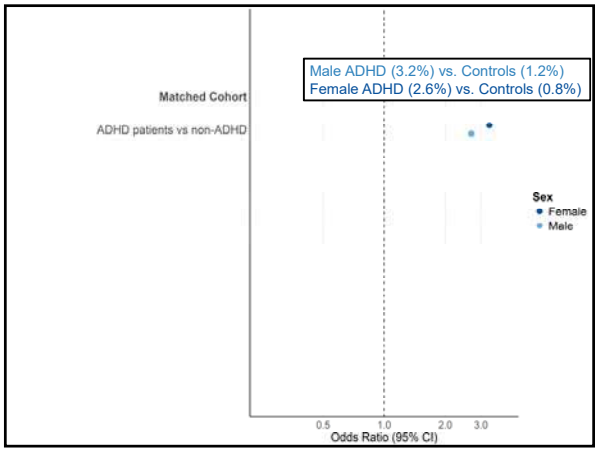
ADHD Medication & Substance Use Problems

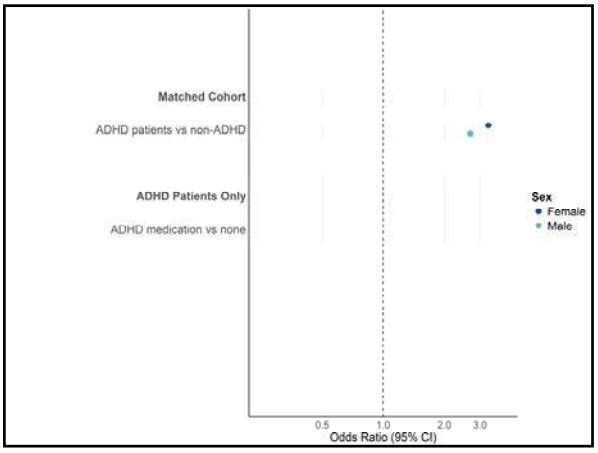
Sample	**Dataset with inpatient, outpatient, and filled prescription claims**	**2,993,887 ADHD patients**

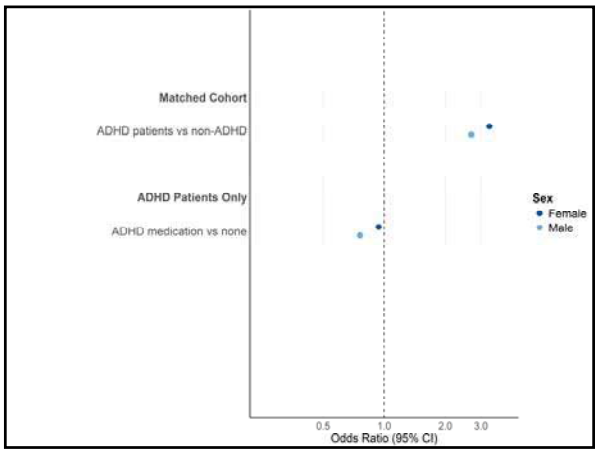
Quinn et al. 2017 *American Journal of Psychiatry*

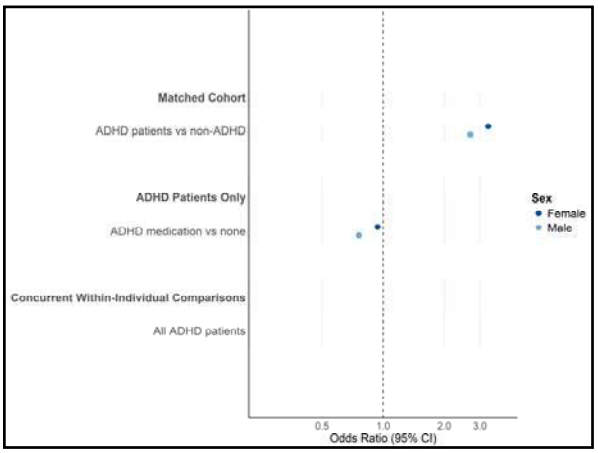


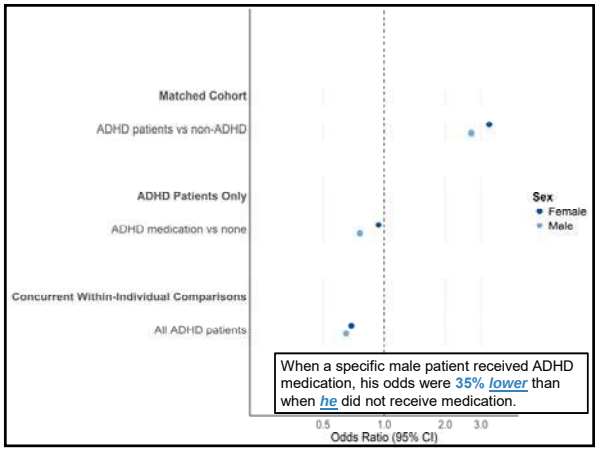


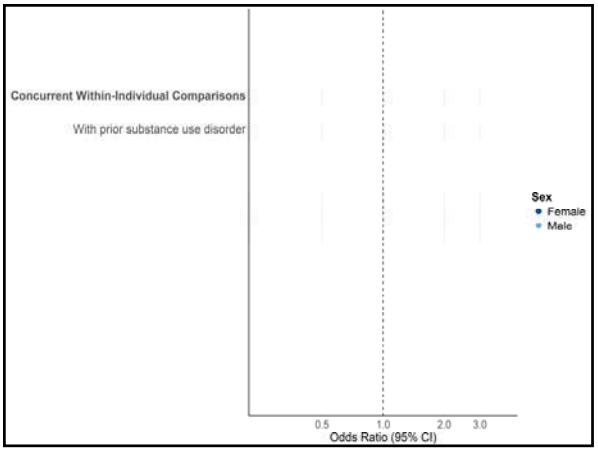


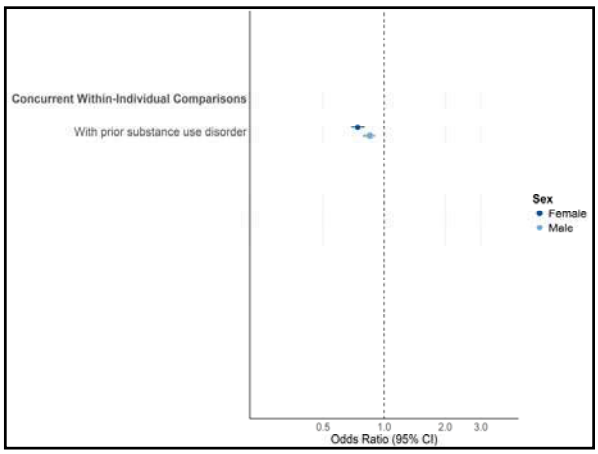


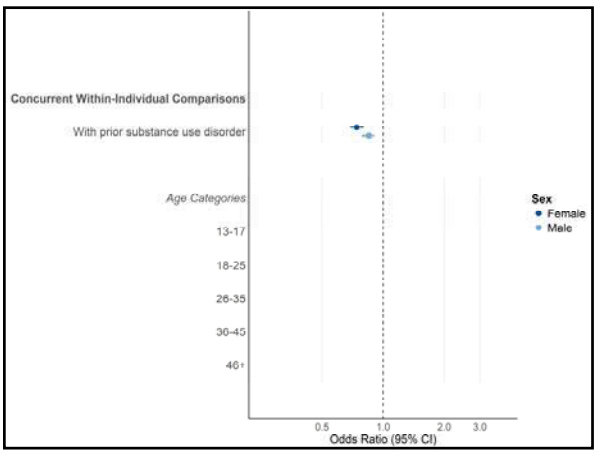

Matched Cohort
ADHD patients vs non-ADHD
ADHD Patients Only
ADHD medication vs none
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

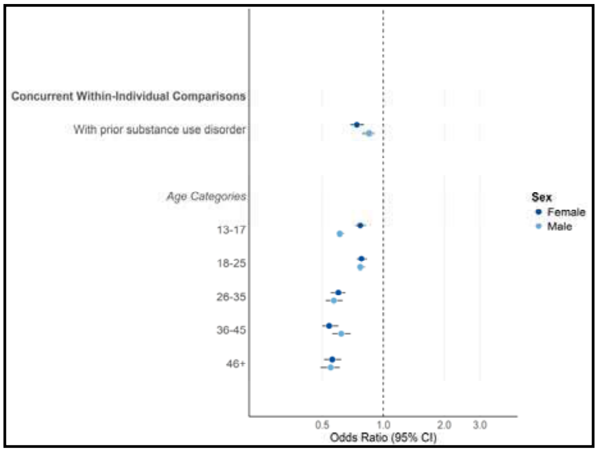

Matched Cohort
ADHD patients vs non-ADHD
ADHD Patients Only
ADHD medication vs none
Concurrent Within-Individual Comparisons
All ADHD patients
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

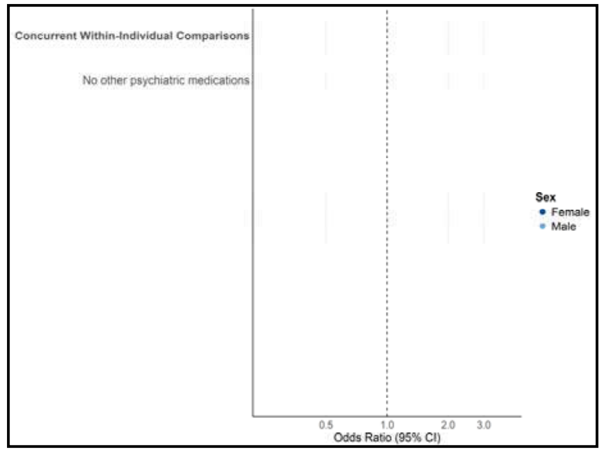

Matched Cohort
ADHD patients vs non-ADHD
ADHD Patients Only
ADHD medication vs none
Concurrent Within-Individual Comparisons
All ADHD patients
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)
When a specific male patient received ADHD medication, his odds were 35% lower than when he did not receive medication.

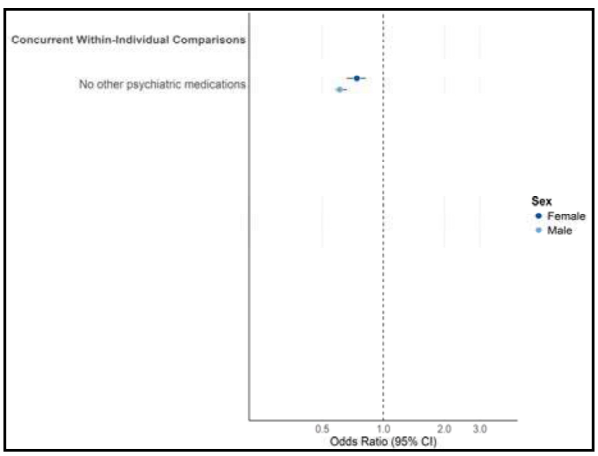

Concurrent Within-Individual Comparisons
With prior substance use disorder
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

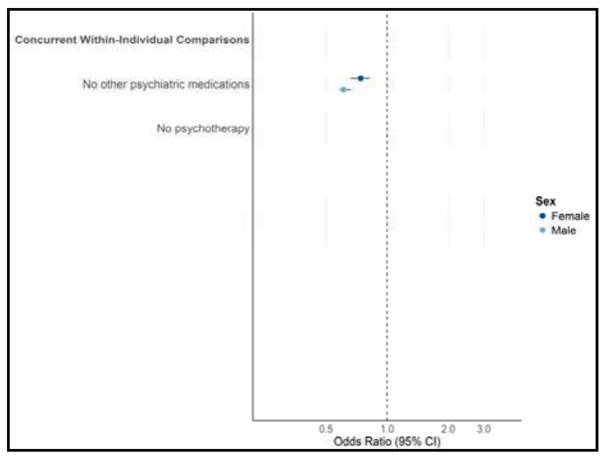

Concurrent Within-Individual Comparisons
With prior substance use disorder
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

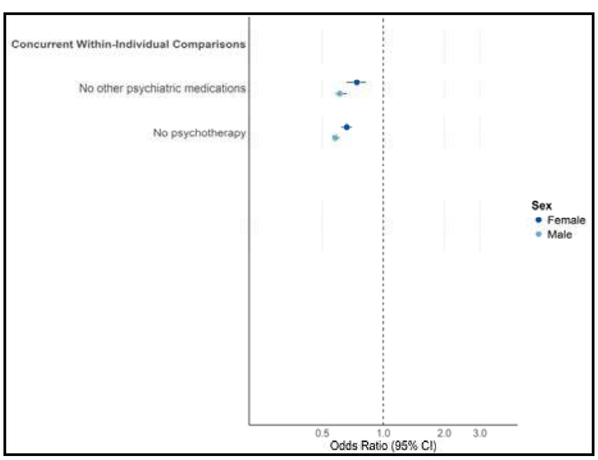

Concurrent Within-Individual Comparisons
With prior substance use disorder
Age Categories
13-17
18-25
26-35
30-45
46+
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

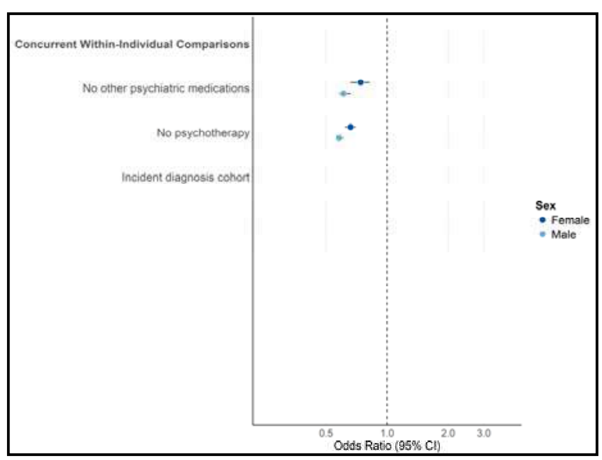

Concurrent Within-Individual Comparisons
With prior substance use disorder
Age Categories
13-17
18-25
26-35
36-45
46+
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

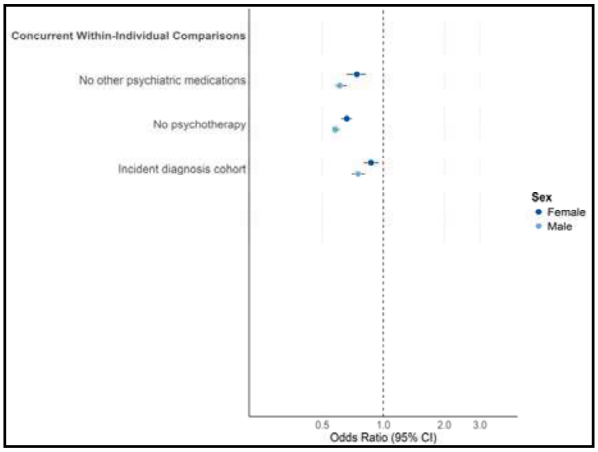

Concurrent Within-Individual Comparisons
No other psychiatric medications
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

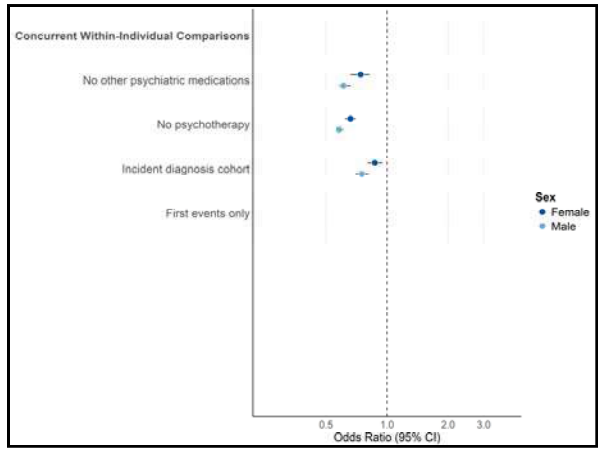

Concurrent Within-Individual Comparisons
No other psychiatric medications
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

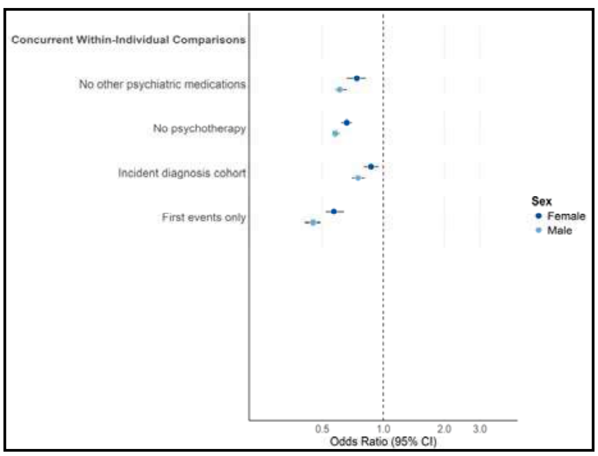

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

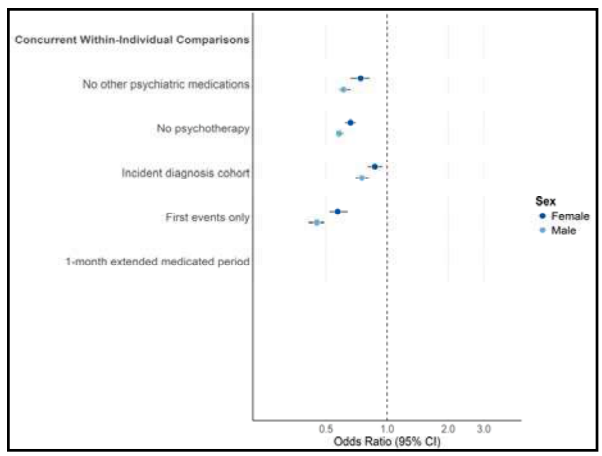

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

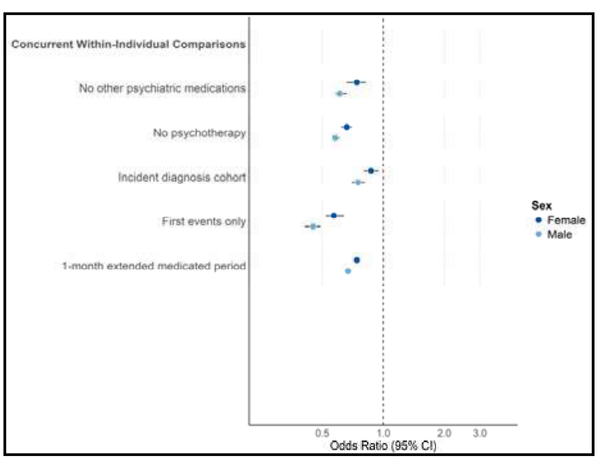

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

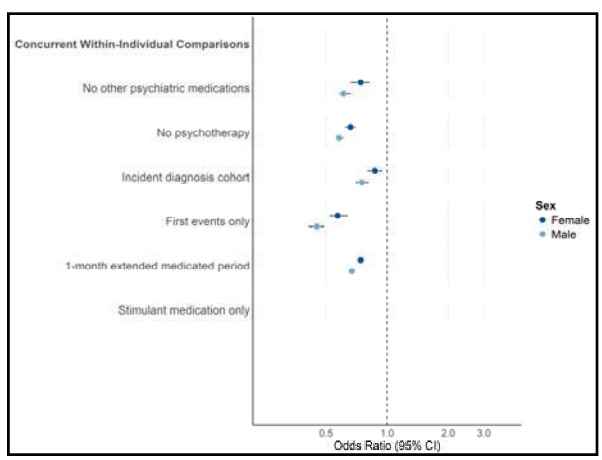

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

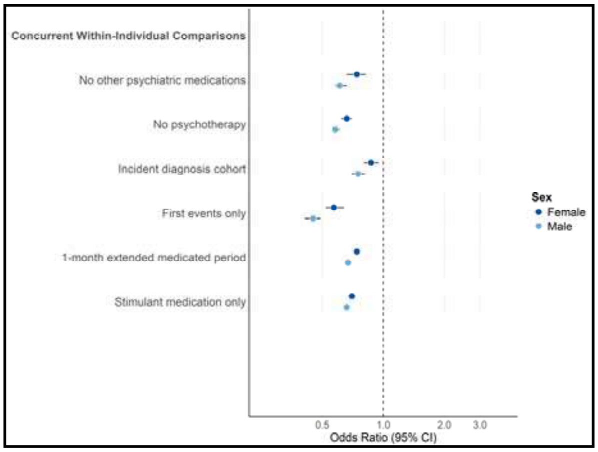

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
First events only
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

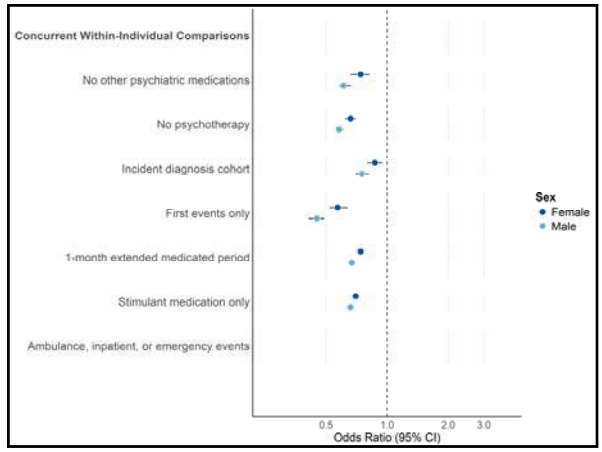

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
First events only
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

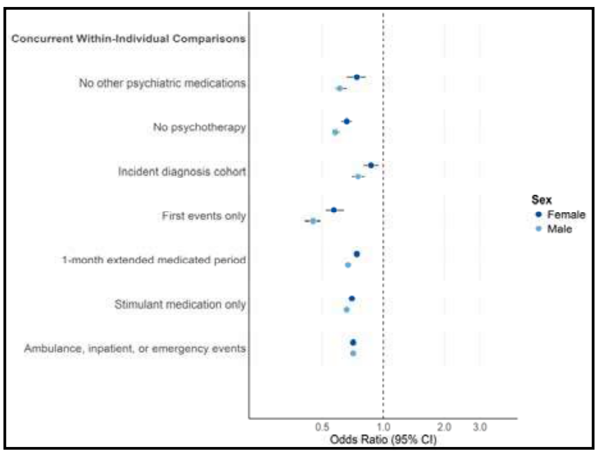

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
First events only
1-month extended medicated period
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

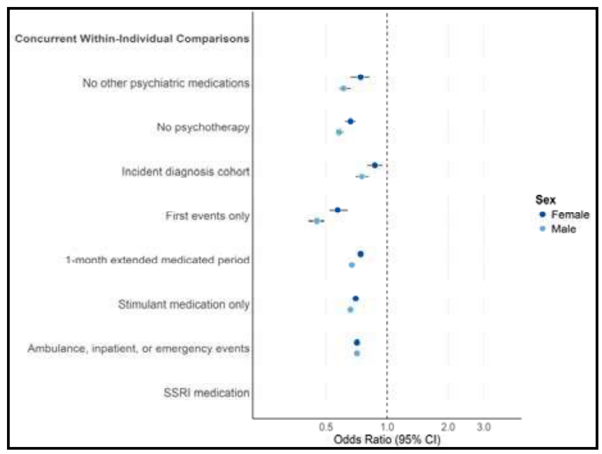

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
First events only
1-month extended medicated period
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

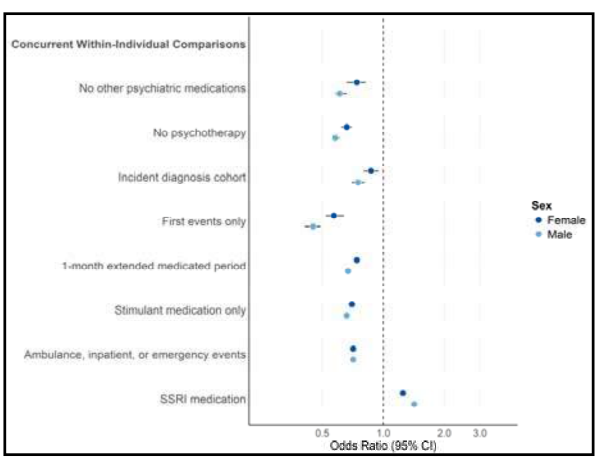

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
First events only
1-month extended medicated period
Stimulant medication only
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

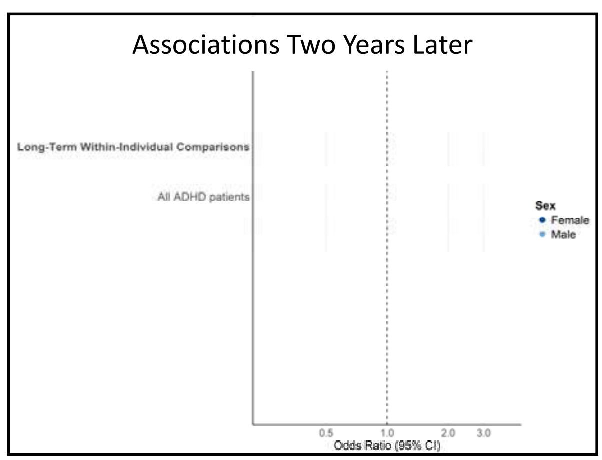

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
First events only
1-month extended medicated period
Stimulant medication only
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)


Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
First events only
1-month extended medicated period
Stimulant medication only
Ambulance, inpatient, or emergency events
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

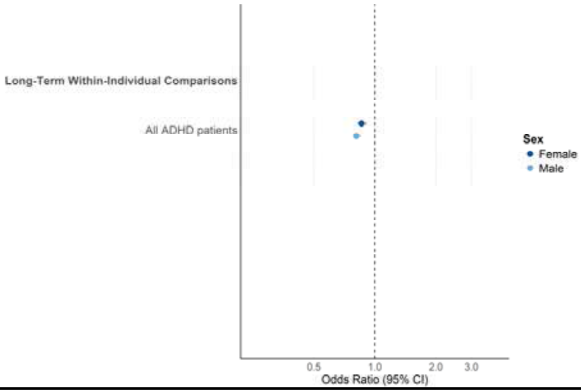

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
First events only
1-month extended medicated period
Stimulant medication only
Ambulance, inpatient, or emergency events
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)


Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
First events only
1-month extended medicated period
Stimulant medication only
Ambulance, inpatient, or emergency events
SSRI medication
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

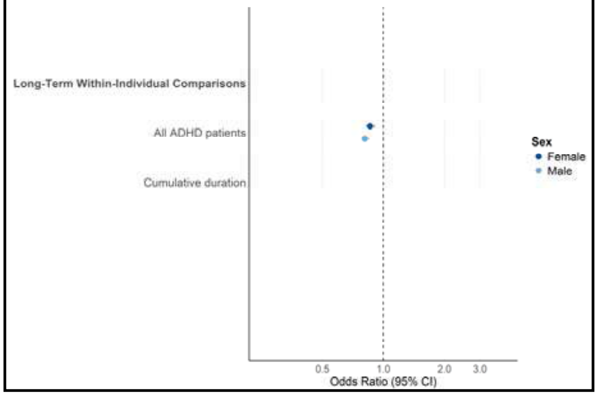

Concurrent Within-Individual Comparisons
No other psychiatric medications
No psychotherapy
Incident diagnosis cohort
First events only
1-month extended medicated period
Stimulant medication only
Ambulance, inpatient, or emergency events
SSRI medication
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)


Associations Two Years Later
Long-Term Within-Individual Comparisons
All ADHD patients
Sex
Female
Male
0.5
1.0
2.0
3.0
Odds Ratio (95% CI)

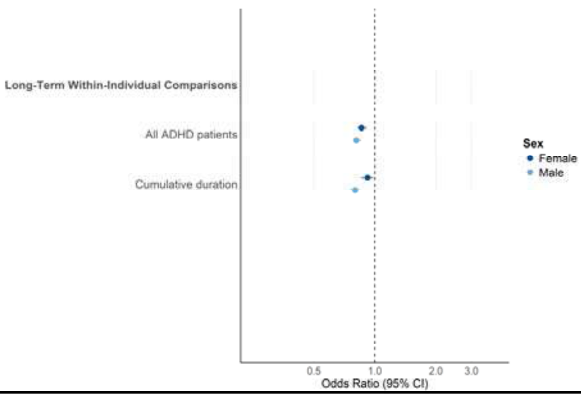
Associations Two Years Later



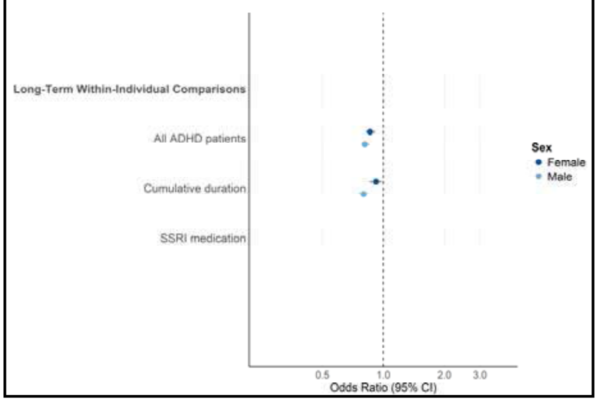
Associations Two Years Later



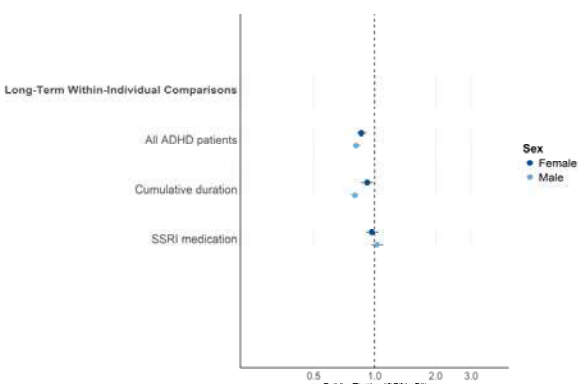
Associations Two Years Later



Associations Two Years Later



Associations Two Years Later



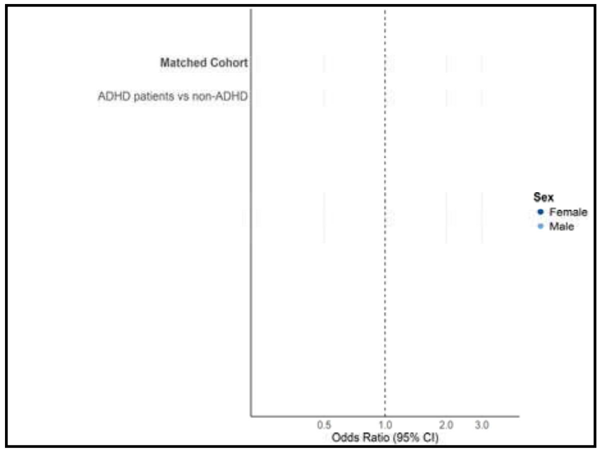
ADHD Medication & Motor Vehicle Accidents

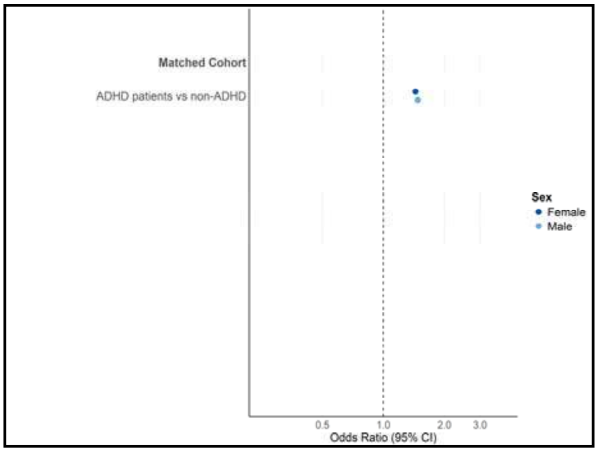
Chang et al. 2017 *JAMA Psychiatry*

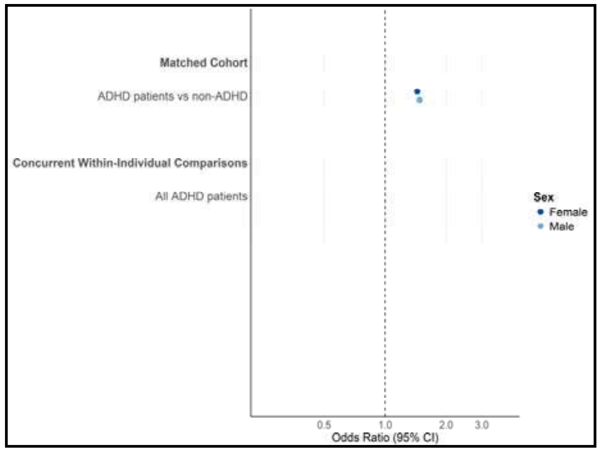
ADHD Medication & Motor Vehicle Accidents

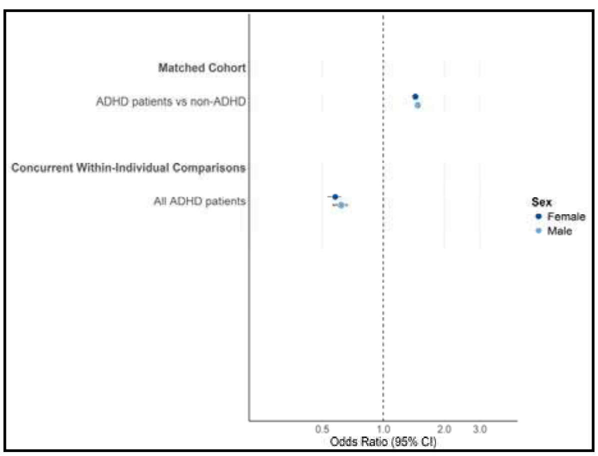
Sample	**Dataset with inpatient, outpatient, and filled prescription claims**	**2,319,450 ADHD patients** (ages 18 to 64, 52% female)

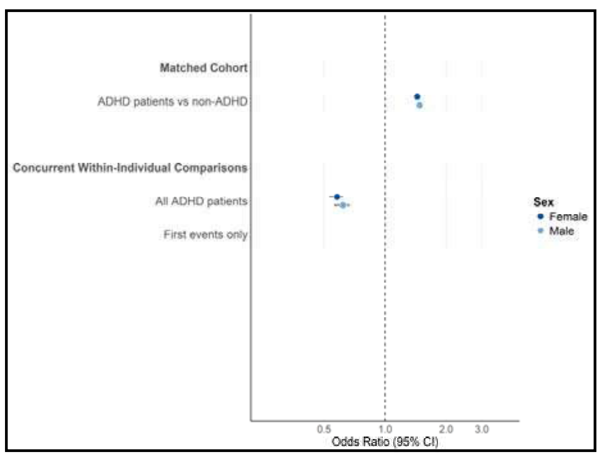
Chang et al. 2017 *JAMA Psychiatry*

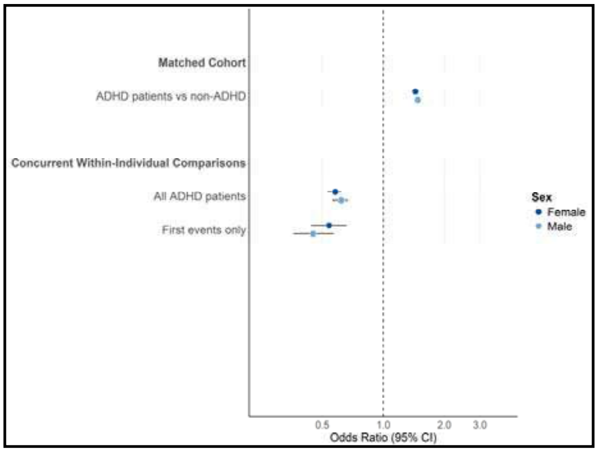


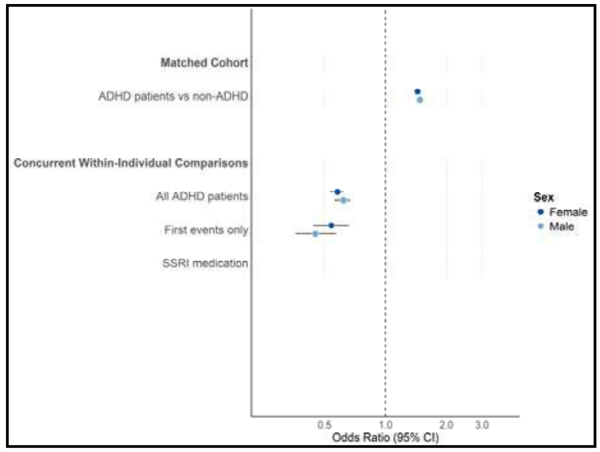


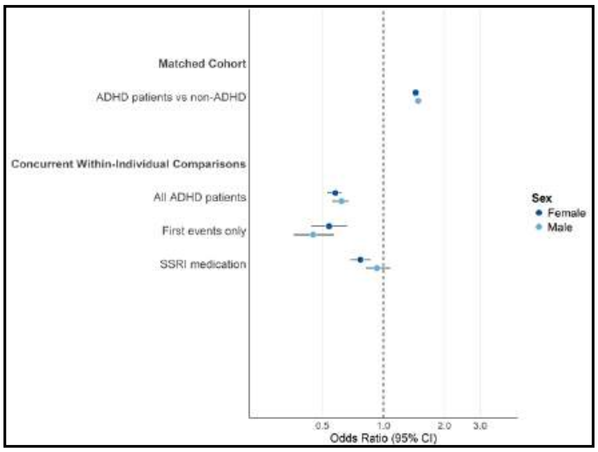


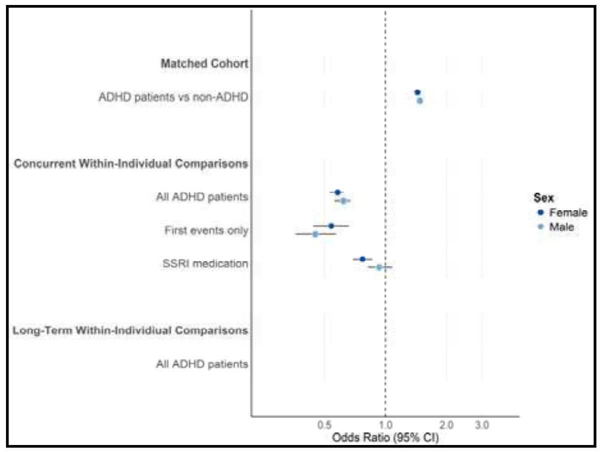


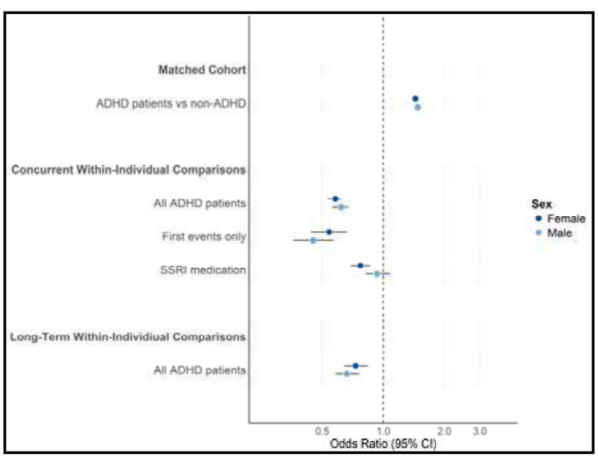






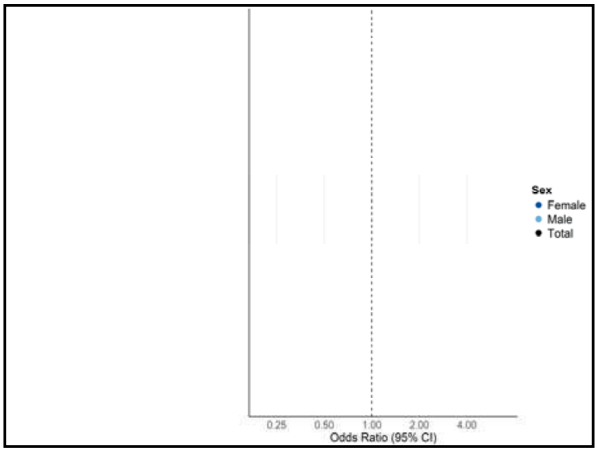


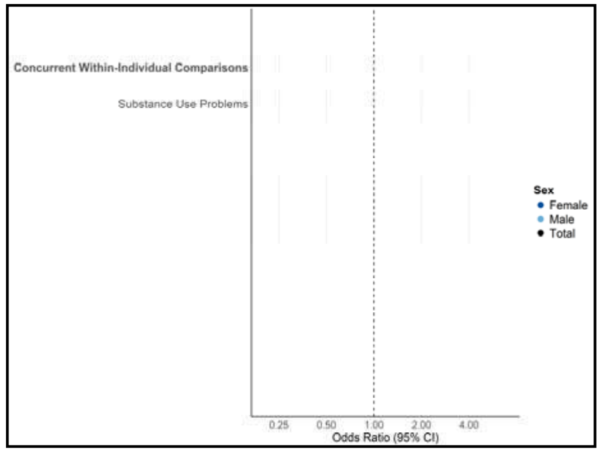


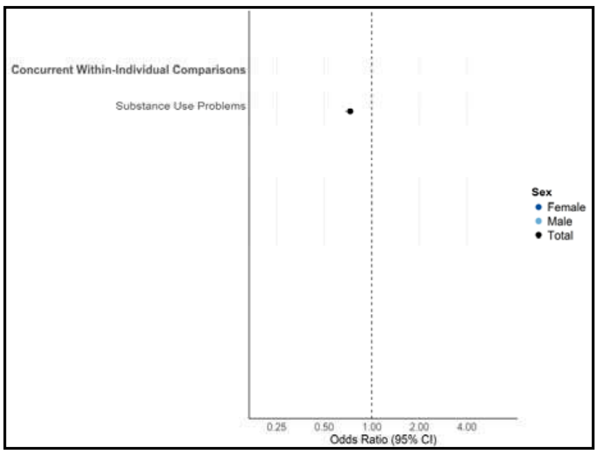


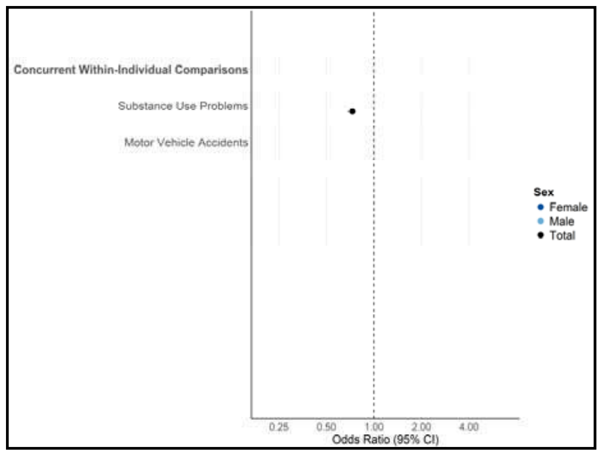
Other Studies

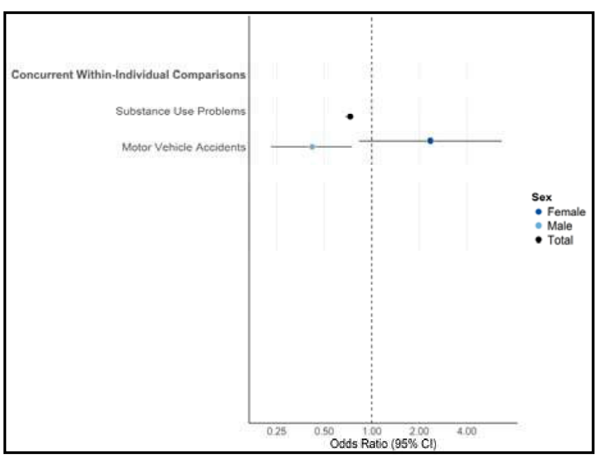
- United States
  - Seizures (Wiggs: Data Blitz at 1:15 and Poster #75)
- Sweden
  - Substance use problems (Chang, 2014; *JCPP*)
  - Motor vehicle accidents (Chang, 2014; *JAMA Psychiatry*)
  - Suicidal behavior (Chen, 2014; *British Medical Journal*)
  - Depression (Chang, 2016; *Biological Psychiatry*)
  - Criminality (Lichtenstein, 2012; *New England Journal of Medicine;* Chang, 2016, *JAMA*)
  - School Achievement (Jangmo: Data Blitz at 1:10 & Poster 64)

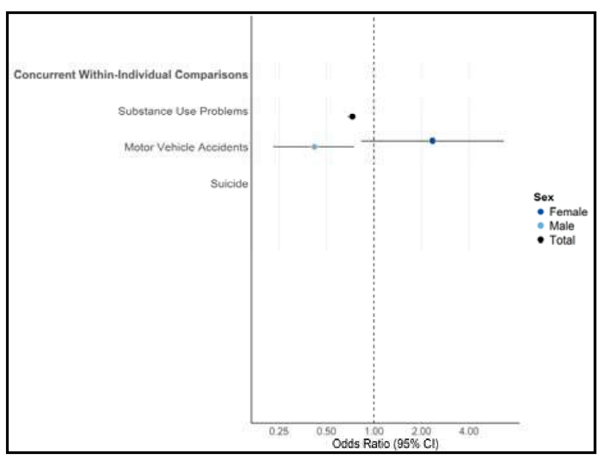

Sex
Female
Male
Total
0.25
0.50
1.00
2.00
4.00
Odds Ratio (95% CI)

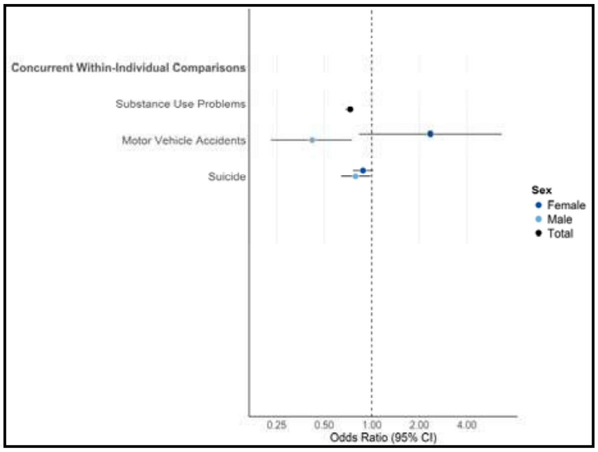

Concurrent Within-Individual Comparisons
Substance Use Problems
Sex
Female
Male
Total
0.25
0.50
1.00
2.00
4.00
Odds Ratio (95% CI)

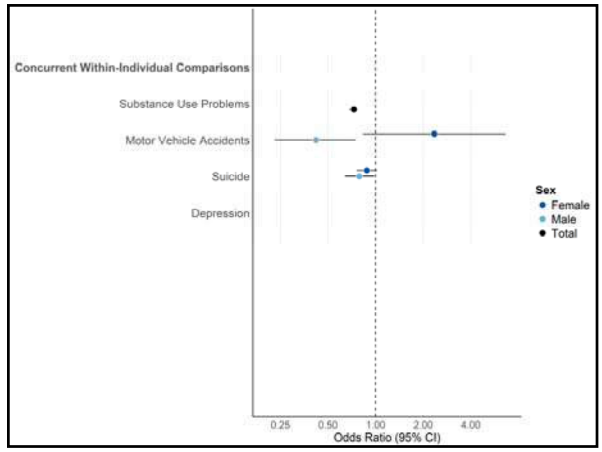

Concurrent Within-Individual Comparisons
Substance Use Problems
Sex
Female
Male
Total
0.25
0.50
1.00
2.00
4.00
Odds Ratio (95% CI)


Concurrent Within-Individual Comparisons
Substance Use Problems
Motor Vehicle Accidents
Sex
Female
Male
Total
0.25
0.50
1.00
2.00
4.00
Odds Ratio (95% CI)


Concurrent Within-Individual Comparisons
Substance Use Problems
Motor Vehicle Accidents
Sex
Female
Male
Total
0.25
0.50
1.00
2.00
4.00
Odds Ratio (95% CI)


Concurrent Within-Individual Comparisons
Substance Use Problems
Motor Vehicle Accidents
Suicide
Sex
Female
Male
Total
0.25
0.50
1.00
2.00
4.00
Odds Ratio (95% CI)


Concurrent Within-Individual Comparisons
Substance Use Problems
Motor Vehicle Accidents
Suicide
Sex
Female
Male
Total
0.25
0.50
1.00
2.00
4.00
Odds Ratio (95% CI)


Concurrent Within-Individual Comparisons
Substance Use Problems
Motor Vehicle Accidents
Suicide
Depression
Sex
Female
Male
Total
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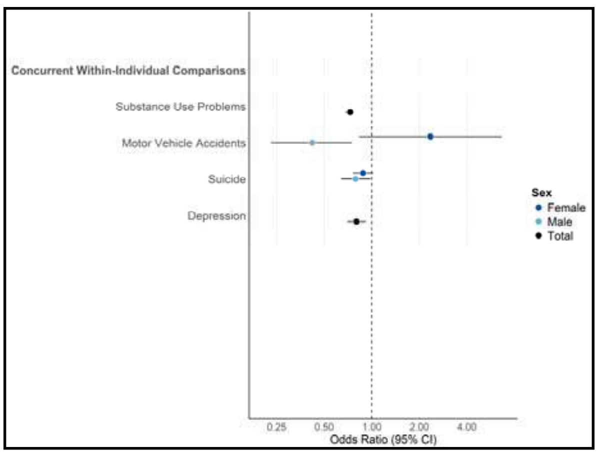
0.50
1.00
2.00
4.00
Odds Ratio (95% CI)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Substance Use Problems
Motor Vehicle Accidents
Suicide
Depression
Sex
Female
Male
Total
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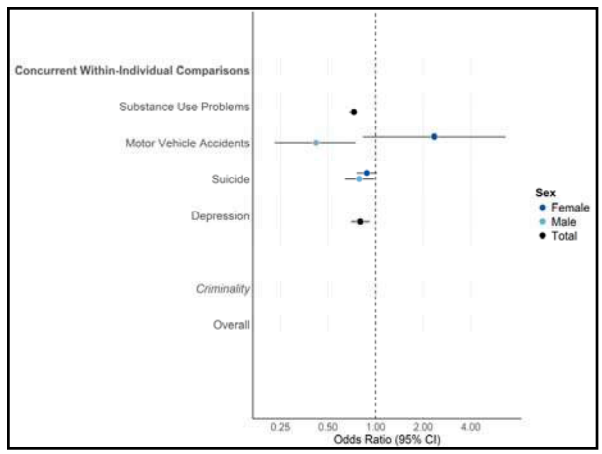
2.00
4.00
Odds Ratio (95% CI)


Concurrent Within-Individual Comparisons
Substance Use Problems
Motor Vehicle Accidents
Suicide
Depression
Criminality
Overall
Sex
Female
Male
Total
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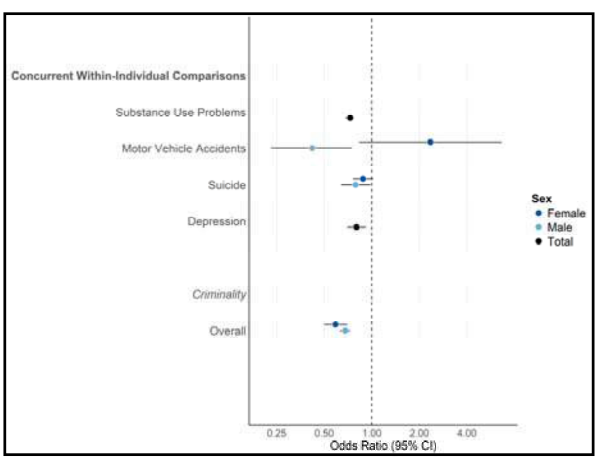
1.00
2.00
4.00
Odds Ratio (95% CI)


Concurrent Within-Individual Comparisons
Substance Use Problems
Motor Vehicle Accidents
Suicide
Depression
Criminality
Overall
Sex
Female
Male
Total
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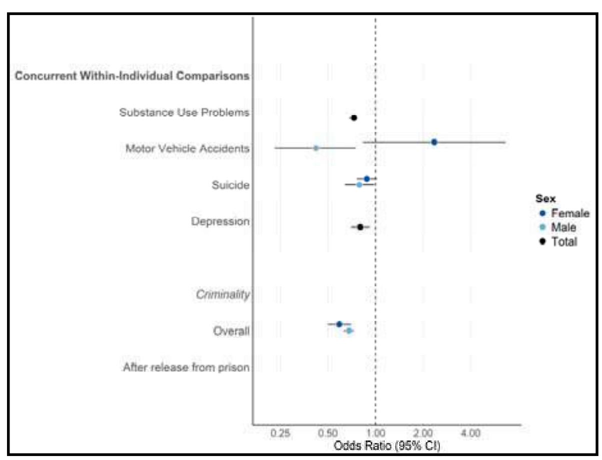
1.00
2.00
4.00
Odds Ratio (95% CI)


Concurrent Within-Individual Comparisons
Substance Use Problems
Motor Vehicle Accidents
Suicide
Depression
Criminality
Overall
After release from prison
Sex
Female
Male
Total
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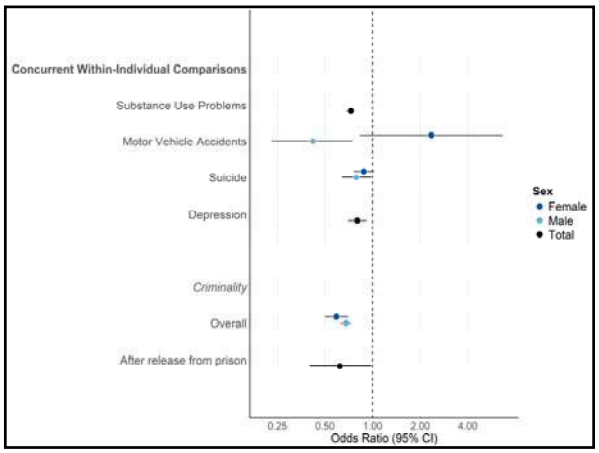
0.50
1.00
2.00
4.00
Odds Ratio (95% CI)



Summary

Findings from Within-Individual Studies

- Results should help mitigate concerns about rare-but-serious consequences
  - Substance use problems, suicide, seizures
- Findings help highlight possible protective effects
  - Motor vehicle accidents & accidental injuries
  - Criminal activities
  - Consistent with findings from RCTs
- Findings even apply to some at-risk subgroups
  - Previous substance use disorder or seizure history
  - Recently released from jail

Limitations

- Can't make definitive causal conclusions
  - Time-varying confounds
- Measurement concerns
  - Exposure – similar to intent-to-treat analysis
  - Outcome – severe events
- Questions about generalizability
  - Uninsured? Those who lost insurance?
  - Findings from Sweden?
- Long-term effects?
- Haven't looked at all possible iatrogenic effects

Clinical Implications

- There may be risk associated with **not** prescribing ADHD medication
  - Generally concerned about errors of commission
  - There may be concerns about errors of omission
- Results also apply to **adult** outcomes
  - Substance use problems
  - Motor vehicle accidents
  - Suicide / depression
  - Criminality

Should we put it in the water?

- Other side effects

Young adult outcomes in the follow-up of the multimodal treatment study of attention-deficit/ hyperactivity disorder: symptom persistence, source discrepancy, and height suppression

- Societal problems with diversion

Meta Messages

- Using large-scale observational studies can inform basic and applied research
- Without the ability to randomize exposure researchers need to rely on advanced design features to help rule out alternative explanations
- Insights from such studies can help patients and their physicians better weigh the risks and benefits of ADHD medication

Thank you!

Odds and Odds Ratios

Odds = probability / (1 – probability)
Odds ratio = odds of exposure / odds of unexposed

Example: Males with ADHD (3.2%) vs. Controls (1.2%)

Odds for ADHD = .032 / (1-.032) = 0.032 / 0.968 = .033

Odds for Controls = .012 / (1-.012) = 0.012 / 0.988 = .012

Odds ratio = .033 / .012 = 2.75

Studies of Accidents

- Children with ADHD are more likely to have accidental injuries, including traumatic brain injuries (e.g., increased risk, OR = 1.5 to 2.0)
- Within-individual comparisons
  - Children and adolescents are less likely to have accidental injuries when dispensed their medication (e.g, decreased risk, OR = 0.90 to 0.60)

82

e.g., Dalsgaard et al., 2015; Man et al. 2015; Mikolajcyk et al., 2015

ADHD Medication and Substance-Related Problems

Patrick D. Quinn, Ph.D., Zheng Chang, Ph.D., Kwan Hur, Ph.D., Robert D. Gibbons, Ph.D., Benjamin B. Lahey, Ph.D., Martin E. Rickert, Ph.D., Arvid Sjölander, Ph.D., Paul Lichtenstein, Ph.D., Henrik Larsson, Ph.D., Brian M. D'Onofrio, Ph.D.

Am J Psychiatry 2017; 174:877–885; doi: 10.1176/appi.ajp.2017.16060686

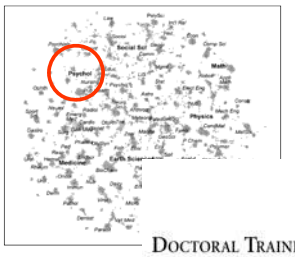
83

"Finding associations in observational data [is] too easy.

"Researchers who report such results are obliged to … whenever possible, use available methods to provide some insight into the possible ***causal*** relationship between their exposure and their outcome."

84

Is this Psychological Science?



Annu. Rev. Clin. Psychol. 2006. 2:21–49
doi: 10.1146/annurev.clinpsy.2.022305.095245

First published online as a Review in Advance on January 16, 2006

DOCTORAL TRAINING IN CLINICAL PSYCHOLOGY

Richard M. McFall
Department of Psychology, Indiana University, Bloomington, Indiana 47405; email: mcfall@indiana.edu

The Multimodal Treatment Study of Children with ADHD

- ***579 children*** with ADHD-CT
  - Selected exclusions
    - Severe comorbidity (e.g., bipolar, psychosis, tic d/o, OCD)
    - Neuroleptic medication
    - Major neurological/medical illness
    - Missed 25% of school days
    - ***Parental stimulant use disorder***
- ***14 months*** of randomly assigned treatment
  - Medication, behavior therapy, or both vs. standard care
- Findings (1999, *Arch Gen Psychiatry*)
  - ***MM > BT*** for ***ADHD symptoms***

86

JAMA®
Online article and related content current as of August 19, 2009.

Registries for Robust Evidence

Nancy A. Dreyer; Sarah Garner

JAMA. 2009;302(7):790-791 (doi:10.1001/jama.2009.1092)
http://jama.ama-assn.org/cgi/content/full/302/7/790

To enhance the evidence base with timely and representative real-world studies such as registries, 2 efforts are needed: methodological research to increase understanding of what constitutes quality in these studies and in the data sources and a more directed effort to meaningfully evaluate the strengths and limitations of different types of evidence for particular questions. As the diversity of the evidence base increases, the focus should turn to what constitutes high-quality research and evidence for a particular purpose and how quickly and reliably the information can be obtained, and less on the label of the particular study design.

"Interpretation of evidence requires judgement" (Rawlins 2008)

Comparison of Evidence of Treatment Effects in Randomized and Nonrandomized Studies

John P. A. Ioannidis, MD
Anna-Bettina Haidich, MSc
Marousdia Pappa, MSc
Nikos Pantazis, MSc
Styliani I. Kokori, MD
Maria G. Tektonidou, MD
Despina G. Contopoulos-Ioannidis, MD
Joseph Lau, MD

Context There is substantial debate about whether the results of nonrandomized studies are consistent with the results of randomized controlled trials on the same topic.

Objectives To compare results of randomized and nonrandomized studies that evaluated medical interventions and to examine characteristics that may explain discrepancies between randomized and nonrandomized studies.

Data Sources MEDLINE (1966–March 2000), the Cochrane Library (Issue 3, 2000), and major journals were searched.

Study Selection Forty-five diverse topics were identified for which both randomized trials (n = 240) and nonrandomized studies (n = 168) had been performed and had been considered in meta-analyses of binary outcomes.

Advantages of "Being Stuck" with Measures

SECONDARY ANALYSIS OF LARGE SOCIAL SURVEYS

JEREMY FREESE

16 October 1964, Volume 146, Number 3642 SCIENCE

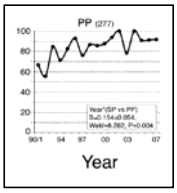
Strong Inference
Certain systematic methods of scientific thinking may produce much more rapid progress than others.

John R. Platt

Is Science Supporting Hypotheses?

Negative results are disappearing from most disciplines and countries

Daniele Fanelli



Fanelli, 2012

Determining a Causal Effect

- John Stuart Mill: A causal relationship exists if:
  - The cause preceded the effect.
  - The cause was related to the effect.
  - We can find no plausible alternative explanations for effect other than the cause.

SickKids

UNIVERSITY OF TORONTO

ADHD and Technology: The Opportunities and Perils

Russell Schachar, MD FRCPC
TD Bank Chair in Child and Adolescent Psychiatry
University of Toronto
The Hospital for Sick Children

Honoraria, consulting fees & equity
Ironshore Pharmaceuticals
Lilly Corp
Purdue Pharma
Ehave

Intellectual property
Stop Signal Task
Mega Team

ADHD and Technology: The Opportunities and Perils

Brenda Curtis, Ph.D.
Perelman School of Medicine
University of Pennsylvania,
Assistant Professor of Psychology in Psychiatry-Addictions
Philadelphia, PA

Scott Kollins, Ph.D.
Duke University, Professor
Durham, NC

Joseph Biederman, M.D.
Massachusetts General Hospital, Chief, Clinical and Research Programs in Pediatric Psychopharmacology and Adult ADHD
Boston, MA

Dimitri Christakis, M.D., M.P.H.
Seattle Childrens Research Institute, Director, Center for Child Health Behavior and Development
Seattle, WA

The application of scientific knowledge for practical purposes, especially in industry.

- We are not the first generation to live through the impact of rapid technological change.
- Each new technological innovation has positive and negative impacts.
- Economic displacement and industrial opportunity.
- Altered environment and altered trait selection.
- Adverse impacts on mental health and innovative means to understand mental illness.

Technology, Big Data, and Predicting Behavioral Health Measures

Brenda Curtis
Assistant Professor
Department of Psychiatry-Addictions

Jan 13, 2018

Perelman School of Medicine
University of Pennsylvania

Outline

- **Realizing the potential of technology in behavioral health treatment**
- **Technology to enhance the delivery and efficacy of treatment**
- **Use of social media data to:**
  - Study patterns and predictors
  - Determine vulnerability to relapse, medication adherence, and treatment dropout using language analysis
- **Privacy Issues**

The limits of conventional BH treatment

- Difficulties in retaining clients in clinic-based treatment
- Heterogeneity in client response but limited menu of available services, especially for non-responders
- Information is obtained only during treatment sessions
- A lot of time between sessions
- Counselor/Provider availability is limited

How might technology & big data help?

- Provide support in locations other than the clinic/office
- Automated support 24/7, between counseling sessions
- Assist clients in self-monitoring, medication adherence, coping, relaxation, and other factors
- Provide data on client status to counselors
- Provide information about clients social networks/social support
- Use both active and passive real-time data
  - Surveillance
  - Predictive ability

⇒ Tailor treatment

Data and Delivery Platforms

Digital Media Use: IOP/OP Philadelphia

- **N = 250, Mean age = 38.9 (SD = 12.24)**
  - 80% Male
  - 63% African American
  - 59% GED/High School
  - 74% never married
  - 62% under 10K income
- **Stratified by generation**
  - Millennial [18-35 years], N=120
  - Generation X [36-51 years], N=84
  - Baby Boomers [52+ years], N=55

Digital Media Use: IOP/OP Philadelphia

- **94% own a cellphone**
  - 64% are smartphones
- **70% pay as you go plans**
  - 81% unlimited calls
  - 90% unlimited texting
- **64% exclusively accessed the internet via cellphone**
- **73% use social media (53% daily)**

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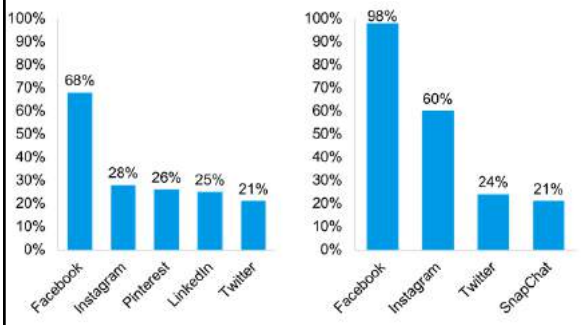
7

National | **Philadelphia AOD cohort**



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8

Digital Media Use: IOP/OP Philadelphia

- **66% believed social media would be a good place to receive relapse prevention info**
- **49% would allow their social media language to be monitored by the treatment center**
- **Would you _____ to help you during your recovery?:**
  - Sign up to receive Text Messages (72%)
  - Put an "App" on my Cellphone (70%)
  - Join Online Support Group (69%)
  - Join a Facebook Support Group (62%)

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9

Opportunity

- Nearly all of the patients had a cellphone and many had smartphones
- Access to the internet was mainly via cellular service
- Patients were receptive to using digital platforms to support clinical treatment
- About half would support surveillance of their social media accounts by the treatment provider.

For this urban AOD treatment population, the design of technology-based interventions will be challenging because many participants will have "pay as you go" telephone plans without data plans…thus limiting internet connectivity.

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Apps and Social Media

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11

Tools for Clients

- Medication Adherence
- Self Monitoring
- Task Initiation
- Emotional Control
- Journaling

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Utilizing social media data in treatment...

- 69% of US adults use social media
  - 86% 18-29
- Social media provides a relatively new and untapped resource for monitoring behavioral health outcomes.
  - Passive data collection
- Goal is to use real-time data to create just in time adaptive interventions.
  - Tailoring treatment to the individual when they are out of the clinical setting

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Predicting AOD Relapse from SM Language

- 504 patients attending Philadelphia community-based outpatient substance abuse treatment programs
  - IOP
  - OP
- Newly enrolled in treatment
- Facebook or Twitter user

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Study Design

- **Participants are asked to:**
  - complete an intake battery
  - report weekly on their AOD via an online survey
  - give permission to extract treatment entry, discharge, and urinalysis data from their clinic record
  - give permission to extract data from their Facebook and/or Twitter accounts
- **Monitoring participants for 26 weeks post-baseline**

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Data Sources

- **Adapted the Twitter Developer API.**
- **Developed a Facebook "plug in" based on Facebook's public "Graph" application programming interface (API).**
  - The primary purpose of the app is to extract status updates, posts, and limited account information from Facebook accounts.
- **Developed Online Weekly Survey with TLFB**
  - Tablet and Smartphone compatible
- **Natural language processing and machine learning methodologies**

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Traditional Measures & Social Media

- **Examined the associations between relapse at 4 weeks and:**
  - Addiction Severity Index (psychiatric and alcohol/drug related)
  - Social media language features (pre-treatment entry)
    - Risky or safe situations
    - Personality (Five Factor Model)
    - Drug/alcohol features

Note: N = **192** participants (>500 Facebook words (the minimum needed to allow for feature extraction)

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Traditional Measures & Social Media

Independent Variable	AIC	-2LogLike	AUC
Demographics	202	194	0.63
Addiction Severity Index (ASI)	190	172*	0.76
Social Media (alcohol/drug features)	208	144**	0.85
ASI + Social Media (alcohol/drug features)	192	119***	0.90

* LR chi-square(5)=22.6, p=0.0004
** LR chi-square(28)=50.3, p=0.006
*** LR chi-square(28)=52.2 relative to the model with ASI variables, p=0.004

AUC (area under the ROC curve) is a measure that ranges between 0.5 for random guessing and 1.0 for perfect accuracy.

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Language and Relapse

- Negative affect states such as loneliness (*lonely, alone, abandoned*; r=0.26), frustration (*life's a bitch, karma, upset*; r=0.28), and hopelessness (*plans, ruined, future*; r=0.23) **were positively correlated with relapse** (p<0.01).
- Functional social support (*family, support caring for*; r= -0.17); self-efficacy (control, serenity, overcome; r= -0.16); and positive affect states (*grateful, happy, joy*; r= -0.16) **were negatively correlated with relapse** (p<0.01) .

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Leveraging Predictive Analytics Within Social Networks

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Smartphone Social Media Recovery App

- 94,000 users who have self-identified as being in recovery or thinking about going into recovery

If in need, a user can select the "Burning Desire" button to let other sober people know they need help.

Users can find other sober people nearby on The Grid— a GPS locator user interface that displays user profiles and distances from them. Users can also choose to remain anonymous.

Users have access to a global newsfeed where they can communicate and share posts with other sober people.

"Wow I'm just checking this whole thing out... I think this will be my new Facebook!" - Byron K.

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Smartphone Social Media Recovery App

- Compiling a database of known triggers (e.g., life stressors, environment/life changes, etc.), comorbidity, and language associated with relapse.
- Identifying factors that correspond with relapse measures (e.g., depression, anxiety, ADHD treatment status, medication adherence states, etc)
- Building "just in time" adaptive interventions
- Testing the feasibility of integrating these real-time algorithms to deploy just in time interventions that complement treatment.

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Relapse-Preliminary Results

- **N=3,837**

	Accuracy	AUC	f1
Age	0.57	0.61	0.43
Gender	0.56	0.51	0.34
Age + gender	0.55	0.55	0.43
Language	0.66	0.70	0.65
Language + age + gender	0.65	0.70	0.65

Classification of binary "**change in sobriety date**" with 500 Facebook topics using logistic regression with 10-fold cross validation and (occurrence threshold, univariate selection and randomized PCA) feature selection pipeline.

AUC (area under the ROC curve) is a measure that ranges between 0.5 for random guessing and 1.0 for perfect accuracy.

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Next Steps: Daily Dynamic Prediction

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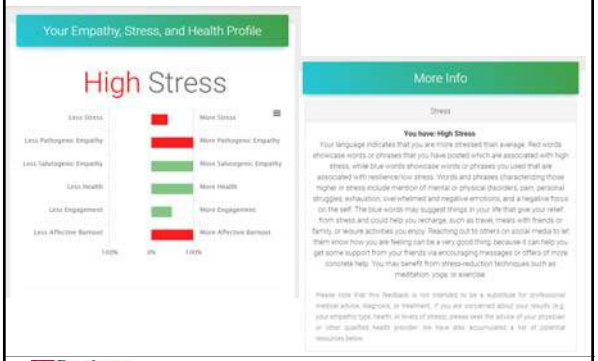
Patient Personalized Feedback Tool



Thanks to Collaborators

- **U Penn**
  - Kevin Lynch
  - Brenda Curtis
  - Hank Kranzler
  - Lyle Ungar
  - Casey Hamilton
  - Salvatore Giorgi
  - Anneke Buffone
- **Former U Penn Staff**
  - Dan Summers
- **Other Institutions**
  - Andrew Schwartz

Digital Therapeutics for the Treatment of ADHD: Results from a Large-Scale Clinical Trial

Scott H. Kollins, PhD
Professor, Department of Psychiatry
Duke University School of Medicine

ADHD & Technology: The Opportunities and Perils
APSARD Annual Meeting
January 13, 2018
Washington, DC

Disclosures (Past 24 months) - Kollins

Industry

Source	Activity
Aevi	Consulting
Akili Interactive	Research Support, Consulting
Arbor	Consulting
Bose	Research Support, Consulting
Ironshore	Consulting
Jazz	Consulting
Kashiv	Consulting
KemPharm	Research Support, Consulting
Neos	Research Support
Otsuka	Consulting
Rhodes	Research Support, Consulting
Shire	Research Support, Consulting
SK Life Sciences	Consulting
Sunovion	Research Support, Consulting
Tris	Consulting

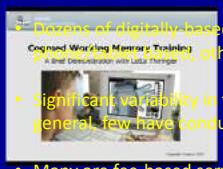
Federal/Foundation

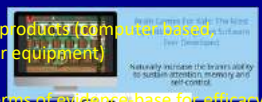
Source	Activity
NIMH	Research Support
NIDA	Research Support
NICHD	Research Support
FDA	Research Support
NIEHS	Research Support
EPA	Research Support
FTC	Consulting
John T. Templeton Foundation	Research Support

OVERVIEW

- Landscape of digital therapeutics for ADHD
- Background/Development of AKL-T01
- Challenges in designing/implementation of a digital device registration trial for ADHD
- Overview of topline study results
- Future Directions

Landscape of Digital Therapeutics for ADHD





- Dozens of digitally based products (computer based software, other equipment)
- Significant variability in terms of evidence base for efficacy; in general, few have conducted rigorous, well-controlled trials
- Many are fee-based services
- Wide range of claims for treatment efficacy
- None are FDA-Approved for Treatment of ADHD

Simons et al., *Psychol Sci*, 2016

Basis of AKL-T01

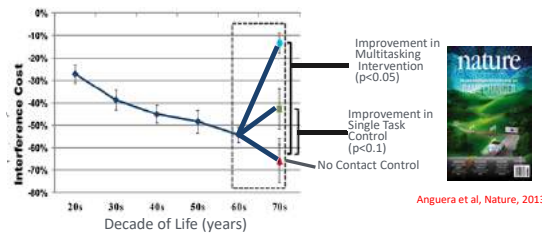
Targeted approach to improving selective stimulus management

- Digital intervention combining:
  - Continuous fine-motor task
  - Perceptual reaction task
- Adaptive algorithms adjust task difficulty based on individual performance
- Reward and advancement within task contingent on performance across both components (motor and RT)
- Task delivered in a video-game format to increase engagement

5

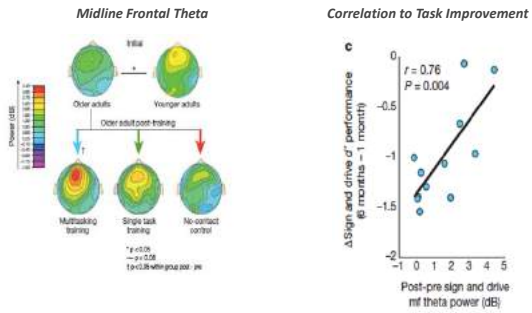
Evaluating effects of Intervention designed to target Selective Stimulus Management

Intervention developed and tested for 1 month (10 hrs of task engagement) in healthy older adults. Examined pre-post intervention and 6 month follow-up



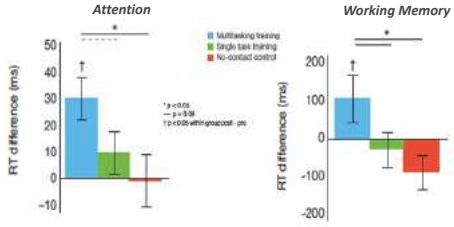
Anguera et al, Nature, 2013

Intervention influenced neural functioning measured via EEG that was correlated to task improvement



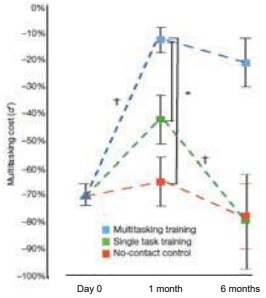
Anguera et al, Nature, 2013

Intervention effects demonstrated generalization to other cognitive domains



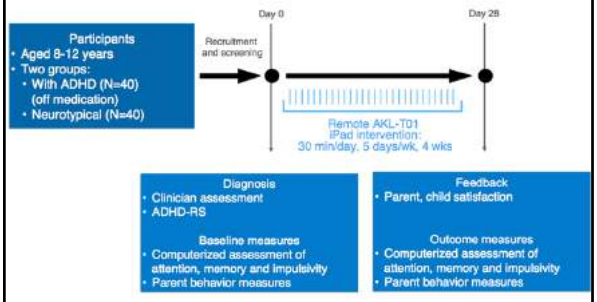
Anguera et al, Nature, 2013

Durable effects of intervention on cognitive function for up to 6 months



Anguera et al, Nature, 2013

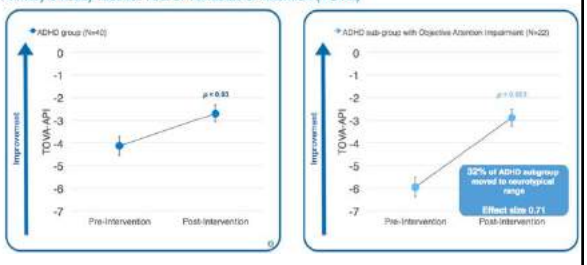
AKL-T01: Pediatric ADHD Pilot/Phase 2 Study Design



Davis et al, (in press) *PLoS One*, 2018

AKL-T01: Pediatric ADHD Pilot/Phase 2 Study Results

Primary efficacy results: Test of Variables of Attention (TOVA)



Davis et al, (in press) *PLoS One*, 2018

AKL-T01: Pediatric ADHD Pilot/Phase 2 Study Results

Safety and adherence

0 Treatment-related adverse events

0 Study dropouts in ADHD cohort

84% Prescribed in-home sessions were completed

77% Parents reported that the time spent was "worthwhile" or "very worthwhile"

Davis et al, (in press) *PLoS One*, 2018

Challenges in designing/implementation of a digital device registration trial for ADHD

Challenge #1: What is the optimal "dose" of digital intervention?

- No preclinical data on which to rely
- Traditional dose-finding studies difficult from a development perspective

Decision for Current Trial: Stick with dose from initial mechanistic study and that showed results on POC study

Challenges in designing/implementation of a digital device registration trial for ADHD

Challenge #2: What is the proper control condition?

- Nearly impossible to have a simple placebo
- Control needs to have comparable expectation of benefit – an "active control"

Decision for Current Trial: Design a control condition with comparable expectation of benefit with similar reward and timing structure

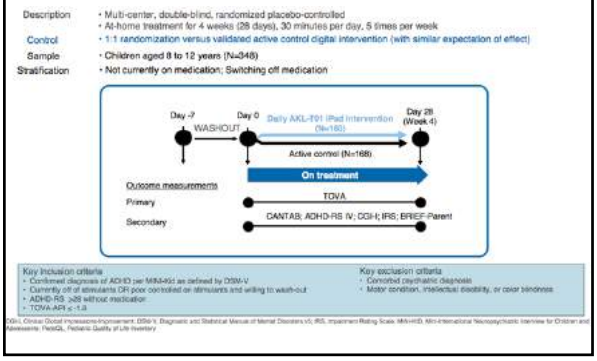
Challenges in designing/implementation of a digital device registration trial for ADHD

Challenge #3: How do you blind/minimize bias?

- Impossible to blind 2 treatments that look different
- Focus on bias minimization

Decision for Current Trial: Explicit protocol procedures for Study PI's, parents/participants, and study staff; monitoring bias minimization and potential unblinding events

AKL-T01: Pediatric ADHD Registration Trial: Design

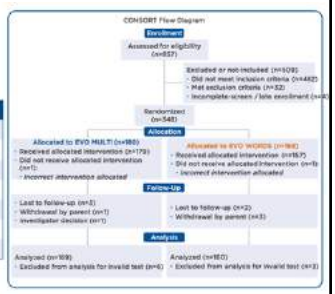


AKL-T01: Pediatric ADHD Registration Trial: Participant Disposition

Compliance

- EVO MULTI: 86%
- EVO WORDS: 95%

Protocol violations	AKL-T01 (EVO MULTI)	Active comparator (EVO WORDS)
Concomitant medications	11	6
Different rates	48	35
Unblinded	3	2
Randomization mis-assignment	1	1
Compliance	26	9
Total ITT	180	168
Total PP	102	118



AKL-T01: Pediatric ADHD Registration Trial: Participant Characteristics

	MULTI	WORDS
N	180	168
Age	9.72 (1.32)	9.6 (1.34)
M/F N	126 / 54	123 / 45
	Baseline Mean (SD)	Baseline Mean (SD)
TOVA API	-5.1 (2.97)	-4.81 (2.85)
IRS	5.48 (1.06)	5.45 (1.2)
RS	39.01 (6.81)	38.22 (6.53)
RS Inattentive	21.86 (3.45)	21.56 (3.63)
RS Hyperactive/Impulsive	17.16 (5.95)	16.66 (5.38)
CGI-S	4.51 (0.72)	4.54 (0.64)

AKL-T01: Pediatric ADHD Registration Trial: Safety

- **11** treatment-related AEs with EVO MULTI (2 with EVO WORDS)
- **0** Serious Adverse events (SAEs)
- **1** treatment-related withdrawal from AKL-T01 group

Event description	AE severity	Relationship to intervention
EVO MULTI		
Frustration	Mild	Definitely related
Dizziness/Nausea	Mild	Possibly related
Frustration	Mild	Possibly related
Frustration	Mild	Definitely related
Frustration	Mild	Definitely related
Headache	Mild	Possibly related
Aggression	Moderate	Possibly related
Emotional Disorder	Moderate	Definitely related
Emotional Disorder	Mild	Possibly related
Frustration	Mild	Definitely related
Headache	Moderate	Possibly related
EVO WORDS		
Headache	Severe	Definitely related
Emotional Disorder	Moderate	Possibly related

AE, adverse event; SAE, serious adverse event

AKL-T01: Pediatric ADHD Registration Trial: Outcomes

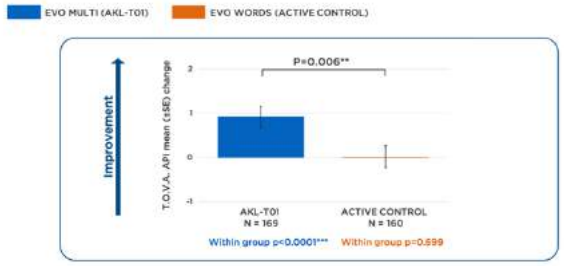
Primary Endpoint: Objective Attention Assessment

- T.O.V.A Attention Performance Index (API)

Secondary Outcome Measures: Subjective Parent-/Clinician Ratings

- Impairment Rating Scale (IRS)
- ADHD-RS - Total Score
- ADHD-RS - Inattentive Score
- ADHD-RS - Hyperactive Score
- Clinical Global Impressions

AKL-T01: Pediatric ADHD Registration Trial: Primary Outcome Results

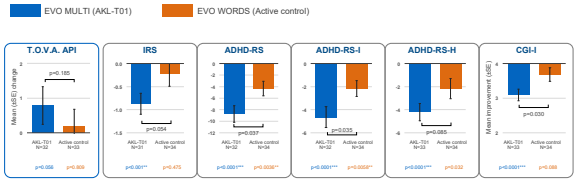


SE, standard error

AKL-T01: Pediatric ADHD Registration Trial: Secondary Outcomes Results

AKL-T01: Pediatric ADHD Registration Trial: Pre-Specified Subgroup Analysis

Children on stimulant medication within the past 30 days



Conclusions/Next Steps

- Digital medicine for ADHD and ADHD/psychiatric disorders in its infancy
- Designing appropriate and meaningful trials for digital therapeutics is challenging
- Important to establish conventions for defining evidence for this category of treatment
- Some indication of benefit from AKL-T01 for improving attentional functioning and, for some subgroups, broader ADHD phenotype

Use of Big Data to Advance Clinical Care

Joseph Biederman, MD
Professor of Psychiatry
Harvard Medical School
Chief, Clinical and Research Programs in
Pediatric Psychopharmacology and Adult ADHD
Director, Bressler Program for Autism Spectrum Disorders
Massachusetts General Hospital

Study 1: Cardiac Safety of Antidepressant Medication Use in Children

Collaborators

- **MGH Pediatric Psychopharmacology Program**
  Joseph Biederman, MD
  Mai Uchida, MD
  Maura Fitzgerald, MPH
- **MGH Bipolar Clinical and Research Program**
  Roy H. Perlis, MD
  Victor M. Castro
- **MGH Cardiology**
  Ana Maria Rosales, MD
  Christopher Newton-Cheh, MD, PhD

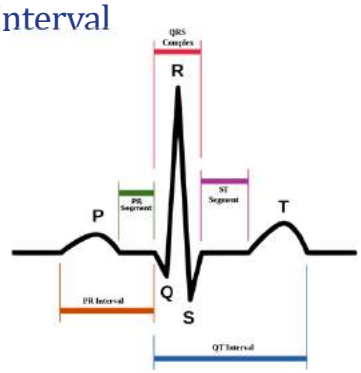
U.S. Food and Drug Administration

FDA Drug Safety Communication: Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide)

- 2011: FDA announced a label change to the selective serotonin reuptake inhibitor (SSRI) antidepressant ***citalopram*** due to dose-related prolongation of the QT interval
  - FDA recommended citalopram no longer be prescribed to adults at >40 mg per day
- 2012: FDA revised recommendation
  - FDA recommended citalopram no longer be prescribed to adults >60 years old at doses >20 mg per day

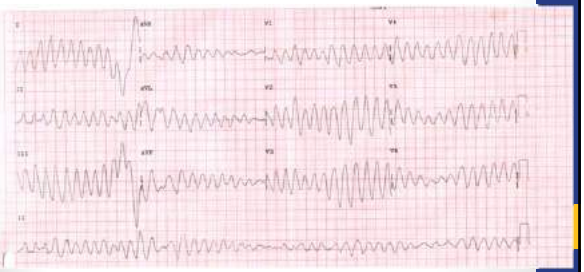
http://www.fda.gov/Drugs/DrugSafety/ucm269086.htm

QT Interval



Lethality of Prolonged QT

- QTc >500 ms increases the risk for developing the lethal arrhythmia "Torsades de Pointes"



Antidepressants Prescribed for Children

- SSRI are widely used (on and off label) to treat many pediatric psychiatric conditions including MDD, GAD, and OCD
- No FDA guidelines regarding their safety in children

Antidepressants Prescribed for Children

- Citalopram and other SSRIs are commonly prescribed to children at adult doses
- Weight-corrected daily dose may be higher than in adults

MGH EMR Study of Cardiac Safety of SSRIs/SNRIs Antidepressants in Children

Methods: Inclusion Criteria

- Systematic review of electronic medical records within Partners Health Care
- All children ages 5-18
- At least one prescription of a non-TCA antidepressant medication (or methadone)
- EKG within 14-90 days of prescription between February 1990 and August 2011

Methods: Extracting QTc

- EKG reports were parsed by text pattern matching algorithm to extract QTc measurements, and then normalized to standardized units

Analysis

- Calculated mean QTc for each medication
- Because there were too few pediatric subjects to reliably examine dose effects per medication, we calculated the difference in mean QTc for each medication compared to the mean across all medications

Analysis

- QTc values were characterized abnormal, borderline, abnormal, or high based on published *adult* thresholds
- Covariates included adjusting for potential confounding effects of psychiatric and medical conditions, age, gender, race, and insurance type

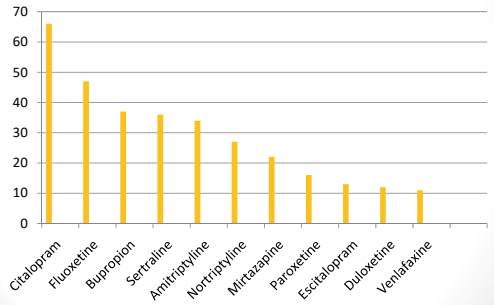
Results

- Of 10,150 children prescribed a medication of interest, 297 (0.03%) had an EKG within 14-90 days following a prescription
- Citalopram (off-label) was the most commonly prescribed

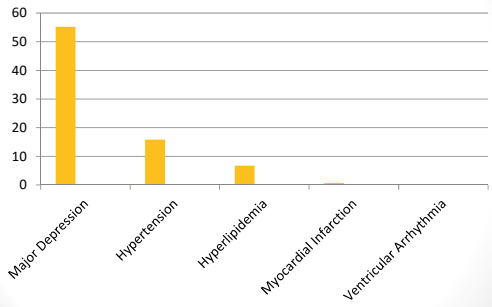
Demographics

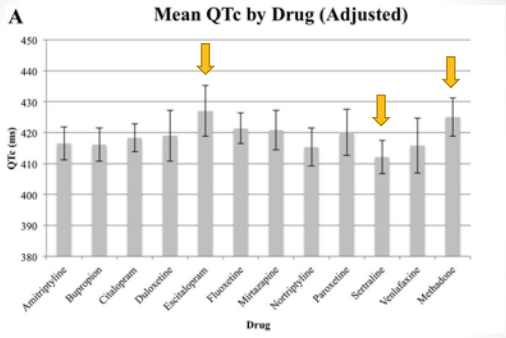
N	297
Age, mean years (SD)	14.2 (4.1)
Female gender	140 (60.0%)
Race/ethnicity	
White	217 (80.0%)
African American	20 (7.2%)
Hispanic	44 (7.8%)
Asian	6 (1.2%)
Other	10 (4.0%)
Insurance	
Public	87 (52.2%)
Private	184 (41.3%)
Other / Unknown	26 (6.5%)
Year of EKG, median (IQR)	2008 (2005-2009)

Medications Prescribed

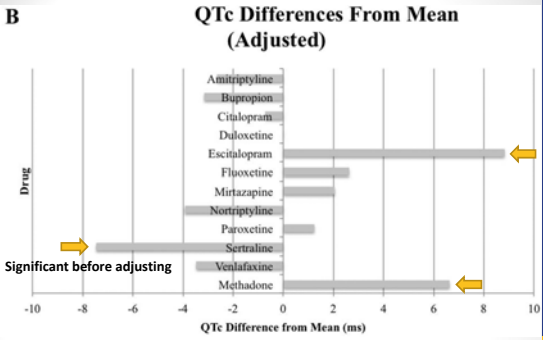


Psychiatric and Medical Conditions (%)





Mean QTc values for each medication were in the normal range, both before and after controlling for confounders (age, gender, race, insurance, and drug year).



When adjusted for age, gender, race, insurance, and drug-year, no QTc differed significantly from the mean.

Summary

- Mean QTc intervals were in the normal range for all medications examined
- No single medication was associated with a significantly greater QTc than others

Conclusion

- Our findings provide reassurance that non-TCA antidepressants can be safely prescribed to children and adolescents

Study 2: A Systematic Evaluation of Patient Engagement in ADHD An Electronic Health Record Study

Collaborators

- Ronna Fried, EdD
- Roy Perlis, MD
- Maura Fitzgerald, MPH
- Stephen V. Faraone, PhD

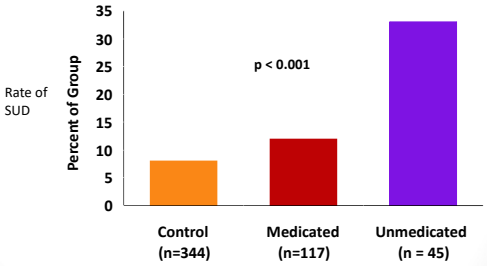
ADHD is a Highly Treatable Disorder

- ADHD is among the most treatable of all psychiatric disorders
- Stimulants are among the most effective treatments in medicine with effect sizes of 1
- **Studies show that many of ADHD-associated poor outcomes can be mitigated by treatment with stimulants**

Number Needed To Treat (NNT) To Prevent the Adverse Outcome

Outcome†	Number Needed to Treat (NNT)
Major Depressive Disorder with Severe Impairment	3
Conduct Disorder	3
Multiple (≥2) Anxiety Disorders	3
Oppositional Defiance Disorder	3
Bipolar Disorder	7
Repeated Grade	3
Substance Dependence Disorder	18
Smoking	12
Motor Vehicle Collisions	4

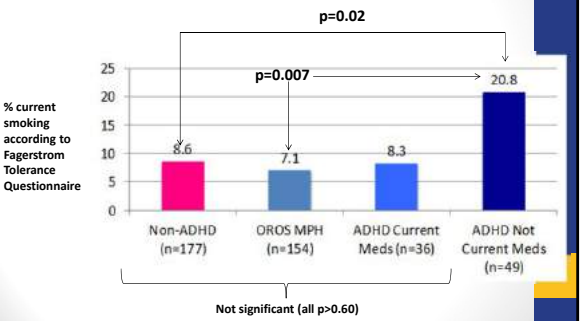
Stimulants are Protective Against Adolescent Substance Use Disorders



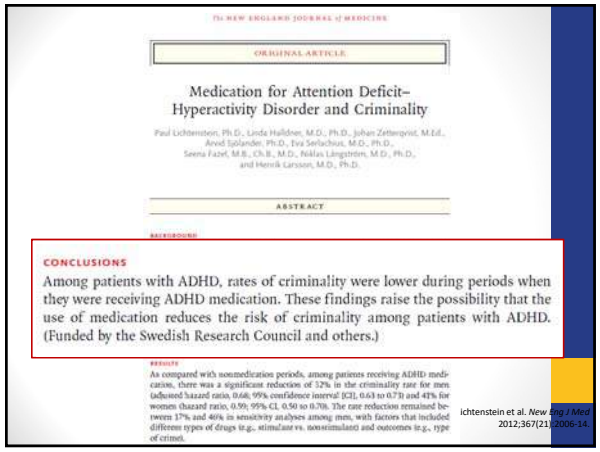
Biederman, Wilens, Mick et al., Pediatric 1999

Stimulants are Protective Against Onset of Smoking in ADHD Youth

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



Hammerness and Biederman, Jounal of Pediatrics 2012



THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

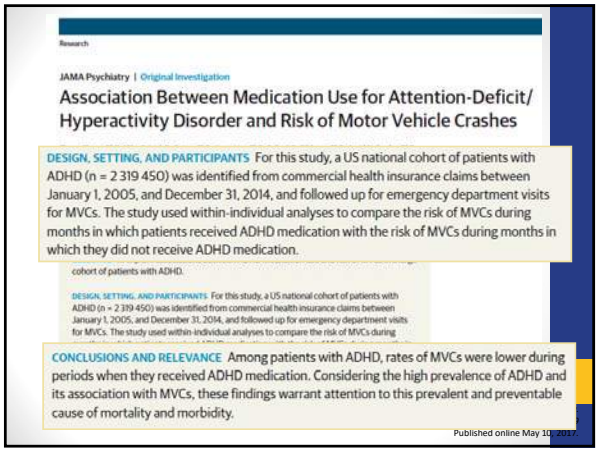
Medication for Attention Deficit–Hyperactivity Disorder and Criminality

ABSTRACT

CONCLUSIONS

Among patients with ADHD, rates of criminality were lower during periods when they were receiving ADHD medication. These findings raise the possibility that the use of medication reduces the risk of criminality among patients with ADHD. (Funded by the Swedish Research Council and others.)

Lichtenstein et al. *New Eng J Med* 2012;367(21):2006-14.



Research

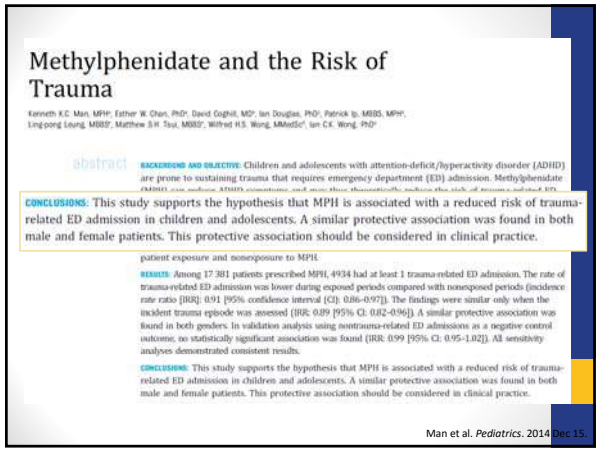
JAMA Psychiatry | Original Investigation

Association Between Medication Use for Attention-Deficit/ Hyperactivity Disorder and Risk of Motor Vehicle Crashes

DESIGN, SETTING, AND PARTICIPANTS For this study, a US national cohort of patients with ADHD (n = 2 319 450) was identified from commercial health insurance claims between January 1, 2005, and December 31, 2014, and followed up for emergency department visits for MVCs. The study used within-individual analyses to compare the risk of MVCs during months in which patients received ADHD medication with the risk of MVCs during months in which they did not receive ADHD medication.

CONCLUSIONS AND RELEVANCE Among patients with ADHD, rates of MVCs were lower during periods when they received ADHD medication. Considering the high prevalence of ADHD and its association with MVCs, these findings warrant attention to this prevalent and preventable cause of mortality and morbidity.

Published online May 10, 2017.



Methylphenidate and the Risk of Trauma

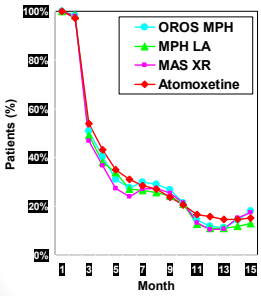
abstract

CONCLUSIONS: This study supports the hypothesis that MPH is associated with a reduced risk of trauma-related ED admission in children and adolescents. A similar protective association was found in both male and female patients. This protective association should be considered in clinical practice.

Man et al. *Pediatrics*. 2014 Dec 15.

Problem: Extremely Poor Adherence to Medications in ADHD

Adherence by Medication Type



- Within 2 to 3 months, a majority of patients with ADHD have stopped taking medication consistently[1,2]
- Patients renewed their monthly prescriptions about 2 to 3 times per year

2. Perwien et al. *J Manag Care Pharm.* 2004;10(2):122-129.
3. Sanchez et al. *Pharmacotherapy.* 2005;25(7):909-917.

32

EMR

- Mining data from electronic medical records (EMR) can help evaluate adherence to stimulants

Mining of EMR has Several Important Advantages:

- Systematic access to large datasets
- Ecological validity, since it reflects actual clinical practice
- Objective metrics of adherence

Main Aim

- To evaluate objective rates and correlates of patient engagement in ADHD treatment

Methods

- We searched the EMR of a large health care organization to systematically examine rates of patient engagement by examining the rate of renewing the first prescription for a stimulant medication
- Time span: 2015-2016
- Altogether these records comprise about three million unique patients

Methods

- Patients were included in the study sample if they were prescribed any stimulant
- We included medications with single prescriptions (30-day supply) or post-dated prescriptions up to three months (60- or 90-day supply)

Main Metric

- Patient Engagement: Renewal of the first stimulant Rx

Methods

- We categorized initial prescriptions by source into psychiatry vs non-psychiatry source
- All tests were two-tailed and performed at the 0.05 alpha level using Stata® (Version 14.2)

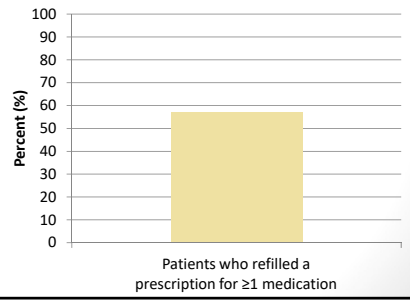
Results

- Our final sample consisted of 2,685 patients with initial prescriptions
- Mean age: 12.4 ± 3.0 years
- 73% percent were male
- 72% were Caucasian
- 92% spoke English as their primary language
- Patients came from all economic classes with 26% upper-class, 43% middle-class, and 30% lower-class

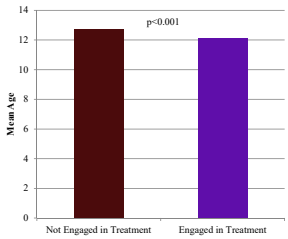
Pediatric ADHD Engagement Data at Partners Healthcare

Percent of Children with ADHD who Renewed their First Stimulant Rx at Partners Healthcare: 2105-2016 EMR Review

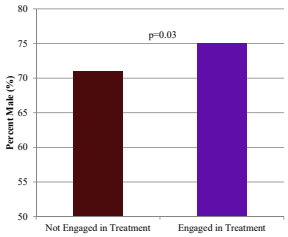
# of patients	# of patients who refilled a prescription for ≥1 medication	% of patients who refilled
2, 685	1, 537	57%



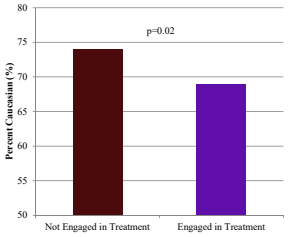
Age



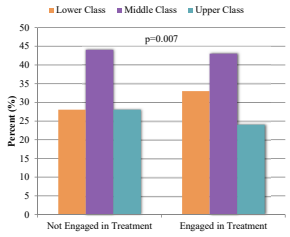
Sex



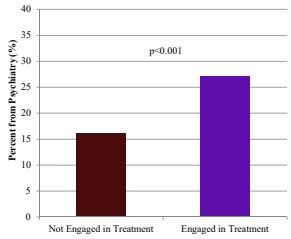
Race (% Caucasian)



Social Class (Zip Code Based)



Prescription Source: Psychiatry vs Non-Psychiatry



Main Findings

- Patients who engaged in treatment were slightly younger, had a greater percentage of males, and a lower percentage of Caucasians
- However these difference were very small and of uncertain clinical significance

Main Findings

- A greater percentage of those who engaged in treatment received their initial prescription from a psychiatry clinic compared to those who did not engage in treatment

Discussion

- These findings suggest that poor engagement in ADHD treatment afflicts all ages, sexes and social class strata
- The findings that more patients were engaged in treatment who were seen in psychiatric clinics suggest that poor adherence to stimulants is particularly acute in the primary care setting

Methodological Limitations

- EMR include limited diagnostic information on severity of ADHD or the presence of psychiatric and cognitive comorbidities
- Because our sample derived from a single healthcare organization in the state of MA, it may not generalize to other parts of the country

Summary

- Using an a priori definition of patients engagement to stimulant treatment for ADHD based on renewal of the first stimulant prescription, 2 year evaluation of EMR data from a large health care organization showed that only 50% of close to 3,000 patients engaged in treatment
- These findings provide compelling new evidence of poor rates of patient engagement in stimulant treatments for ADHD

DISCLOSURE

Source	Consultant	Advisory Board	Speaker	Research Support
Genomind		X		
Supernus		X		X
Kenpharm		X		
Ironshore		X		X
Arbor	X			
Akili		X		X
NIMH				X
Shire		X		X
Sunovian		X		

OUTSIDE THE PILL BOTTLE: ASSESSMENT AND MANAGEMENT OF ADULT ADHD

Mark Stein Ph.D.

APSARD 2018

WASHINGTON, D.C.

CHARLES BRADLEY (1937)

"...a spectacular change in behavior...remarkably improved school performance...a large proportion became subdued without losing interest in their surroundings."

Bradley, C. & Bowen, E. (1937). The behavior of children receiving benzedrine. *American Journal of Psychiatry, 94*, 577-585

Bradley, C. (1950). Benzedrine and dexedrine in the treatment of children's behavior disorders. *Pediatrics, 5*, 24-37

Limitations/Controversies Regarding ADHD Pharmacotherapy in Adults

- Less robust research literature
  - Effects sizes differences
  - Industry sponsored studies
  - Few comparator trials
- Safety Issues
  - Health
  - Drug/drug interactions
  - Less consistent monitoring

MORE BARRIERS

- Risk of diversion/abuse
  > Extreme heterogeneity
  College student
  Software engineer
  Mother
  Senior
- Manpower, service delivery issues
  > Not emphasized in physicians who treat Adults
  > Inconsistent training of mental health providers

PSYCHOSOCIAL TREATMENTS

- Expanded targets beyond ADHD symptoms
  Comorbidity
  Impairment/function
- Can be combined with medication or as monotherapy

SUMMARY

Efficacy-effectiveness gap

Disconnect between clinical trials, symptom reduction, and outcomes

Little evidence of impact on impairment

- Accessibility to EBT in real world

Disconnect between clinical trial regimens, recommendations, and practice

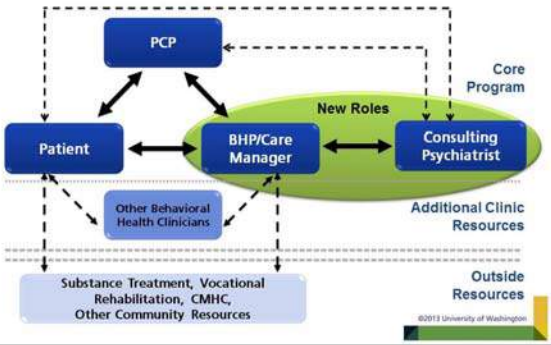
- IR stimulants preferred
- Poor adherence to pharmacotherapies
- Few predictors or moderators of response
- Little guidance on how to select and sequence treatment

OUTSIDE THE PILL BOTTLE: ASSESSMENT AND MANAGEMENT OF ADULT ADHD

Thomas Brown Ph.D.
Jeanette Wasserstein Ph.D.
Kathleen Nadeau Ph.D.
J. Russell Ramsay

OPTIONAL SLIDE

Collaborative Care Team Structure



DIABETES MODEL FOR ADHD RESEARCH

Primary deficit/Lack of focus, **in all ADHD, similar to insulin response**

- Biomarker?
- In the absence, refine the phenotype-behavioral , describe method, rating of cognitive symptoms (Self-report-neuropych, imaging)

Type 1 ADHD: Childhood onset-

- Highly heritable
- Response to stimulants
- Persistence and outcome related to severity and comorbidity, especially CD

Type 2 -Adult ADHD

- 2A. Child onset and persistent ADHD
  - Highly heritable
  - Cumulative effects of ADHD and comorbidity
- **Emotional regulation and personality disorders part of clinical picture**
- 2B. New onset?- prone to misdiagnosis
  - Impaired
  - Prone to Misdiagnosis (cognitive deterioration, performance enhancement, especially over time as ADHD is so widely diagnosed in children)-
  - ? Etiology
  - ? Response to treatment

Collaboration Between Prescribers & Other Clinicians

In Managing ADHD

Thomas E. Brown, PhD

Brown Clinic for Attention and Related Disorders
Manhattan Beach, California

Adjunct Clinical Associate Professor of Psychiatry
Keck Medical School of University of Southern CA

Persistence in Use of ADHD Meds is often low & inconsistent in kids

Retrospective study of 1 yr of scrips for ADHD written for pop-based sample of 46K children with ADHD:

Average number of days of med use:

- short-acting 79 days per year
- intermed acting 76
- long-acting 104

Palli, et al (2012)

Adherence to ADHD Med Regimen is often low & inconsistent among adults

- Pharmacy records of 24, 964 adults showed
  - .62 adherence for long-acting amphetamines
  - .52 adherence for long-acting MPH

(Christensen, et al. 2010)

Impediments to Effectiveness & Persistence of Med Treatments for ADHD

- Insufficient or unrealistic pt/family understanding of how med works and how it may help them
- Lack of drug or dose effectiveness
- Unacceptable side effects or rebound
- Insufficient coverage duration for daily activities

Problems Faced by Many Prescribers

- Insufficient time to educate patients about meds for ADHD (15 min)
- Insufficient training for "fine-tuning" of medications to fit individual differences in needs and response
- Insufficient time for follow-up on patient responses to medication
- Liability concerns for Schedule II

Problems Faced by Non-Prescribing Clinicians Treating ADHD

- Insufficient training about ADHD meds, variety of factors impacting individual responses to these meds
- Insufficient understanding of prescriber concerns re: liability
- Difficulty in communicating with prescribers
- Scope of practice limitations

How Adequately Prepared Non-Prescribing Clinicians can assist patients and prescribers

- Help to educate patients about medications, possible side effects and process of dose adjustments
- Help pts identify benefits and any limitations of their current regimen
- Help patients to share info and questions with their prescriber

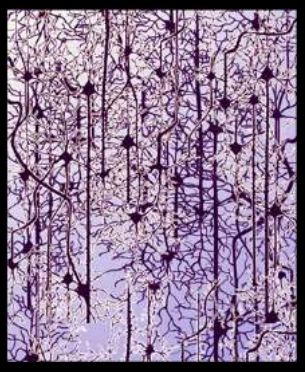
Misunderstanding a Chemical Problem

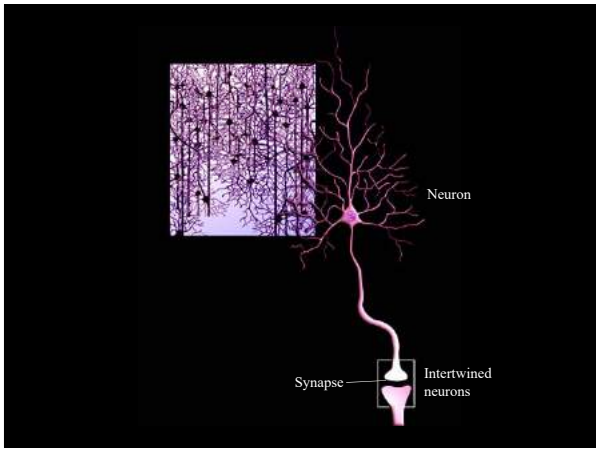
- "ADHD is fundamentally a simple chemical problem"
- "It's just a chemical imbalance in the brain—too much or too little"
- "You take some medicine to fix the imbalance and then you're OK"

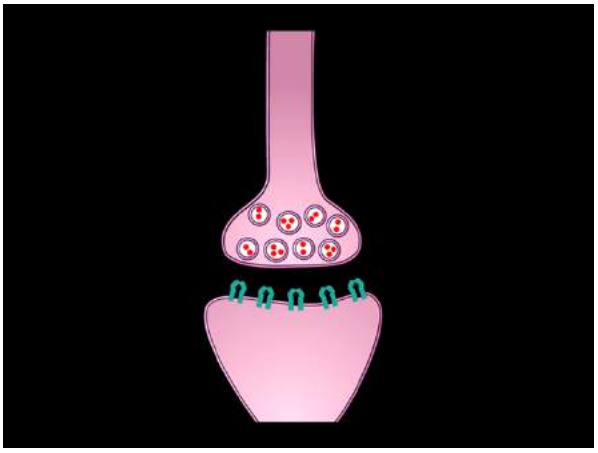
In the Human Brain

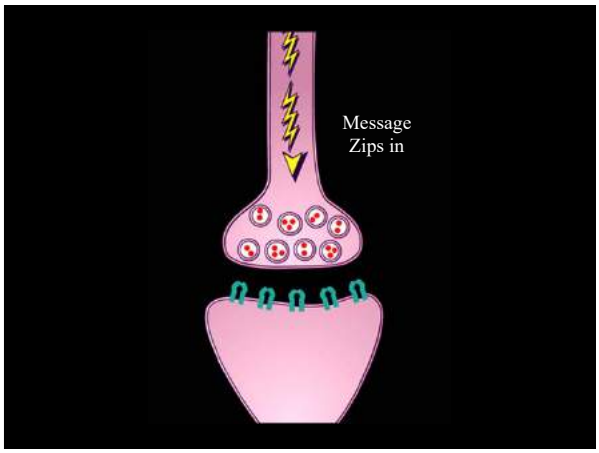
- 100 billion neurons (1 millionth inch across)
- each one linked to >1000 others
- in complex shifting sub-systems
- that have to "talk to each other"
- using low voltage electrical impulses
- that have to jump across gaps
- so fast that 12 can cross in 1/1000 sec.

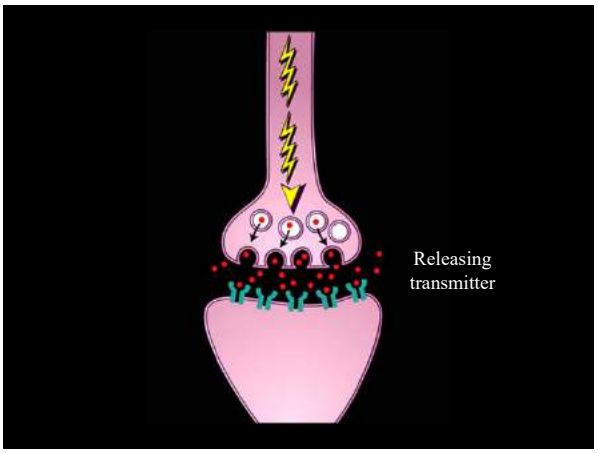
The Jungle

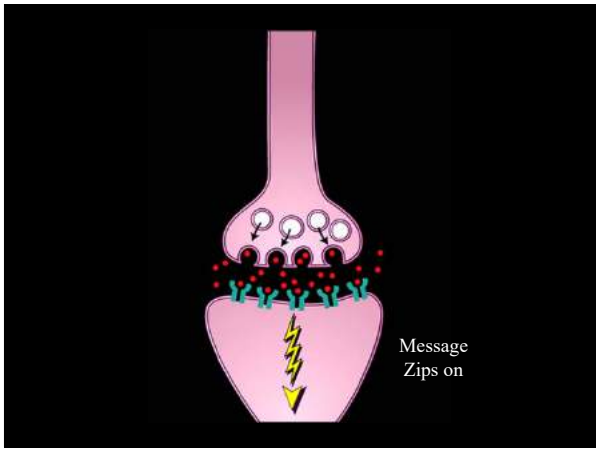


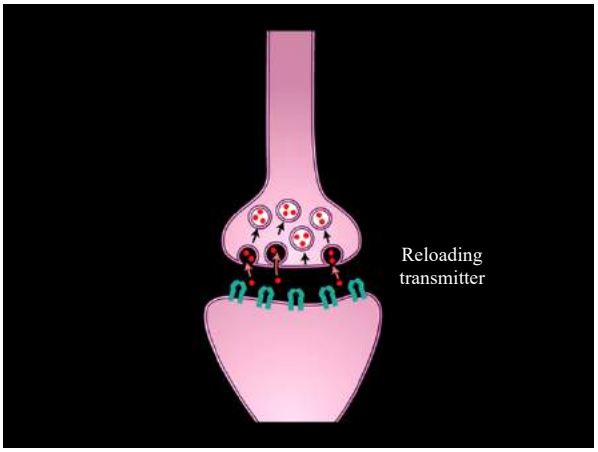


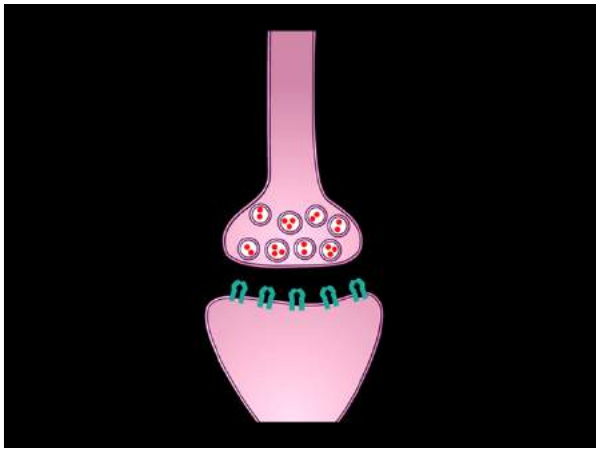












2 crucial chemicals: (dopamine, noripinephrine)

- control most of functions impaired in ADHD
- Brain of person with ADHD makes these chemicals, as does everyone else
- but does not release & reload effectively→ control messages often not connecting
- For 80% of those with ADHD medications improve this problem.

Chemicals Jump the Gaps

- Inside brain >50 different chemicals are continuously made
- every neuron system uses 1 of them
- stored in little vesicles near tip of neuron
- when electrical impulse comes, mini-dots of that chemical are released,
- cross the gap, fire next neuron, then reload in fractions of a second

Single Neuron to Cascades

- Until recent technological developments emphasis was on communication from one neuron to another
- More recent research highlights communication between transient, neuronal networks, in shifting cascades of intra-regional communication.(Hanson, 2012, Nicolelis,1997)

Regional Network Communications

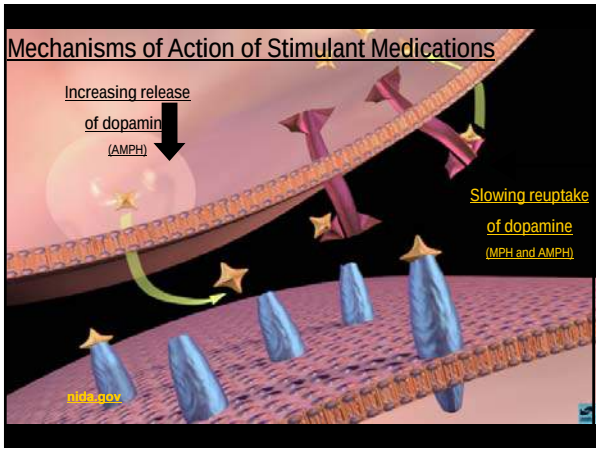
- Most communication within brain is not between solitary neurons. Most intra-brain messages are carried by large ensembles of neurons joined transiently to convey related bits of information across networks of countless neurons. Not like Morse code, but more like symphony.

(Hanson, 2012, Nicolelis, 1997, Brown, 2017)

All cross-neuronal signals are not equal! Why and How?

Signals differ in strength based upon how important the brain considers the signal to be.

Strength- shown in persistent sequential release (one knock on door or many)



Mechanisim of Action in Stimulants

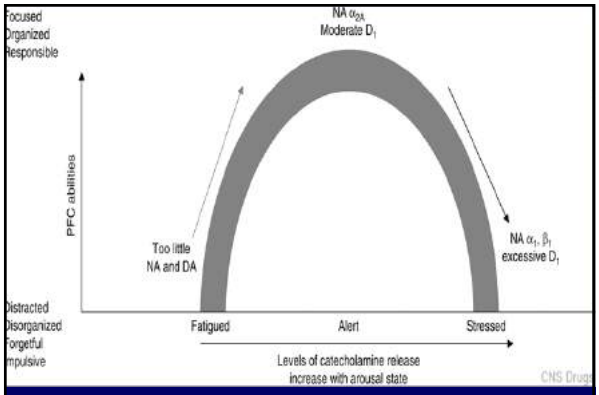
- Both methylphenidate and amphetamines slow reuptake of neurotransmitters
- Amphetamines also stimulate added release of neurotransmitter from pre-synaptic vesicles.
- Added transmitter can bring positive or negative effects.

How do ADHD Impairments of EF Usually Respond to Medication?

- This wide range of cognitive impairments responds to medication treatment in 70-90% of cases in children, adolescents and adults
- Symptom improvement varies from modest to very dramatic
- Adverse effects are usually transient, not significant

Factors Shaping Medication Response n = 1

- Not age, weight or symptom severity
- Sensitivity of individual's body chemistry to that medication
- Speed of absorption & metabolizing
- Other chemicals in body at that time (other scrips, OTC, THC, etoh)
- Cs and Ucs expectations



Toward a New Understanding of Attention-Deficit Hyperactivity Disorder Pathophysiology: An Important Role for Prefrontal Cortex Dysfunction Arnsten, Amy F.T.*CNS Drugs*. 23():33-41, Aug 1, 2009.

Patients' Fears of Medications for ADHD

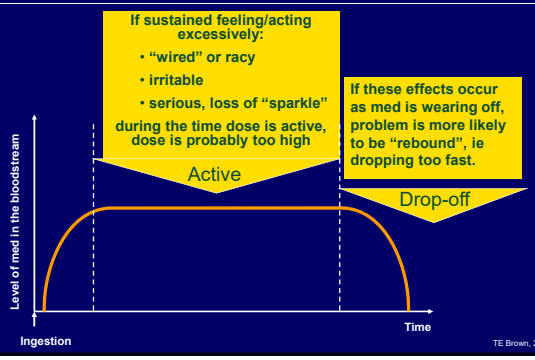
- Change personality "zombie"?
- Slow growth? Start tics?
- Lose appetite? Sleep?
- Later drug or alcohol problems?
- Dependence on meds for lifetime?
- Being labeled, attribution problems?
- Reactions of family, teachers, peers?

Patient Education is needed about ADHD medications

Need to be "fine-tuned" in collaboration with each patient

- Set patient expectations to collaborate
- med, dose or timing need to be adjusted to individual needs, body chemistry and schedule
- Be alert to stimulant "rebound"
- Need to report any side effects

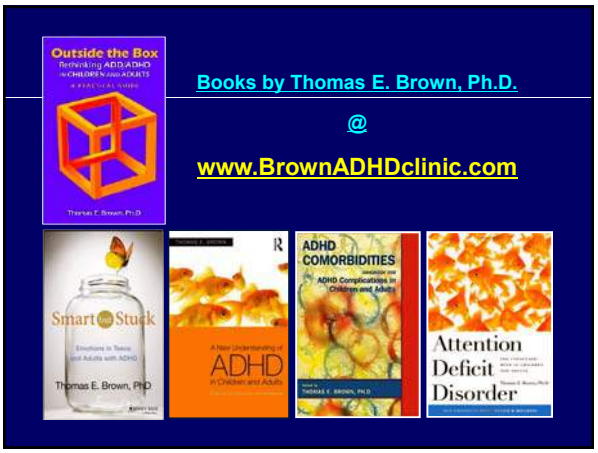
Time Frames and Rebound



Common Issues

- Appetite diminished, sleep probs
- prn use
- Increased anxiety, mood problems
- Generics vs branded meds
- Concurrent etoh and/or THC
- Switching betwn long/short-acting

risks of med tx vs risks of no med tx



Books by Thomas E. Brown, Ph.D.

@

www.BrownADHDclinic.com

Outside the Pill Bottle: What does Neuropsychological Evaluation Add to Diagnosis and Treatment of ADHD?

JEANETTE WASSERSTEIN, PHD-ABPP-CN

2018 APSARD ANNUAL MEETING JANUARY 12-14, 2018

Major issues in Adult ADHD

1. Problems extend beyond the core symptoms of inattention, hyperkinesis and impulsivity
2. Wide range of life impairments in education, work, family life and emotional functioning
3. This complexity make comprehensive assessment essential for optimal diagnosis, treatment choice and treatment monitoring

Review of Assessment Goals

1. Ascertain current symptoms and their severity
2. Retrospectively establish childhood diagnosis of ADHD
3. Rule out other primary disorders which may account for symptoms (either psychiatric like bipolar illness or major depression, or medical like sleep disorder, TBI or toxin exposure)
4. Ascertain existence of comorbid conditions (learning disorders, anxiety, substance abuse, depression)
5. Determine extent of symptoms and impairment, as well as establish priority of interventions…neuropsych eval. can be helpful here

Usual Assessment Approaches

R. Ramsay, 2017:13, 223-232

OPTIONS	EXAMPLES
1. Clinical Interview: Personal and family history	
2. Structured Clinical Interview	Adult ADHD Clinical Diagnostic Scale (ACDS), Len Adler at adultADHD@med.nyu.edu Conner's Adult ADHD Diagnostic Interview for DSM-IV (CAADID) at WWW.mhs.com
3. ADHD Scales	Conners' Adult ADHD rating Scales (CAARS), Wender-Reimherr Adult ADHD scale (WRAADDS)
4. Executive Function Scales	Brown Attention Deficit Disorders Scales(BADDS), Barkley Deficits in EF Scale for Adults(BDEFS), Behavior Rating Inventory of EF-Adult (BRIEF-A)
5. Emotional Functioning (BDI, BAI, MCMI, MMPI)	
6. Functional Impairment	Barkley Functional Impairment Scale (BFIS)

Usual Assessment Approaches continued

Depending on the goals of the evaluation, may need additional outside data:

1. School records
2. Standardized test results
3. Report of spouse, parent, sibling or close friend

Possible Content of Full Neuropsychological Examination

Lezak, Howieson & Loring, 2004

Note: red most likely effected in ADHD

Clinical Interview	
Aptitude	WAIS, WASI, Word Reading
Attention and orientation	WAIS Digit Span for short term storage, Symbol search, CPT for vigilance
Executive Functions	DKEFS, RCFT, WCS, Trails (shifting, inhibition, planning, conceptualization) and BRIEF, Mathematical procedures
Learning and Memory	CVLT, WMS, RCFT, Rey Auditory-Verbal learning, Buschke Selective Reminding
Fine-Motor Functions and Construction	Beery VMI, WAIS BD & Coding
Language	Boston Naming, OWLS, WAIS language subtests, Language based academic skills (reading, spelling, comprehension)
Sensory and visual perception	
Symptom Validity	Free standing (e.g., TOMMS, ACS-Word Choice) and Embedded (e.g. WAIS Reliable Digits, CVLT Forced Choice, BRIEF Validity Subscales)
Emotional Functioning	
Academic Skills	

MG2

Preliminary thoughts about neuropsychological evaluations

1. Very detailed and comprehensive
2. The majority of domains target neurocognitive skills 'at risk' in ADHD
3. Batteries can be extremely variable MG1
4. Always time consuming (3-8 hours)
5. Essential to rule/in or rule/out learning disorder or other cognitive impairment
6. Helpful to document level of impairments and possibly response to meds.

What does the science show? All based on group effects unless indicated otherwise.

1. 1998, Seidman, Biederman, Weber &Hatch found deficits in attention, executive functions and academic achievement in ADHD adults
2. 2000, Doyle, Biederman et al found only a minority (30%) of ADHD children showed deficits on EF tests.
3. 2002, Woods, Lovejoy & Ball found 'subtle impairments' on attention, EF, verbal list learning and processing speed in ADHD adults
4. 2004, Hervey, Epstein and Curry, first meta-analysis found deficits in multiple domains, with 'notable impairments in attention, inhibition and memory'. Effect sizes were modest.

What does the science show continued:

1. 2005, Boonstra, Oosterlaan, Sergent &Buitelaar, Meta-analysis in ADHD adults. Found deficits in both EF tasks (inhibition, set shifting and verbal fluency) and non EF domains (color naming, word reading, response consistency). Effect sizes .57-89
2. 2005, Willcutt, Doyle, Nigg, Faraone & Pennington, Meta-analysis of EF tasks in ADHD adults, found most consistent effects on response inhibition, vigilance, working memory and planning. Effect sizes .46-.69. *EF deficits were not universal*, suggesting "EF weaknesses are neither necessary nor sufficient" for ADHD diagnosis
3. 2005, Engel & Schoechlin, Meta-analysis found complex attention and verbal memory discriminated best, and *EF was not generally reduced* in this adult ADHD population. Effect size 0.5-0.6

What does the science show continued:

1. 2006, Seidman found not all ADHD persons have EF deficits.
2. 2006, Biederman, Petty, Fried, Fontanella et. al. found performance based deficits in EF identify subgroups of ADHD adults (30%) at greatest risk for occupational or academic underachievement.
3. 2009 and 2010, Barkley& Murphy and Barkley & Fisher, showed that self ratings deficits on his DEFI scale better at predicting adaptive impairment than neuropsychological results, including measures of EF.
4. 2017, Thorell, Holst, Chistiansen, Kooij, et. al. found that " a majority of older" ADHD adults performed within average ranges on neuropsychological tests. 20% showed no clear deficit in any domain.

What does the science say? Summary

1. No single deficit area, including executive dysfunction, is a gold standard (performance based EF measures share 12-20% of their variance….on individual level only 35-50% show EF deficits)
2. Greater neuropsychological dysfunction, especially in EF, is associated with greater dysfunction in life, school or at work
3. Most studies are based on group differences and findings often do not apply to all individuals
4. Effect sizes in meta analyses tends to be medium
5. Executive Dysfunction in ADHD is best measured via scales (closer to 80-90%)

Several Vignettes from My Practice

1. MD-PHD student seeking updated documentation of her dyslexia for extended time accommodation on boards. Evaluation led to first identification of ADHD and introduction of medication.
2. First Year Psychiatry Resident who showed poor organization and written expression. Sent for evaluation and found to have 'frontal findings.' Neuropsychologist was alarmed to find these markers for 'poor impulse control' and advised against continuation in program.
3. Trader successfully treated pharmacologically for many years. When his original doctor retired, new doctor questioned the ADHD diagnosis and refused to treat, despite obvious unraveling of patient's day to day life. Patient stayed because this doctor diagnosed and treated his depression.
4. Senior Psychiatry Resident, already treated for ADHD, was tested for accommodations on Boards. He was found to still be undermedicated. Dose adjusted up.

Outcomes from Vignettes

1. MD-PHD student -Went on to a brilliant career, much improved by additional diagnosis and treatment…… testing uncovered hidden diagnosis and changed life
2. First Year Psychiatry Resident - Forced to leave medicine despite lawsuit (after the fact)….poor understanding and misattribution destroyed his career
3. Trader- With anchors of objective and subjective data, new psychiatrist felt comfortable medicating ADHD. Patient felt validated and no longer accused of 'drug seeking behavior.' He had renewed control of his life and sought out executive functioning remediation.
4. Senior Psychiatry Resident- Gained 20 IQ points! (125 to145). But was not given accommodations on boards. Failed yet again due to continuing slow processing speed. Another try may be worth a shot based on another case with 4 failures, before getting accommodations for the 5th.

Inferences from Vignettes

1. Neuropsychological Evaluations can be very powerful and need to be wielded by people familiar with ADHD (e.g., know that frontal signs do not always mean dangerously poor impulse control, know that really smart and educated people can be ADHD)
2. Neuropsychological Evaluations can find hidden diagnoses (e.g., comorbid LDs, mood disorder) and generally help deepen understanding of the individual
3. Neuropsychological Evaluations can help fine tune treatment, both medication and other
4. Neuropsychological Evaluations are essential for 'high stakes' testing, but do not always get the applicant what they want.
5. Neuropsychological Evaluations can provide, but not always, objective documentation of core deficits.

MG3

Conclusions about Neuropsychological Evaluations

1. It is neither necessary nor sufficient for diagnosis, but can have tremendous clinical utility
2. Clinical utility includes that it identifies those at greatest risk and their specific risk areas (sustained attention, working memory, memory and learning, overload, slow processing speed, behavioral impulsivity, conceptual rigidity, etc).
3. Can protect from excessive subjectivity by evaluators
4. Can help design treatment and monitor response. Can repeat with a targeted re-evaluation.
5. Evaluations are costly in both time and money. Consequently, we must asses if makes sense for a given person
6. Most usual referral issues: high stakes testing, evaluation for LD, and validation of diagnosis in ambiguous context (here one would expect to find something, but not necessarily in EF or CPT).

Still Distracted After All These Years

The Unexplored Territory of ADHD after 60

Kathleen G. Nadeau, Ph.D.

MY PROJECT To Explore:

- The primary challenges faced by older adults with ADHD
- What ADHD looks like in older adults
- Whether the challenges different?
- Whether the challenges increase or decrease in older years

Diagnosing ADHD in older adults

- **Harder to obtain clear history** of ADHD patterns in earlier years
- **No screening tool** yet developed for older adults; using a standard adult ADHD screener with a lower cut-off score may be good way to begin
- **Look for younger family members with ADHD** – strong sign that the older adult may have it too

Crisis for Older Adults in Diagnosis and Treatment

- No training for ADHD professionals in diagnosing and treating "senior ADHD"
- Need training to distinguish ADHD from MCI
- Reluctance to prescribe stimulants to older adults with multiple medications and health problems
- Even those already diagnosed have difficulty finding new treatment providers

Sad, but true

- 40% of primary care physicians say they have never seen an adult patient with ADHD
- ADHD in older adults even LESS recognized

Does ADHD increase risk of dementia in later life?

- In those with Alzheimers greater number retrospectively reported ADHD-like symptoms.
- Seems to be an association between Dementia with Lewy Body (DLB) and ADHD
- Recent review article suggests that most likely connection between ADHD and dementia is lifestyle based

Classic ADHD patterns in older adults

- ADHD has "always been there"
- "Swiss Cheese Memory"
- Working memory issues
- Misplacing things
- Forgetting words & names of things
- Brain sometimes goes completely blank
- Need more planners, reminders, timers
- Harder to learn new things

There's a Chicken in the Basement!

Normal cognitive changes with age

- Less blood flow to the brain – exercise important
- Changing hormones
- Poorer sleep patterns – may be very related to memory challenges

Challenges for older adults can parallel those of young adults

- **Lose much-needed structure** as they leave home or leave the workplace; for stay at home moms, lose structure of children's schedules. Benefit from finding a more structured situation
- **At risk for developing poor sleep patterns and poor nutritional habits**

Poor self-care May Contribute to Symptoms

- May neglect health needs
- Disrupted sleep pattern
- Little or no exercise
- Poor nutrition – doesn't cook,

HOW CAN WE REDUCE COGNITIVE DECLINE?

- Optimize diet – low glycemic index – to reduce inflammation
- Fast for 3 hours before bed – don't eat for 12 hours between dinner and breakfast
- Sleep 8 hours per night – melatonin
- Reduce stress – yoga, meditation
- Exercise 30-60 min. 4-6 days per week
- Engage in brain stimulation activities

ADHD and Aging in women

- Cognitive changes for women around age 50
- Stimulant medication can feel ineffective if estrogen levels are low
- Hormone replacement can play an important role in the treatment for ADHD in post-menopausal women

#1 Challenge reported by older adults

Not getting things done

- Procrastination
- Poor self-discipline
- Trouble getting started on a task
- Lack of motivation – no "round tuit"
- Staying on task

2nd GREATEST CHALLENGE

Emotions not under control

- Irritability
- Emotional meltdowns
- Emotional reactivity – easily angered, frustrated
- Feeling very overwhelmed
- Anxiety

3rd greatest challenge

Time management challenges

- Difficulty setting and maintaining a daily routine
- Difficulty being flexible in the daily routine
- Time management difficulties
- Time awareness is poor

4th Greatest Challenge

Remnants of Hyperactivity

- Driven-ness/continual restlessness
- Random thoughts whirling in my head
- Talk too much
- Can't relax – need to keep doing, going
- Take on too many things constantly

5th greatest challenge

Social challenges

- Feeling misunderstood/judged
- Need to be a better listener
- Use wrong tone of voice
- Say wrong thing
- Talk too much
- Miss social cues

WORN OUT AFTER ALL THESE YEARS

- Spousal burn-out
- The salve of a good second marriage – finding acceptance and tolerance
- Don't marry a jerk!

Still Cluttered After All These Years

- Father about to be evicted due to chaotic clutter
- Mother who moved, then never unpacked

Free to be Me After All These Yearas

- Finally free to be me
- Chance to pursue gifts and talents
- Less pressure on executive functions

All Alone After All These Years

- "Chaos" – Can't have anyone over syndrome
- More likely to be alone
- Social life requires planning and initiation
- Coexisting depression
- Benefit from living in a community

Feeling Broke After All These Years

- Less likely to have managed finances well
- Less likely to have saved enough for retirement
- Problems with bill-paying and paperwork continue
- More medical paperwork piling up

Never Happier After All These Years

- No job stress
- Strong community connections
  - Involved in her church
  - Volunteering in her community
  - Has active social life through several groups

Still working after all these years

- 85 years old
- Continues to be very active
- Owns his own company – inventor and IT guy – LOVES his work
- Two failed marriages – second wife continues to work with him and run the business for him
- Has a very elderly companion toward whom he is very caring and nurturing – "She doesn't control or criticize me."

Still Hyper After All These Years

- ROY – 70 YEARS OLD – DIAGNOSED AT 42
- Married once, no kids – intentionally – marriage has lasted because we've spent to much time apart
- College grad that ended up in blue-collar job as electrician for General Motors
- Has done sky-diving, heli-skiing, double-century bike rides - Continues to downhill ski each winter despite many injuries and multiple surgeries
- BIGGEST PROBLEMS – ADHD is worse in retirement because of boredom, can't do what I want any more because of multiple health problems

What I'm Learning…..

- Great need to educate healthcare providers
- Many greatly benefit from stimulant medication
- Broad range of outcomes highly affected by circumstances
- Decrease in ADHD challenges seems related to
  - A decrease in demands
  - Increase in self-acceptance
  - Better choices of life partners

"TURNING INTENTIONS INTO ACTIONS:"

IMPLEMENTATION-FOCUSED CBT FOR ADULT ADHD

JANUARY 13, 2018

APSARD

J. Russell Ramsay, Ph.D.
Adult ADHD Treatment & Research Program
University of Pennsylvania Perelman School of Medicine

DISCLOSURES (PAST YEAR)

- **Speaker honoraria**:
  - Kaiser Permanente Health System (Calif.)
  - Maimonides Hospital (NY)
- **Paid CE/royalties** for presentations/webinars (J&K Seminars, TZK Seminars)
- **Book royalties** (Routledge/Taylor&Francis, American Psychological Association)
- **Honoraria as reviewer** of book proposals (Routledge, OUP, APA)
- **Honoraria** for *ADHD Report* article and chapter contributions to edited books

OBJECTIVE

How do we get adults with ADHD to follow through on recommendations, coping strategies, and other behaviors that will improve functioning using CBT?

CBT FOR ADULT ADHD FOCUSED ON IMPLEMENTATION

PSYCHOSOCIAL TREATMENT: REVIEWS AND META-ANALYSES (SINCE 2010)

- *Jensen et al. (2016). *Atten Def Hyper Dis, 8*, 3-11. doi: 10.1007/s12402-016-0188-3
- Knouse (2015). In R. A. Barkley (Ed.), *Attention-deficit hyperactivity disorder: A handbook for diagnosis & treatment* (4th ed.) (pp. 757-773). NY: Guilford.
- Knouse & Safren (2010). *Psychiat Clin of North Am, 33*, 497-509. doi: 10.1016/j.psc.2010.04.001
- *Knouse et al. (2017). *J of Clinical and Consulting Psychology*. Online. doi: 10.1037/ccp0000216
- Manos (2013). *Postgraduate Medicine, 125*, 51-64. doi: 10.3810/pgm.2013.03.2641
- Mongia & Hechtman (2012). *Curr Psych Rep, 14*, 561–567. doi: 10.1007/s11920-012-0303-x
- *Moriyama et al. (2013). *CNS Spectrums, 18*, 296-306. doi: 10.1017/S109285291300031X
- Ramsay (2011). *Journal of Clinical Outcomes Management, 18*, 526-536.
- Ramsay & Rostain (2015). *Cognitive-behavioral therapy for adult ADHD* (2nd ed.). NY: Routledge.

* = meta-analysis

SUMMARY OF CBT FOR ADULT ADHD: INTERVENTION CATEGORIES

- Cognitive modification
- Behavioral modification and coping skills
- Acceptance, mindfulness, persistence
- Implementation strategies

Ramsay & Rostain (2015). *Cognitive behavioral therapy for adult ADHD (2nd ed.)*. NY: Routledge.

CBT FOR ADULT ADHD: PREMISES FOR THE ADAPTED MODEL *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 on and reacts to various contexts and roles and relationships.

Ramsay (in prep). *Thinking through adult ADHD*. DC: APA

CBT FOR ADULT ADHD: PREMISES FOR THE ADAPTED MODEL *PSYCHOSOCIAL INTERVENTION*

1. ADHD is a **quantitative** (and not a qualitative) difference in functioning, falling at the disordered end of a continuum of normative functioning (in terms of frequency and magnitude of sxs)
2. ADHD is an **implementation** problem related to difficulties performing the necessary skills and strategies needed to effectively manage a task, endeavor, role, or situation (and not a lack of knowledge of what needs to be done or ability to perform the skills).
3. These implementation problems stem from **chronic developmental difficulties related to impaired self-regulation**. Overall, these self-regulation problems involve difficulties organizing, initiating, and sustaining actions over time in order to achieve a future-focused outcome that is personally salient and desired by an individual. **The self-regulation deficits also contribute to**:
   i. Procrastination
   ii. Poor motivation for behavior (both initiating and sustaining over time)
   iii. Poor task endurance
   iv. Difficulties sustaining efforts across time, working towards a deferred reward
   v. Tendency to discount deferred rewards, which are experienced as less salient than proximal rewards
   vi. Corresponding difficulties with initiating and sustaining attention, disorganization, poor working memory, and emotional dysregulation which **punctuate** experience and efforts
   vii. Difficulties executing otherwise known + effective coping strategies for managing these problem areas

Ramsay (in prep). *Thinking through adult ADHD*. DC: APA
Ramsay & Rostain (2016). *Practice Innovations, 1*, 36-52.

CBT FOR ADULT ADHD: PREMISES FOR THE ADAPTED MODEL *PSYCHOSOCIAL INTERVENTION (2)*

4. These difficulties magnify and are magnified by co-existing psychiatric and learning disorders, as well as other life stressors and that result in "**disengagement**" from what are otherwise feasible and personally-salient tasks, endeavors, roles, duties, goals, and other objectives.
5. These self-regulatory deficits and impairments affect different levels of patient experience, which are targets for interventions[1]:
   a) *Cognitive/Justification*: self- and other-directed
   b) *Behavioral/Investment*: meeting goals, needs, and obligations
   c) *Emotional/Experiential*: affective reactions + goal-value motivations
   d) *Implementation*: targeted self-regulatory tactics to employ coping strategies
   e) *Relationships/Influence*: **social capital** with others to meet needs + roles
6. The tx alliance is a vital source of empathy, support + focus on **effecting**

Ramsay (in prep). *Thinking through adult ADHD*. DC: APA
Ramsay & Rostain (2016). *Practice Innovations, 1*, 36-52.
[1]Henriques (2011). *A new unified theory of psychology*. NY: Springer.

CLINICAL EXAMPLE: "PROCRASTIVITY"

LESSONS LEARNED FROM "PROCRASTIVITY"

- **PROCRASTIVITY** – Avoiding a higher priority task by engaging in a lower priority, less time-urgent (but productive) endeavor that is ultimately self-defeating.[1]

- Elements of procrastivity task (compared with priority task):
  - **Manual** – physical > cognitive (or clear cognitive > vague cognitive)
  - Existing template or **behavioral script** of actionable steps
  - Better sense of what can be accomplished in a **time frame**
  - Clearer sense of task **progress** and maintenance of gains
  - Clear **end point** and **completion** of task
  - Procrastivity task may actually require ***more time and effort***, but is viewed as **more in harmony with one's perceived efficacy than priority task**

[1] Ramsay (2017). *Professional Psychology: Research and Practice, 48,* 62-69.

LESSONS LEARNED FROM "PROCRASTIVITY" (BEHAVIORAL)

- Use lessons from procrastivity to develop priority task plan
  - Make the task "manual" or actionable (at least getting "**on task**")
    - "**Go** to work/study station"
    - Spend first few minutes **reviewing** assignment, outlining, etc.
    - **Re-read** last two paragraphs you wrote
    - **Get / touch an item** you need for the task
    - "**Behavioral priming**" / progressive exposure / graded task

LESSONS LEARNED FROM "PROCRASTIVITY" (BEHAVIORAL 2)

- Use lessons from procrastivity to develop priority task plan
  - "**Lower the bar**" in terms of expectations and "progress"
    - Time based
    - Task based
    - Terrain based
  - Define a realistic time frame with **start time and end time** ("See the shore" and see beyond the shore), **bounded task**
  - Draw on existing "**scripts**" that have been effective

LESSONS LEARNED FROM "PROCRASTIVITY" (EMOTIONAL MANAGEMENT)

- "Acceptance" of discomfort/emotion to maintain "commitment" to a valued task. (i.e., **Do not have to be "in the mood"**)[1]
- "Mindful" recognition of ADHD symptoms, emotional discomfort without escape reaction (feeling does not dictate action)[2]
- State/acknowledge what you are feeling[3] or "emotional labeling"[4]
- **Feel discomfort AND engage in task**

[1]Hayes et al. (1999). *Acceptance and commitment therapy*. New York: Guilford.
[2]Zylowska (2012). *The mindfulness prescription for adult ADHD*. New York: Trumpeter.
[3]Lieberman et al. (2007). *Psychological Science, 18*, 421-428.
[4]Brooks et al.,(2017). *Social Cognitive and Affective Neuroscience*. doi: 10.1093/scan/nsw121

LESSONS LEARNED FROM "PROCRASTIVITY" (IMPLEMENTATION STRATEGIES)

- Identify task goal but focus on implementation plan
  - Goal = Do homework
  - Implementation intention = "If I sit at desk, then I can start math."
- Identify plans for handling the "tipping points" of:
  - Starting a task
  - Handling distractions, interruptions, barriers (back on task)
  - Re-engaging in a task after breaks or interruptions
- **Implementation plan = "IF/WHEN X, THEN I WILL DO Y."**

Gawrilow et al. (2011a). *Journal of Social and Clinical Psychology, 30*, 615-645.
Gawrilow et al. (2011b). *Cognitive Therapy and Research, 35*, 442-455.

INTERVENTIONS: COGNITIVE MODIFICATION

"What are you thinking about this task?"

WHY IS THE TOPIC OF THOUGHTS, BELIEFS, AND ADULT ADHD RELEVANT?

OLD VIEW	NEW VIEW
• Cognitions only relevant to the degree that they are associated with comorbidity	• Cognitions relevant in cases of pure ADHD and make distinct contribution to treatment
• Behavior change is the ultimate outcome measure	• Yes, but cognitions play a key role in the implementation of coping strategies, motivation, and behavior change
• c - B - T	• C - B - T

MALADAPTIVE THOUGHTS + ADULT ADHD

- Recent findings on the association of distorted thoughts and impairments common to adult ADHD:
- Unique and overlapping association with MDD, depressive sxs, cog **avoidance**[1]
- Present in cases of ADHD with and **without** depression > controls[2]
- Associated with high **emotions**, high **escape-avoidance** coping[3]

[1]Knouse et al. (2013). *Cognitive Therapy & Research, 37,* 1220-1232.
[2]Mitchell et al. (2013). *Cognitive Therapy & Research, 37,* 851-859.
[3]Torrente et al. (2014). *Journal of Attention Disorders, 18,* 412-424.

MALADAPTIVE THOUGHTS + ADULT ADHD(2)

- ADHD > controls on "intrusive/worrisome thoughts" (particularly **frequency** + **removal difficulty**)[4]
- Positive, significant, small correlation of distorted thoughts and ADHD sxs (**controlling for mood/anxiety**) [5]
- Development of an "ADHD Cognition Scale for Adults" ("**positive bias**") [6,7]

[4]Abramovitch & Schweiger (2009). *Psychiatry Research, 168*, 230-233.
[5]Strohmeier et al. (2016). *Psychiatry Research, 238*, 153-158.
[6]Knouse et al. (2017). *Journal of Attention Disorders,* online ahead of print
[7]Knouse & Mitchell (2015). *Cognitive & Behavioral Practice, 22*, 192-202.

WHAT IS THE "IDEATIONAL CONTENT" OR "THEME" OF COGNITIONS?[1]

- Depression = loss (self, experiences, future)
- Anxiety = danger, risk, (uncertainty)
- Hypomania = inflated gains, positives
- Obsessions = warning, doubt

[1]Beck (1976). *Cognitive therapy and the emotional disorders*. NY: Meridian.

CBT FOR ADULT ADHD: PREMISES FOR THE ADAPTED MODEL

- CBT – Extended Release or Implementation Focus / **"Sticky"**
- Main cognitive issue/theme = **impaired self-regulatory efficacy**
  (Ramsay [in preparation]. *Thinking through adult ADHD*. DC: APA)
  [***Self-distrust*** cognitions, ***Self-mistrust*** schema]
- Main behavioral issue = **engagement**, scripting, challenging escape/avoid
- Main emotional issue = task-demoting emotions: **discomfort (ugh)**
  task-promoting emotions: **motivation (oh, ok)**
- Main implementation issue = **plan into action**, switching modes, agility

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

ADULT ADHD: COGNITIVE THEME (3)

- **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

PUTTING IT TOGETHER

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ADHD: progress in identifying genetic and environmental risk factors

Anita Thapar

Selected findings and a clinical perspective

Disclosures

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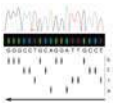
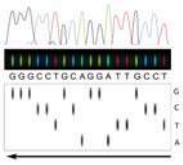
- Royalties from Wiley and payments from universities for talks go to Cardiff University

Genetic designs

- Traditional designs-genetic contributions statistically inferred (e.g. twin design)
- Direct genomic assessments
  - common gene variants
  - rare variants



Common gene variant discovery in GWAS



- Single nucleotide difference (SNPs)
- Multiple SNPs, small effect, need very large sample size for GWAS
- International discovery consortium ADHD
- 12 genome hits

Demontis et al 2017

Molecular genetics: what it has taught us about the nature of ADHD

A composite of common risk alleles (polygenic risk scores) and other methods to test genetic correlations between ADHD and other phenotypes

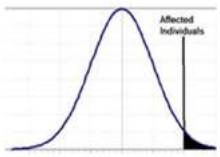
common variants above threshold p>0.5

Hamshere, Langley et al, Am. J Psychiat 2012; Demontis et al 2017

Consider

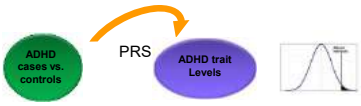
- Composite genetic risk score/polygenic risk score has very low predictive value
- But useful indicator of genetic liability to address specific hypotheses

ADHD as a concept



- Diagnosis can be useful for categorical decisions
- ADHD behaves as a trait in terms of adverse outcomes
- Akin to blood pressure/hypertension

Patient diagnoses→ Population trait



rg=0.943, SE = 0.204

Martin et al, Biol. Psychiat. 2014; Groen-Blokhuis et al 2014. Demontis et al 2017

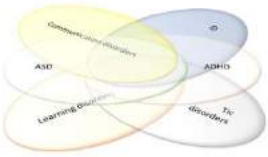
Population trait→ Diagnosis

UK ALSPAC population cohort→ clinical cases vs. controls
OR 1.17 95%CI: 1.08 -1.28

Stergiakouli et al, JAACAP 2015

ADHD behaves as a dimension: epidemiological, twin and now molecular genetic findings

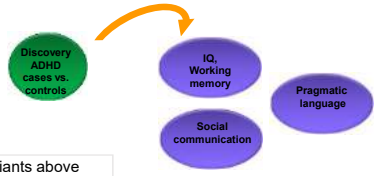
ADHD: DSM 5 Neurodevelopmental Disorders



Early onset, overlap, male excess, neurocognitive impairments

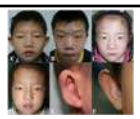
Thapar, Cooper & Rutter 2017

ADHD polygenic risk scores→ neurodevelopmental population traits



common variants above threshold p>0.5

Martin et al, JCPP 2015

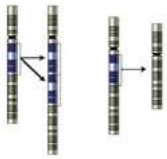


Rare mutations: known syndromes

- Risks of different neurodevelopmental disorders well established
- Tuberous Sclerosis → ASD, Intellectual Disability and also ADHD
- 22q11 micro deletion → psychosis, ID, ASD and also ADHD
- Fragile X → ID, ASD like, ADHD like

Copy number variants CNVs

chromosomal deletions or duplications



Elevated rate in Intellectual Disability

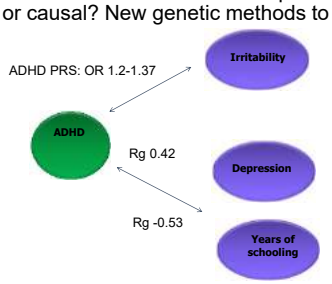
Copy number variants-chromosomal deletions and duplications

- ↑ Large, rare CNVs in ADHD
- Also ASD, ID, SCZ, epilepsy
- Significant overlap
- CNVs → multiple types of neurodevelopmental disorders

Williams et al, 2010 2012;
Elia et al, 2012; Lionel et al, 2011, Jarick et al, 2012.

ADHD behaves as a neurodevelopmental disorder but caveat….

ADHD genetic correlations with non ND phenotypes: pleiotropy or causal? New genetic methods to test this

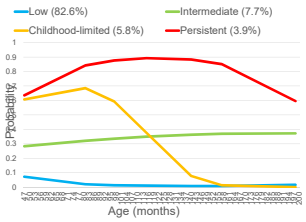


Riglin et al, 2017
Demontis et al 2017

ADHD persistence

Elevated familial risk
Faraone et al 2000

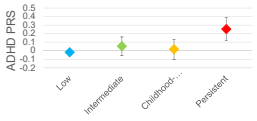
ADHD trajectories in ALSPAC: SDQ ages 4 to 17 years



Riglin et al. JAMA Psychiatry 2016

ADHD genetic risk scores

- ADHD PRS differed across the four trajectories:
  Higher scores in the persistent trajectory compared to the other 3
  ($\chi^2(1)$=4.70-14.67, p<.001-0.030)
  No association with schizophrenia, bipolar or MDD PRS



Neurodevelopmental multi-morbidity as a clinical index of genetic loading

- ADHD PRS was associated with multi-morbidity (>3 ND problems)
- Multi-morbidity levels differed across the four trajectories:
- Higher scores in the persistent trajectory compared to the other 3
  ($\chi^2(1)$=6.73-225.86, p<.001-0.009)

Genetic testing?

- Common variants, polygenic risk scores: no
- Rare mutations: causal, clinical implications
- Kir6.2 or SUR1 mutations of the pancreatic K-ATP channel in persistent neonatal diabetes

- Rare mutations: screening in intellectual disability including mild ID, autism
- Rare mutations in ADHD?

(Gloyn et al NEJM 2014)

No psychiatric disorder is entirely genetic

Evidence that environmental factors contribute-which ones?

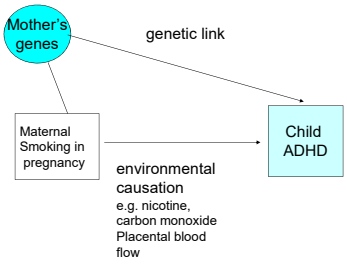
Challenge to work out whether causal

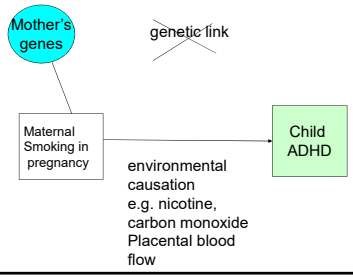
Early life risk factors

- maternal smoking in pregnancy ** Pooled OR= 2.39 (Langley et al, 2005)
- maternal stress/anxiety in pregnancy*
- maternal alcohol and drug use
- low birth weight/preterm ** pooled odds ratio= 2.64
- lead*, PCB exposure
- low income

Thapar et al JCPP 2013

Association ≠ causation: need quasi experimental designs and triangulation of evidence to remove unmeasured confounders etc.





A novel design Children born by in-vitro fertilisation (IVF)

- Some offspring are genetically unrelated to mother who undergoes the pregnancy
  - Egg donation
  - Embryo donation
  - Gestational Surrogacy

- Others are related
  - Homologous IVF
  - Sperm donation

What can we test?

Rice et al. PNAS 2008; Thapar et al. Biol Psychiat 2009

- If maternal smoking in pregnancy has real risk effects on the child, it will not matter if the child is related or unrelated to the woman undergoing the pregnancy
- Related: β=0.102 P=0.02
- Unrelated: β-0.052 P>0.10

Maternal smoking in pregnancy and ADHD using genetic designs

- Maternal vs. paternal exposures
  e.g. Langley et al. 2012;
- Siblings discordant for prenatal exposure
  e.g. D'Onofrio et al, 2014 Obel et al 2016
- Systematic review: 12 informative studies Rice et al. Development and Psychopathology. In press
- ADHD PRS predict prenatal exposures (smoking, acetaminophen use)
  e.g. Havdahl et al in preparation

Conclusions

ADHD

- Strongly heritable- common and rare gene variants
- ADHD behaves as a trait (although diagnosis needed for clinical purposes)
- Neurodevelopmental overlap: shared genes
- ADHD persistence higher genetic burden-look out for multi-morbidity
- Genetic testing in clinical settings: look out for practice changes in the future

Identifying environmental risks is important

- A challenge to identify what is causal
- Is the environmental factor an index of parent or offspring genetic risk?
- Causality needs rigorous testing
- Genetic designs can elucidate environmental risk factors and causal E not just genes

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- PGC ADHD group
- Clinical colleagues and families who participated

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Beyond heritability – Have studies of the effects of institutional deprivation changed how we conceptualise ADHD?

THE ERA TEAM

APSARD 2018

WASHINGTON

OVERVIEW

- Can extraordinary environments have extreme neuro-plastic effects that override genetic effects.
- Early institutional deprivation and adult ADHD – A recap.
- The ERA Brain Imaging Study
- The effects of early deprivation on neuropsychological functioning.
- Do deprivation-related ADHD cases differ from typical clinical adult ADHD cases?

IF A DISORDER IS HIGHLY HERITABLE CAN EXTRAORDINARY ENVIRONMENTS "CAUSE" IT?

- ADHD highly heritable => focus G not E.
- Given observational nature - H estimates depend on type of experiences in studied populations (typically normative environments).
- Say little about the **potential** of extraordinary environments to cause disorder.
- While genes strongly implicated in normative environments, extraordinary environments may override genetics to..
  - *provoke disorder even in an otherwise "strong" brain*
  - *prevent/remediate disorder in a vulnerable brain*

EXTREME NEUROPLASTIC RESPONSES: *A DOUBLE EDGED SWORD?*

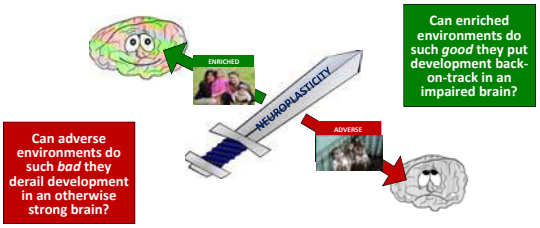
Normative environments interact with genetic factors to mould the mammalian brain in complex/subtle ways to bring about learning and development.

EXTREME NEUROPLASTIC RESPONSES: *A DOUBLE EDGED SWORD?*

Moving beyond *ordinary environments* may produce extreme *neuro-plastic responses* that have profound consequences for development.

EXTREME NEUROPLASTIC RESPONSES: *A DOUBLE EDGED SWORD?*

Moving beyond *ordinary environments* may produce extreme *neuro-plastic responses* that have profound consequences for development.



THE CONDITIONS IN THE ROMANIAN ORPHANAGES WHEN THE CEAU$ESCU REGIME FELL

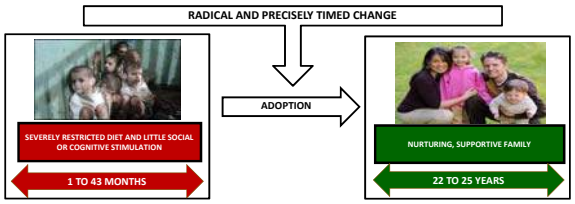
Severely restricted diet
High rates of communicable disease
Little social/cognitive stimulation
No personalised care – no chance to establish selective attachments

How did this actually impact development?

ENGLISH & ROMANIAN ADOPTEES STUDY

A UNIQUE NATURAL EXPERIMENT OF THE EFFECTS OF EARLY DEPRIVATION ON DEVELOPMENT

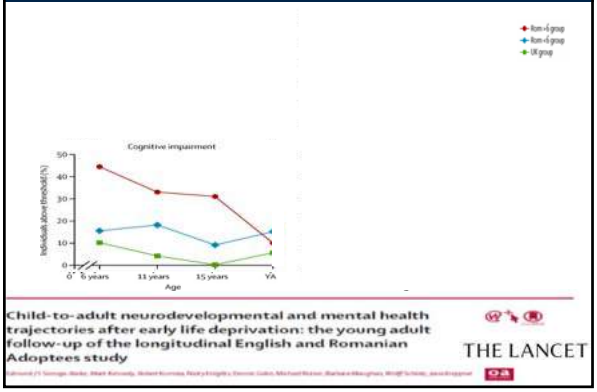
ADOPTION OF PROFOUNDLY DEPRIVED INFANTS FROM THE ROMANIAN ORPHANAGES PRE-1990's



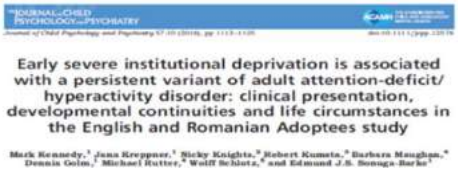
Deprivation duration likely un-confounded with genetic liability

- ***Children placed in institutions in early infancy/Adopted at regime fall***
- ***No reason why most deprived would also be most at genetic risk genetically***

REMISSION OF COGNITIVE IMPAIRMENT BUT PERSISTENCE OF OTHER NEURO-DEVELOPMENTAL DISORDERS



IS THE PERSISTENCE OF I/OA REFLECTED AT THE DIAGNOSTIC LEVEL?

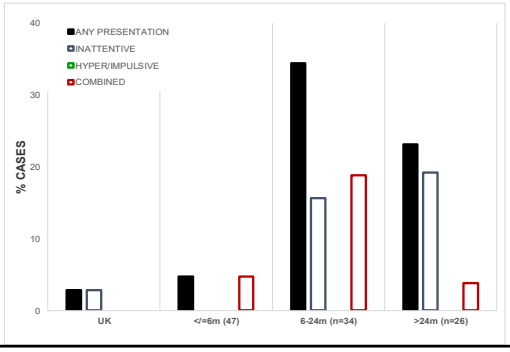


Early severe institutional deprivation is associated with a persistent variant of adult attention-deficit/ hyperactivity disorder: clinical presentation, developmental continuities and life circumstances in the English and Romanian Adoptees study

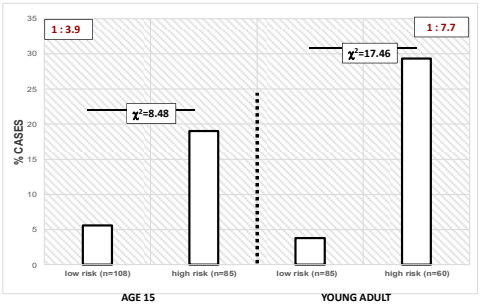
Is there an unusually high persistence and continuity in deprivation-related ADHD?

Is there a distinctive pattern of subtype/comorbidity/sex ratio/impairment?

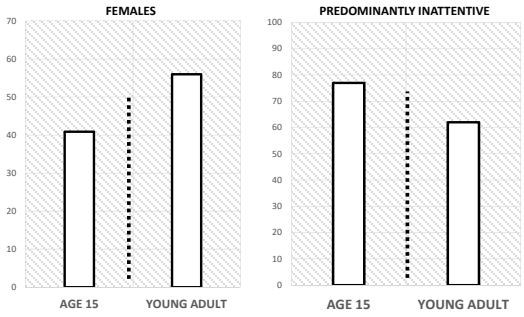
ADULT ADHD



ADOLESCENT & YOUNG ADULT COMPARISON



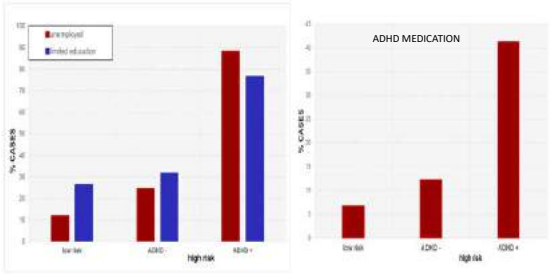
SEX AND PRESENTATION



COMORBIDITIES

	LoRisk (n=79)	Rom>6			
		ADHD- (n=41)	ADHD+ (n=17)	LoR *vs* ADHD+	ADHD- *vs* ADHD+
DSE	0.1 (0.63)	1.0 (1.58)	1.6 (1.84)	**t=-3.32, *p*=.004**	t=-1.29, *p*=.20
AUTISM	1.3 (2.14)	1.8 (2.45)	5.3 (4.18)	**t=-3.82, *p*=.001**	**t=-3.89, *p*<.001**
IQ	102.7 (16.09)	96.0 (13.11)	93.3 (10.62)	t=1.88, *p*=.06	t=0.62, *p*=.54
CD	46.4 (10.78)	48.4 (13.45)	51.4 (11.16)	t=-1.42, *p*=.16	t=-0.64, *p*=.52
CU	26.0 (7.0)	26.7 (7.91)	35.8 (6.30)	**t=-5.05, *p*<.001**	**t=-3.97, *p*<.001**
Depression	54.3 (13.96)	58.2 (14.97)	65.0 (12.60)	**t=-2.40, *p*=.02**	t=-1.34, *p*=.19
Anxiety	54.1 (13.63)	58.0 (14.03)	62.7 (11.86)	**t=-2.00, *p*=.05**	t=-0.99, *p*=.33

IMPAIRMENT AND TREATMENT



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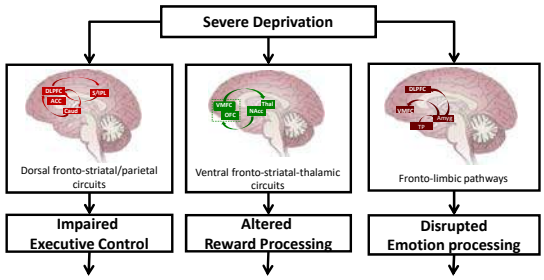
- Jonathan Mill
- Hanna Kovshoff

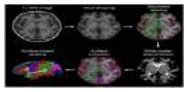
Department of Health, MRC, Nuffield Foundation, ESRC, Jacobs Foundation.

ERA BRAIN IMAGING STUDY
Putative Deprivation Related Brain Networks



ERABIS DESIGN

BRAIN STRUCTURE



Voxel and Surface-based Morphometry

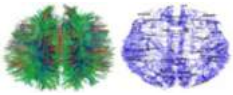
BRAIN FUNCTION

Inhibition *SSP*	Reward *MID*
Empathy *EAT*	Emotion Processing *NimStim*

CONNECTIVITY

Diffusion Tensor Imaging

Resting State Connectivity



NEUROPSYCHOLOGY

Inhibition *GNG*	Risk Taking *RCT*
Prospective Memory *EAT*	Emotion Processing *EBT*

ERABIS DESIGN

	N (%)*
Romanian adoptees (Rom: dep)	**60 (49)**
v	
UK adoptees (UK: no dep)	**23 (44)**
v	
Non-adopted adults (NAA; no dep)	**65**
v	
Clinic recruited ADHD (Clin-ADHD: no dep)	**18**
v	
Clinic recruited ASD (Clin-ASD: no dep)	**16**

* Of original ERA sample

SELECTIVE ATTRITION?

		UK	Rom<6	Rom>6
percent sample	**ERA YAF**	24	21	45
	ERABIS	22	21	46
percent female	**ERA YAF**	35	34	59
	ERABIS	39	40	54
IQ	**ERA YAF**	105	101	95
	ERABIS	105	101	92
percent DSP at age 11	**ERA YAF**	4	6	43
	ERABIS	4	9	38
percent ADHD at YAF	**ERA YAF**	8	10	44
	ERABIS	13	10	30

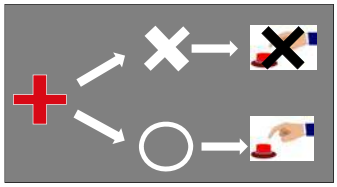
PROACTIVE INHIBITION

- ADHD and early deprivation associated with inhibitory control (IC) test performance.
- IC involves reactive processes (phasic) but also proactive states (tonic).
- Proactive IC rarely studied but relevant to everyday life.
- Proactive IC may carry more sustained EF requirement.
- Criaud et al. (2012) argued proactive IC is default setting.
- Proactive and reactive IC are confounded in classical tasks – both "go" and "nogo" trials engage proactive IC.
- GNG task developed to isolate proactive IC.

PROACTIVE INHIBITION

Always "Go" target to follow: No proactive inhibition needed

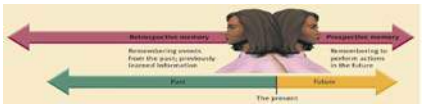
50% chance of "NoGo" target – proactive inhibition needed.

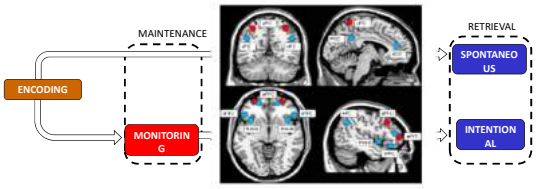


Proactive IC = RT "Go" v "possible NoGo" trials

PROSPECTIVE MEMORY

Remember to do a future task when invited or at a pre-specified time uninvited.





Mcdaniel et al. 2015

Conal et al. 2015

PROSPECTIVE MEMORY

Memory For Intentions Test

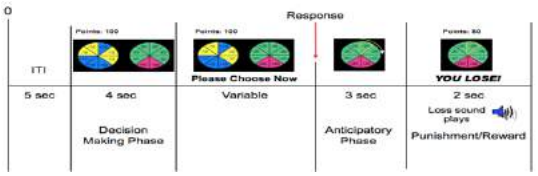
	Cue	Response	Delay	Task
é	Time	Verbal	15	"In 15 min, tell me that it is time to take a break"
í	Event	Action	15	"When I hand you a red pen, sign your name on paper"
Ð	Time	Verbal	2	"In 2 min, ask me what time the session ends today"
î	Event	Action	15	"When I hand you a postcard, self-address it"
®	Event	Action	2	"When I hand you a records form, write your doctors' names"
¦	Time	Action	15	"In 15 min use paper to write the medications you take"
þ	Event	Verbal	2	"When I take out my phone, please remind me to turn it off"
Ã	Time	Verbal	2	"In 2 min, please tell me two things you forgot to do this week"

Participants complete a word-search puzzle during task (distractor)

Raskin, Buckheit & Sherrod, 2010

RISK TAKING FOR REWARDS

- **ADHD individuals are presumed risk takers – institutionally deprived may be risk averse.**
- Traditional gambling paradigms often compounded by attention to/learning about contingencies.
- Clark et al (2010) developed a gambling task with explicit contingencies.



- **Both ends of the economic spectrum are tested.**
  - *Risk beneficial - choosing the risky option will gain you points*
  - *Risk detrimental - choosing the risky option will loose you points.*

EMOTIONAL RECOGNITION

Deficits in emotion recognition found in ADHD and institutionally deprived.

Face

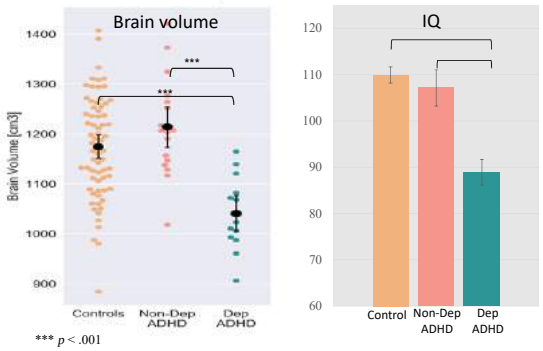
Child | Young adult | Middle-aged | Older Adult

Task measures facial emotional identification.

Happy, sad, angry., fearful faces presented on a screen.

Controls task identify age of face.

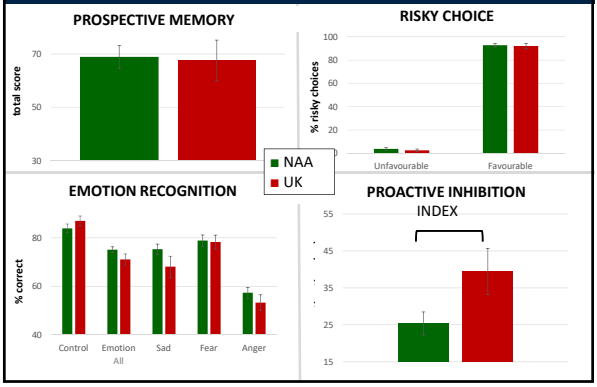
IMPORTANT NEURO-DEVELOPMENTAL CONTEXT



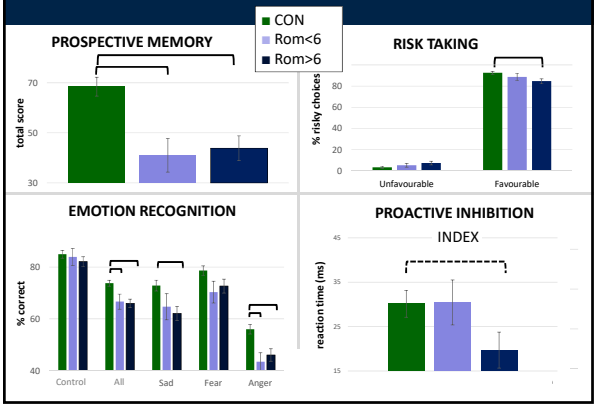
RESULTS

GENERAL EFFECTS OF DEPRIVATION AND SUBSEQUENT ADOPTION

EFFECT OF ADOPTION



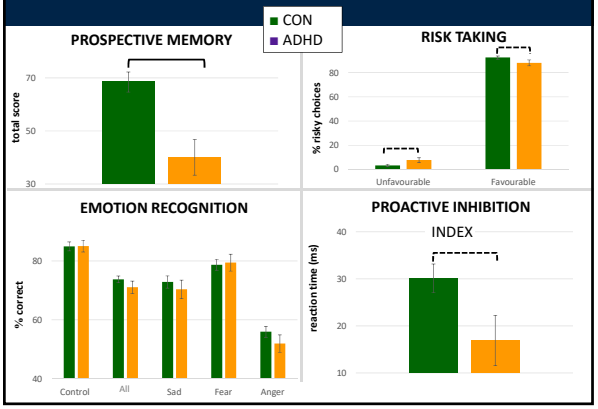
EFFECT OF DEPRIVATION



RESULTS

Do deprivation and non-deprivation related ADHD cases differ neuropsychologically?

EFFECT OF ADHD



EFFECT OF DEPRIVATION ON ADHD

DISCUSSION

- ADHD is common in adults who experienced institutional deprivation in the first four years of life.
- Individuals who experienced extended deprivation
  - weakened prospective memory
  - slower information processing
  - reduced proactive inhibitory control
  - impaired processing of negative emotions
  - altered decision making in the face of risk
- ADHD in general was associated with impairment on prospective memory and proactive inhibition largely independent of deprivation status.
- Emotion recognition deficits may be a specific correlate of ADHD following deprivation.

ESTABLISHING THE PERSISTENCE OF ADHD BETWEEN AGE 15 AND YAF

- **General Principle:** As far as possible compare like with like.
- **Problem:** Not same measures available at 15 and YAF
  - CAPA interview at 15 – 3 DSM INAT, 3 HYP, 3 IMP symptom items.
  - CBRS at YAF (all items).
- **Solution: In general**
  - Use DSM-5 "child" thresholds at both time points.
  - Map 9 DSM available CAPA items onto those at YAF.
  - Establish face validity – check for comparative rates in non-derived groups.
- **Solution: Specifics**
  - Use only DSM CBRS items also available in CAPA.
  - Last three months CAPA; last month CBRS.
  - Take standard thresholds for symptom presence – "definite" - CAPA "often" - CBRS.
  - Adapt DSM thresholds – 2/3 for INAT, 4/6 for HYP/IMP
  - Severe impairment – CAPA "definite"; CBRS "always" in at least 2 settings.

DSM	AGE 15 CAPA	YAF CBRS
INATTENTION		
Fails to give close attention to details/makes careless mistakes in work		Doesn't pay attention to details; makes careless mistakes.
Trouble holding attention on activities.	**Jumps from between things without finishing task?**	**Trouble keeping mind on work or leisure activities for long.**
Does not listen when spoken to directly.		Does not listen to what is said.
Does not follow through on instructions and fails to finish work.	**Follows through on instructions**	**Does not follow through on instructions.**
Trouble organizing tasks.		Trouble organising tasks/activities.
Avoids, doing tasks that require mental effort over a long period of time		Avoids or dislikes things that take a lot of effort and are not fun.
Loses things necessary for tasks		Loses things
Easily distracted	**Difficulty paying attention when could look out window etc?**	**Easily distracted by sights or sounds.**
Forgetful in daily activities.		Forgetful in daily activities.
HYPERACTIVITY/IMPULSIVITY		
Fidgets, taps, squirms.	**Squirm/wiggle in seat?**	**Fidgets/squirms in seat.**
Leaves seat when not expected.	**able to remain seated**	**Leaves seat when should stay**
Runs about inappropriately(Rsrestless).	**Restless, and rushing about**	**Restless or overactive**
Unable to play quietly.		Noisy/loud during leisure activities.
"On the go" - "driven by motor".		Driven by a motor.
Talks excessively.		Talks too much.
Blurts out answers.	**Blurts out answers.**	**Blurts out answers.**
Trouble waiting turn.	**Able to wait turn?**	**Difficulty waiting turn.**

Questions Raised by Critics of ENIGMA ADHD

- **Because group differences in brain volumes between ADHD and control participants are small, can we conclude ADHD is a brain disorder? Isn't this just normal variation, not "disorder"?**
- **If ADHD is a brain disorder, why couldn't ENIGMA find brain changes in ADHD adults? Do Hoogman et al.'s findings prove that brain changes in ADHD *cause* the disorder?**
- **Does concluding ADHD is a brain disorder mean that social, psychological and environmental issue are not relevant to the etiology of ADHD?**

DONDERS INSTITUTE

APSARD 2018 Annual Meeting, Washington DC, January 12-14 2018

ADHD as a brain disorder: evidence from the ENIGMA-ADHD Working Group

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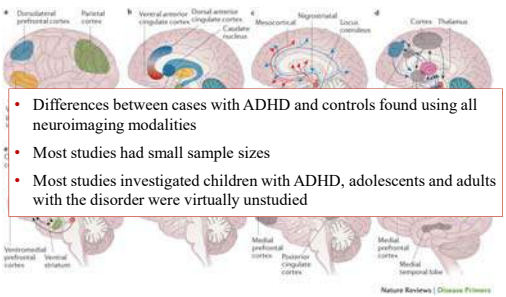
HORIZON 2020
imi innovative medicines initiative

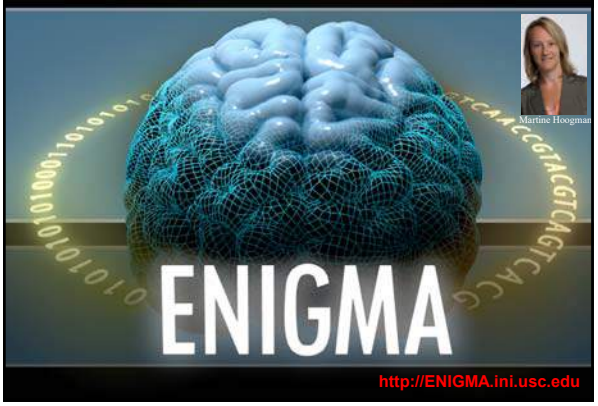
Brain mechanisms in ADHD

Faraone et al., Nature Reviews Disease Primers, 2015



- Differences between cases with ADHD and controls found using all neuroimaging modalities
- Most studies had small sample sizes
- Most studies investigated children with ADHD, adolescents and adults with the disorder were virtually unstudied

Enhancing Neuro Imaging Genetics through Meta-Analysis



Our cohorts for the first ENIGMA-ADHD analysis

	COHORTS		N cases	N controls	Age (SD)
Children	ADHD_Aachen	Aachen, GER	102	79	11.2 (2.7)
	ADHD200_OHSU	Oregon, USA	42	69	9.1 (1.3)
	ADHD200_KKI	Baltimore, USA	25	69	10.2 (1.3)
	ADHD200_NYU	New York, USA	151	109	11.4 (2.9)
	ADHD200_Peking	Peking, China	102	143	11.7 (2.0)
	NIH	New York, USA	205	251	10.0 (3.1)
	ADHD_Rubia	London, UK	44	33	14.0 (2.2)
	Bergen_SVG	Bergen, NOO	25	29	10.1 (1.2)
	Niche	Utrecht, NL	78	80	10.4 (1.9)
	ZI_CAPS	Mannheim, GER	25	13	12.7 (1.2)
Adolescents	CEG_DAT	London, UK	27	29	15.6 (2.1)
	NeuroImage_ADAM	Amsterdam, NL	97	85	17.2 (3.2)
	NeuroImage_NUM	Nijmegen, NL	139	39	16.9 (3.4)
Adults	ADHD_Würzburg	Würzburg, GER	62	56	39.8 (11.3)
	ADHD_DUB1	Dublin, IRL	36	39	22.3 (5.2)
	ADHD_DUB2	Dublin, IRL	20	0	33.7 (10.2)
	ADHD_Mattos	Rio de Janeiro, BRA	17	0	22.9 (1.4)
	Bergen_adultADHD	Bergen, NOO	44	49	31.6 (6.7)
	IMpACT_NL	Nijmegen, NL	125	120	35.5 (11.4)
	MGH ADHD	New York, USA	78	69	35.8 (12.0)
	NYU ADHD	New York, USA	40	40	31.6 (9.4)
	UAB_ADHD	Barcelona, SPA	103	95	25.8 (13.0)
	MTA	Irvine, USA	88	41	24.6 (1.4)
	Total		**1713**	**1529**	**18.4 (12.0)**

ENIGMA ADHD projects and data

Project 1

- Subcortical volumes and ICV (FreeSurfer 5.1 and 5.3)
- Age, gender

- Lifespan perspective
- Segmentation using harmonized protocol
- Sharing of data (mega-analysis)

Project 1: mega-analysis of subcortical brain volume and intracranial volume (ICV) in ADHD


Martine Hoogman

		Mega-analysis	
Brain volume	**n Cases/Controls**	**Cohen's *d***	**p-value**
Amygdala	1598/1463	-0.19	3.69x10**
Nucleus Accumbens	1652/1471	-0.15	4.98x10^{-9}**
Putamen	1660/1497	-0.14	6.36x10^{-9}**
Caudate Nucleus	1659/1489	-0.11	0.001**
Hippocampus	1599/1436	-0.11	0.004**
ICV	1693/1513	-0.10	0.006**
Thalamus	1405/1242	-0.03	0.39
Pallidum	1651/1471	-0.00	0.95

Case-control differences controlling for age, gender, intracranial volume (ICV); **significant after correction for multiple testing

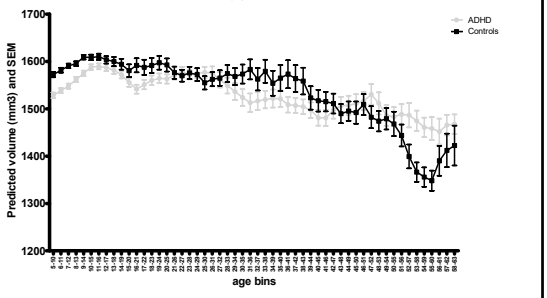
- No obvious left right differences
- Analysis without ICV as covariate did not change the results
- No effect of medication

Hoogman et al., 2017, The Lancet Psychiatry

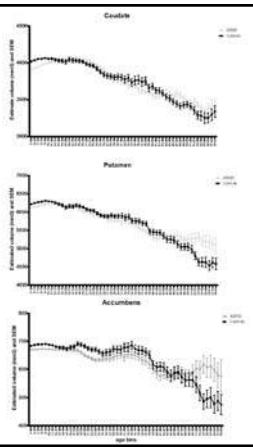
Altered amygdala volumes in ADHD

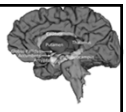
Link to emotional dysregulation in ADHD?


Martine Hoogman



Hoogman et al., 2017, The Lancet Psychiatry





Striatal volumes across the lifespan

Delayed maturation in subcortex

Hoogman et al., 2017, The Lancet Psychiatry

ENIGMA ADHD projects and data


Martine Hoogman

Project 1
- Subcortical volumes and ICV (FreeSurfer 5.1 and 5.3)
- Age, gender

Project 2
- Cortical thickness, cortical surface area (FreeSurfer 5.1 and 5.3)
- Age, gender

The ENIGMA ADHD Working Group

36 cohorts, n=4360

- Segmentation using harmonized protocol
- Sharing of data

	COHORTS	Location	N cases	N controls
children	Bergen-SVG	Bergen, NOR	25	29
	ADHD200-OHSU	Oregon, USA	42	67
	ADHD200-KKI	Baltimore, USA	25	69
	ADHD200-NYU	New York, USA	151	99
	ADHD200-Peking	Peking, CHN	102	143
	ADHD-UKA	Aachen, GER	102	79
	NICHE	Utrecht, NLD	78	80
	OHSU	Oregon, USA	125	112
	ADHD_Russia	Moskou, RUS	10	-
	ACPU	Victoria, AUS	39	28
	NICAP	Victoria, AUS	88	77
	Dundee	Dundee, UK	22	23
	ZI-CAPS	Mannheim, GER	22	13
	CAPS-UZH	Zurich, CHE	39	36
	ADHD-Rubia	London, GBR	44	33
	NIH	Bethesda, USA	251	251
adolescents	NeuroImage-ADAM	Amsterdam, NLD	97	85
	NeuroImage-NUM	Nijmegen, NLD	139	39
	Olin research centre	Hartfort,USA	74	110
	DAT-London	London, GBR	27	29
adults	ADHD-WUE	Würzburg, GER	62	56
	ADHD-DUB1	Dublin, IRL	36	39
	ADHD-DUB2	Dublin, IRL	20	-
	ADHD-Matos	Rio de Janeiro, BRA	17	-
	Bergen-adultADHD	Bergen, NOR	38	43
	IMpACT-NL	Nijmegen, NLD	125	120
	MGH-ADHD	New York, USA	79	69
	NYU ADHD	New York, USA	42	40
	UAB-ADHD	Barcelona, SPA	103	95
	MTA	Irvine, USA	88	41
	UCHZ	Zurich, CHE	39	39
	Sao Paulo	Sao Paulo, BRA	81	66
	Tübingen	Tübingen, GER	21	-
	ePOD	Amsterdam, NLD	97	-
	Total		**2350**	**2010**

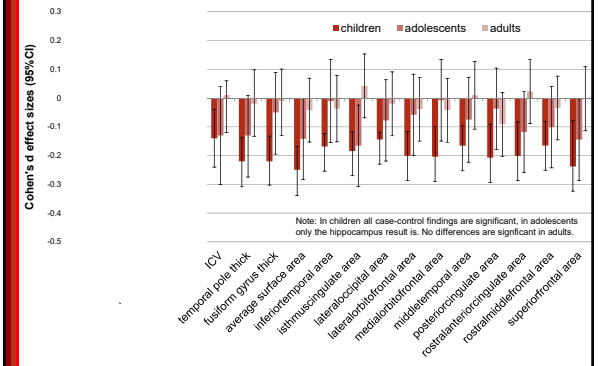
Cortical main results of case-control differences in ENIGMA-ADHD children (<15 years; n>2000): regions surviving cross-validation*

Cortical feature	Cohen's d (ADHD vs HC)	95% confidence interval			N controls	N ADHD	FDR p-value
Surface area							
Total surface area	-0,25	-0,339	to	-0,169	1052	1087	**2,22E-07**
rostral middle **frontal** gyrus	-0,16	-0,250	to	-0,080	1048	1084	**4,25E-04**
superior **frontal** gyrus	-0,24	-0,324	to	-0,153	1047	1077	**1,01E-06**
lateral **orbitofrontal** cortex	-0,20	-0,286	to	-0,116	1050	1084	**2,35E-05**
medial **orbitofrontal** cortex	-0,20	-0,290	to	-0,119	1040	1067	**2,35E-05**
isthmus **cingulate** cortex	-0,19	-0,270	to	-0,100	1044	1085	**1,09E-04**
posterior **cingulate** cortex	-0,21	-0,293	to	-0,122	1045	1084	**1,88E-05**
rostral anterior **cingulate** cortex	-0,20	-0,287	to	-0,116	1042	1069	**2,35E-05**
middle **temporal** gyrus	-0,17	-0,253	to	-0,078	997	1019	**0,001**
inferior **temporal** gyrus	-0,17	-0,254	to	-0,083	1044	1067	**3,77E-04**
lateral **occipital** cortex	-0,14	-0,229	to	-0,059	1051	1084	**0,002**
Thickness							
fusiform gyrus	-0,22	-0,303	to	-0,132	1047	1081	**1,22E-05**
temporal pole	-0,22	-0,309	to	-0,138	1045	1081	**1,19E-05**

*cross-validation = median split of the data: is association seen in both split-halves?

Hoogman, Muetzel, et al., in preparation

Effect sizes of case-control differences for subcortical and cortical brain regions across the lifespan (ENIGMA-ADHD, n>4000)



Hoogman, Muetzel, et al., in preparation

Resulting questions

- Are those effects homogeneously distributed across patients?
  - Lifespan effects – YES!
  - Gender effects – NO!
  - Subgroups?
- Are those effects the consequence of living with a disorder?

Analysis of subgroups through community detection

Ting Li

Participants: 17 cohorts in ENIGMA-ADHD Working Group

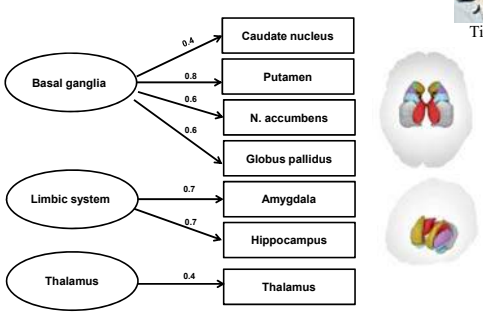
	Children(4-14 years)	
	Boys	Girls
Patients	563	135
Controls	429	265

Measurements:

Subcortical volumes: n. accumbens, amygdala, caudate n., hippocampus, globus pallidus, putamen, and thalamus

Results of exploratory factor analysis

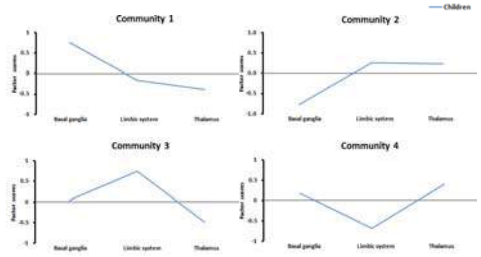
Ting Li



Li et al., preliminary result

Four communities derived from community detection in patients and controls (children <15 years, n=1392)

Ting Li



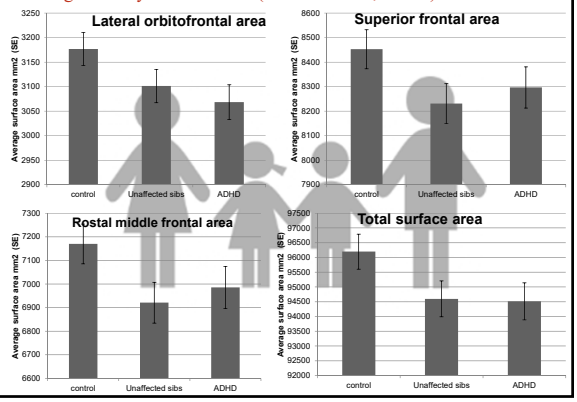
Patients and controls show same substructure, but patients are somewhat more extreme

Li et al., preliminary result

Resulting questions

- Are those effects homogeneously distributed across patients?
  - Lifespan effects – YES!
  - Gender effects – NO!
  - Subgroups – YES, but this needs further investigation
- Are those effects the consequence of living with a disorder?

Familiality of affected cortical regions: unaffected siblings differ significantly from controls (NeuroIMAGE, n~500)



Affected surfacea area regions also show a highly significant association with CBCL attention problems scale in children (9-10 years old) of the Generation-R study (n>2900)… but not for thickness

Cortical Feature	B	SE	CI_{Lower}	CI_{Upper}	β	FDR p-value
Surface area						
Total surface area	-923.87	145.21	-1208.60	-639.14	-0.10	**3.95E-09**
Rostral middle **frontal**	-78.13	15.51	-108.53	-47.72	-0.09	**2.11E-06**
Superior **frontal**	-66.88	17.06	-100.33	-33.43	-0.07	**0.00010**
Medial **orbitofrontal**	-18.74	4.38	-27.32	-10.16	-0.08	**2.70E-05**
Lateral **orbitofrontal**	-26.52	6.23	-38.74	-14.30	-0.08	**2.82E-05**
Posterior **cingulate**	-13.86	3.02	-19.78	-7.95	-0.08	**8.52E-06**
Rostral anterior **cingulate**	-11.13	2.48	-15.99	-6.27	-0.08	**1.15E-05**
Isthmus **cingulate**	-13.17	2.57	-18.21	-8.12	-0.09	**1.92E-06**
Inferior **temporal**	-39.85	8.34	-56.20	-23.50	-0.08	**3.95E-06**
Middle **temporal**	-38.23	7.71	-53.35	-23.11	-0.09	**2.11E-06**
Lateral **occipital**	-69.80	12.74	-94.77	-44.82	-0.09	**3.97E-07**
Thickness						
Fusiform gyrus	0.004	0.002	0.000	0.008	0.038	0.389
Temporal pole	0.012	0.007	-0.001	0.026	0.035	0.389

Resulting questions

- Are those effects homogeneously distributed across patients?
  - Lifespan effects – YES!
  - Gender effects – NO!
  - Subgroups – YES, but not clearly linked to pathology
- Are those effects the consequence of living with a disorder?
  - NO – they are also observed in unaffected siblings of patients
  - NO – brain structure also correlates with ADHD symptoms in the general population

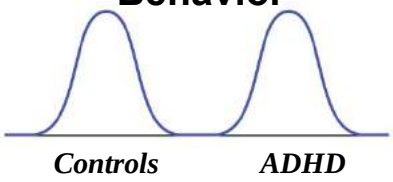
Brain & Adult ADHD

John Gabrieli
Department of Brain and Cognitive Sciences
& Martinos Imaging Center at the
McGovern Institute for Brain Research, MIT

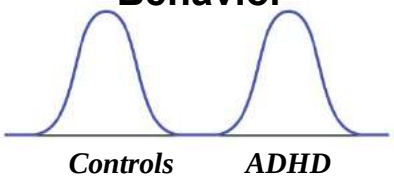
Financial Disclosure

- ***spouse grant support from Sunovion Pharmaceuticals***

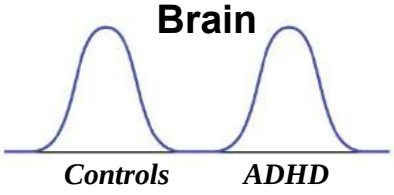
Behavior



Behavior



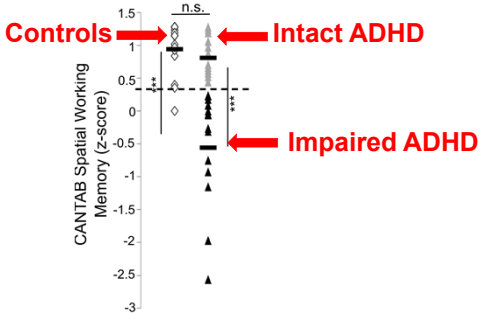
Brain



Why Are Psychiatric Differences So Modestly Related to Measureable Brain Differences?

- Noninvasive neuroimaging has poor signal-to-noise, i.e., *measurement error*
- Neuroimaging is poor at detecting *developmental* differences
- Neurobiology within a diagnosis is stunningly *heterogeneous*

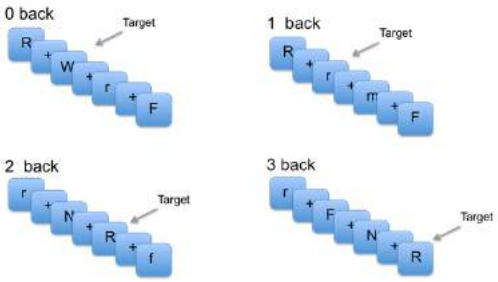
Working Memory: Intact & Impaired ADHD Groups



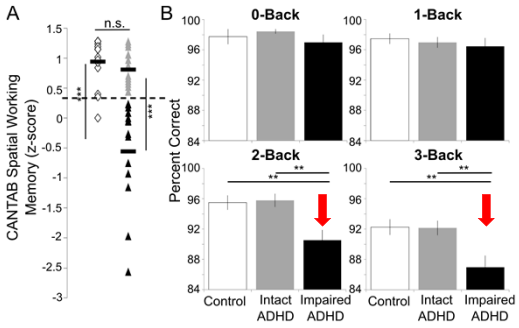
Mattfeld et al., *NeuroImage Clinical*, 2016

N-Back Working Memory Task

Parametric Test of Working Memory Capacity



Intact & Impaired ADHD Groups: Impairment for High Loads



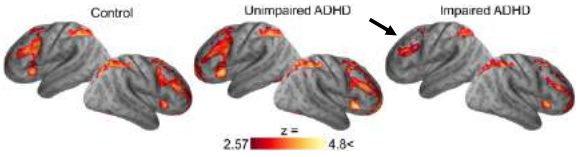
Mattfeld et al., *NeuroImage Clinical*, 2016

WM-Intact & WM-Impaired ADHD Groups

- **Increased activation with increased WM load in fronto-parietal WM network**

3-back > 2-back > 1-back > 0-back

- **Reduced activation only in WM-Impaired ADHD group**



Mattfeld et al., *NeuroImage Clinical*, 2016

Why Are Psychiatric Differences So Modestly Related to Measureable Brain Differences?

- **Neurobiology within a diagnosis is stunningly *heterogeneous***

- **rarely are there *non-overlapping* brain measures between controls and patient groups (even schizophrenia)**
- **autism spectrum disorder is even *more elusive* in the brain**
- **dyslexia is less elusive because it is defined by a single, overt, objective measure - reading**

ADHD as a Brain Disorder: Why Is This So Difficult to Establish?

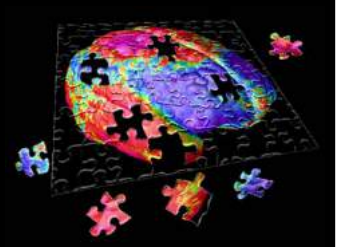
Jay N. Giedd, M.D.

Director, Child and Adolescent Psychiatry, UCSD/Rady Children's Hospital

APSARD 2018 Annual Meeting

Washington, DC

January 14, 2018



Subcortical brain volume differences in participants with ADHD across the lifespan: an ENIGMA collaboration

"ADHD is a disorder of the brain"

"most pronounced … ADHD is a disorder of brain maturation delay"

"Biggest effect in the amygdala is an important message"

Subcortical brain volume differences in participants with ADHD across the lifespan: an ENIGMA collaboration

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Pediatric Neuroimaging Historical Progression

1. Gross Pathology
2. Group Average Size Difference
3. Developmental Trajectories
4. Neural Network Characterization

Pediatric Neuroimaging Historical Progression

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2. Group Average Size Difference
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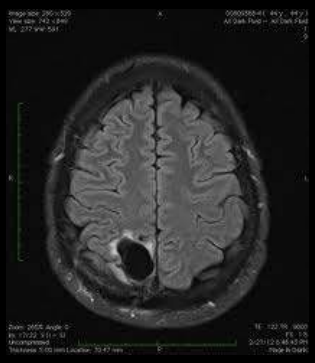

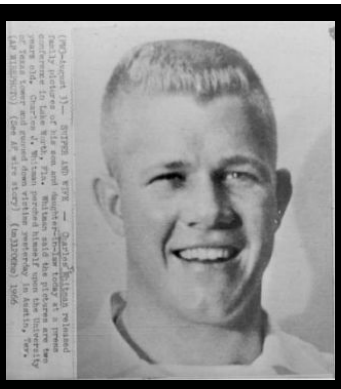

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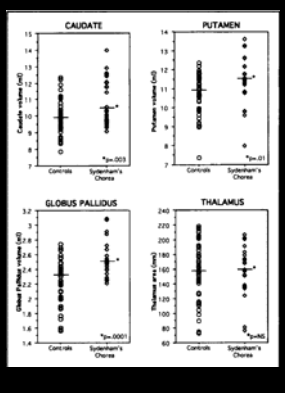

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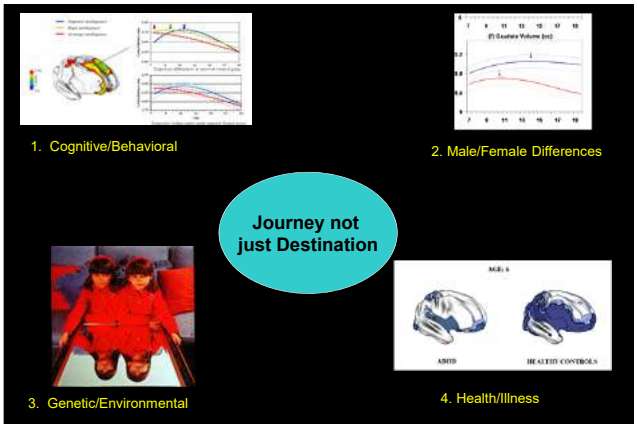

Pediatric Neuroimaging Historical Progression

1. Gross Pathology
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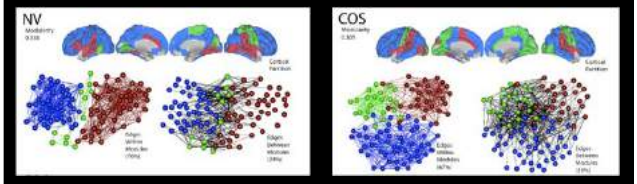
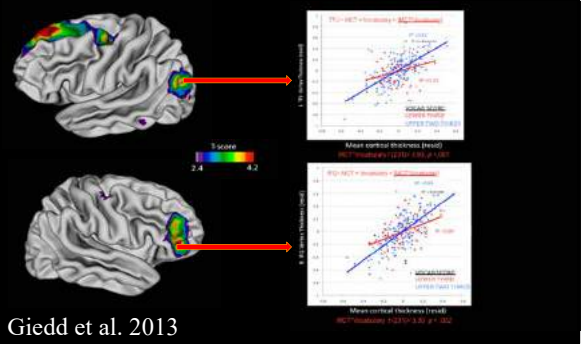
3. Developmental Trajectories
4. Neural Network Characterization

Disrupted modularity and local connectivity in childhood onset schizophrenia



Alexander-Bloch, Giedd, Bullmore (2010)

↑ anatomical coupling correlates with ↑ vocabulary scores in linguistically relevant regions



Lee, Giedd et al. 2013

Subcortical brain volume differences in participants with ADHD across the lifespan: an ENIGMA collaboration

"ADHD is a disorder of the brain"

"most pronounced … ADHD is a disorder of brain maturation delay"

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Age of attaining peak cortical thickness for the ADHD and healthy control groups: ADHD has "shift to the right"

AGE: 6

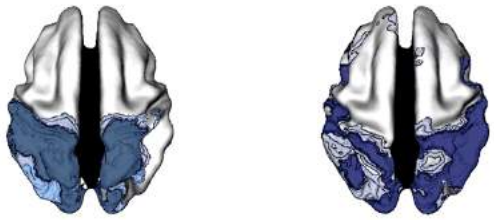
ADHD HEALTHY CONTROLS

calculated, or that the peak age was estimated to lie outside the age range covered

Shaw et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *PNAS, 104(49): 19649-19654*

Age of attaining peak cortical thickness for the ADHD and healthy control groups: ADHD has "shift to the right"

AGE: 5



ADHD HEALTHY CONTROLS

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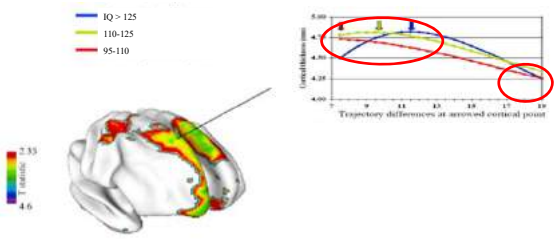
IQ and cortical thickness



Philip Shaw, 2006

Subcortical brain volume differences in participants with ADHD across the lifespan: an ENIGMA collaboration

"ADHD is a disorder of the brain"

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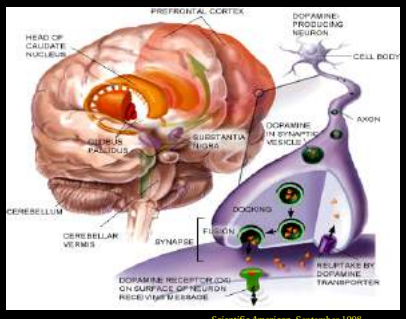
Brain Regions Implicated in ADHD

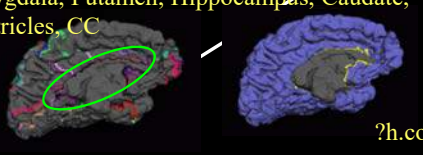


Scientific American, September 1998

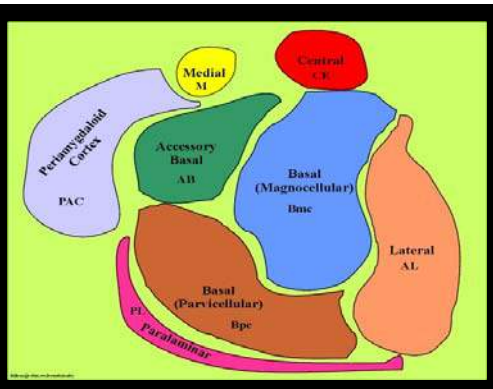
Non-Cortical Areas of Surface

Amygdala

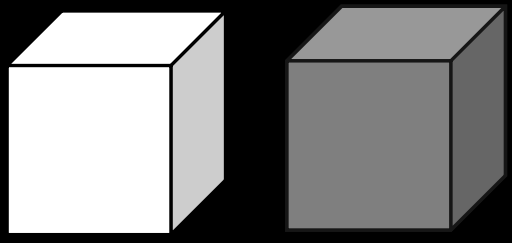
Amygdala, Putamen, Hippocampus, Caudate, Ventricles, CC



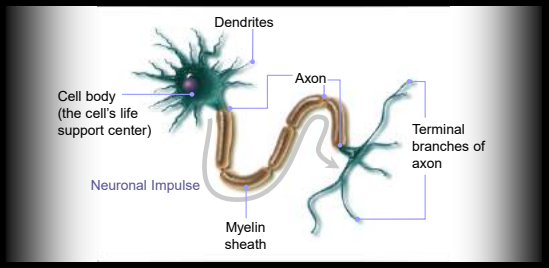
?h.cortex.label



How the Brain Looks to MRI

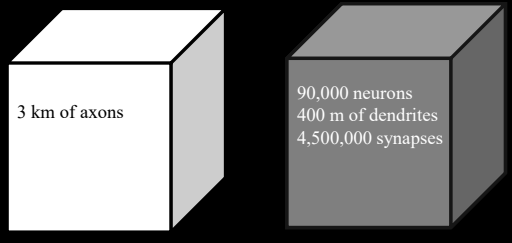


The Neuron

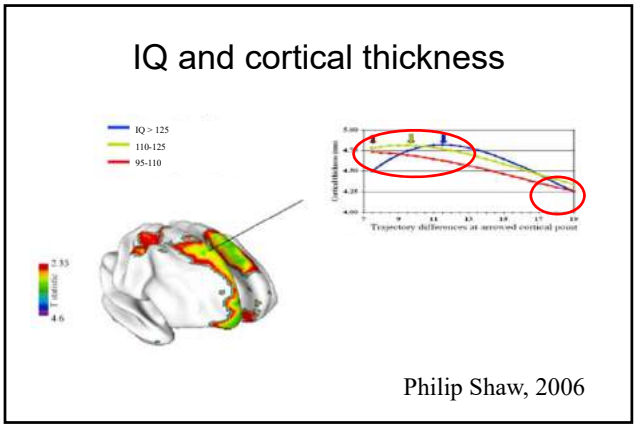


Donald Bliss, MAPB, Medical Illustration

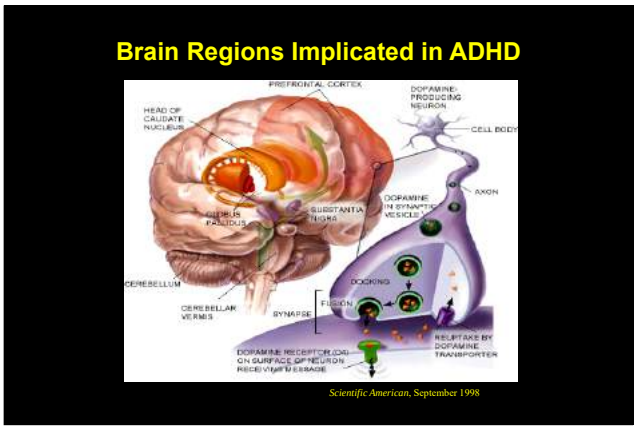
How the Brain Looks to MRI

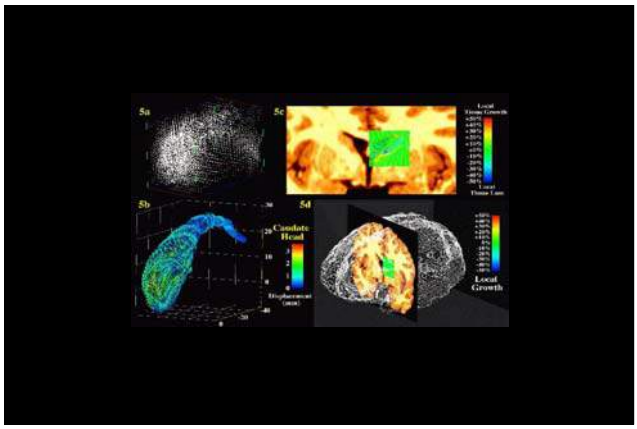


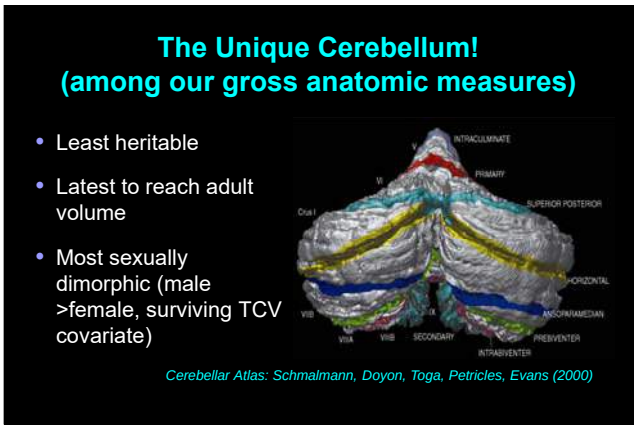

nature Vol 440|30 March 2006|doi:10.1038/nature04513
LETTERS
Intellectual ability and cortical development in children and adolescents
Scans Show Different Growth for Intelligent Brains
The New York Times
Study Makes Case for Late Bloomers
npr
capitalistimperialistpig
IQ and Brain Growth


IQ and cortical thickness
IQ > 125
110-125
95-110
Philip Shaw, 2006


1. Cognitive/Behavioral
2. Male/Female Differences
Journey not just Destination
3. Genetic/Environmental
4. Health/Illness


Brain Regions Implicated in ADHD
PREFRONTAL CORTEX
HEAD OF CAUDATE NUCLEUS
DOPAMINE-PRODUCING NEURON
CELL BODY
AXON
GLOBUS PALLIDUS
SUBSTANTIA NIGRA
DOPAMINE IN SYNAPTIC VESICLES
CEREBELLUM
CEREBELLAR VERMIS
SYNAPSE
DOCKING
FUSION
DOPAMINE RECEPTOR (D4) ON SURFACE OF NEURON RECEIVING EMBRACE
REUPTAKE BY DOPAMINE TRANSPORTER
Scientific American, September 1998


5a
5b
5c
5d
Caudate Head
Local Growth


The Unique Cerebellum!
(among our gross anatomic measures)
Least heritable
Latest to reach adult volume
Most sexually dimorphic (male >female, surviving TCV covariate)
INTRACULMINATE
PRIMARY
SUPERIOR POSTERIOR
HORIZONTAL
PARAMEDIAN
SECONDARY
PREINTERVENTER
INTRAINTERVENTER
Cerebellar Atlas: Schmalmann, Doyon, Toga, Petricles, Evans (2000)

Subcortical brain volume differences in participants with ADHD across the lifespan: an ENIGMA collaboration

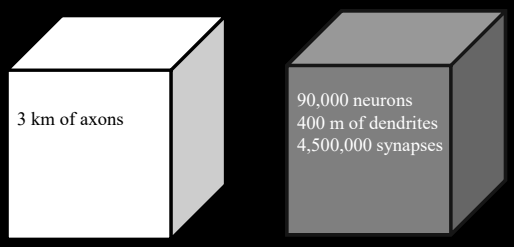
What was measured on whom?

How were they measured?

How were the measures "adjusted"?

How were the adjusted measures interpreted?

How the Brain Looks to MRI



Treatment of offenders with ADHD

Philip Asherson MRCPsych, PhD
Professor of Molecular Psychiatry & Honorary Consultant Psychiatrist,
Social Genetic Developmental Psychiatry, Institute of Psychiatry
Psychology and Neuroscience, King's College London, UK

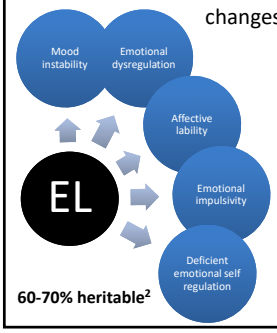
The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007– 2013) under grant agreement n° 602805

Child ADHD → **Criminal behaviour**
Aggression
Antisocial PD
Emotional instability
Personality disorder
Substance abuse

Potential mediators
- Educational failure
- Peer influences
- Poor parenting (supportive/unstructured, abusive)
- Poor engagement in treatment
- Substance abuse disorders
- Conduct Disorder
- Specific and general Learning Difficulties
- Genes (e.g. COMT)
- **SEVERITY and PERSISTENCE OF ADHD**

Emotional lability (EL)

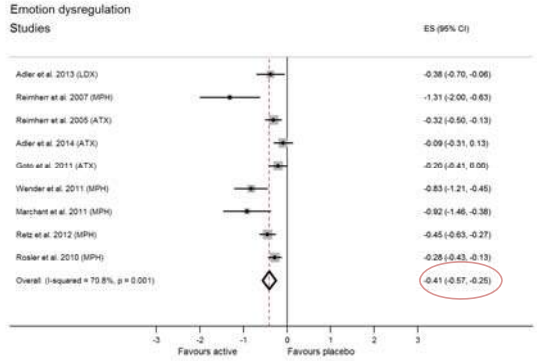
Excessive emotional reactions, frequent mood changes: Irritability, volatility, hot temper[1]



60-70% heritable[2]

[1]Skirrow et al (2009); [2]van Beijsterveldt et al (2004)

Meta-analysis of ADHD Drug Treatments on emotional Dysregulation



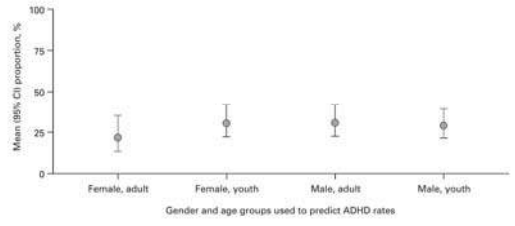
Moukhtarian et al., 2017, European Psychiatry

Psychological Medicine, Page 1 of 12. © Cambridge University Press 2014
doi:10.1017/S0033291714000762

REVIEW ARTICLE

A meta-analysis of the prevalence of attention deficit hyperactivity disorder in incarcerated populations

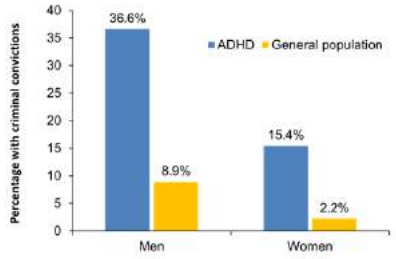
S. Young[1,2*], D. Moss[3], O. Sedgwick[4], M. Fridman[5] and P. Hodgkins[6]



Estimated prevalence = 25.5%

Impact of adult ADHD on criminality

Proportion of Swedish adults with criminal convictions over a 4-year period (Jan 1, 2006 to Dec 31, 2009)



Lichenstein P, et al. *N Engl J Med*. 2012;367:2006-14.

Medication for ADHD and criminality: observational Swedish database analysis

Hazard ratio for conviction for any crime during ADHD medication (2006–2009) vs. non-medication periods

Treatment	Men (n = 16,087) Hazard ratio (95% CI)
All medications	0.68 (0.63–0.73)
Stimulants	0.66 (0.61–0.71)
Atomoxetine	0.76 (0.63–0.91)
SSRI medication	1.04 (0.93–1.17)

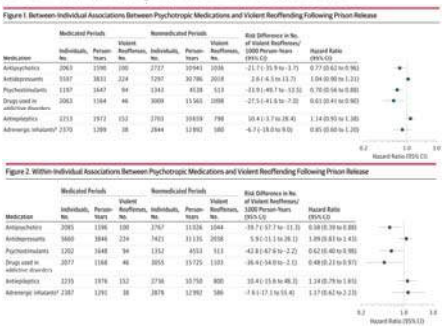
- Crimes occurred less often during medication periods:
  - men 32% reduction
  - women 41% reduction

Lichenstein P, et al. *N Engl J Med*. 2012;367:2006-14.

JAMA | Original Investigation

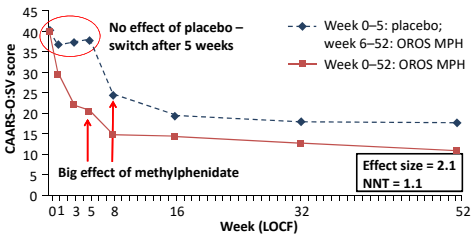
Association Between Prescription of Major Psychotropic Medications and Violent Reoffending After Prison Release

Zheng Chang, PhD; Paul Lichtenstein, PhD; Niklas Långström, MD; Henrik Larsson, PhD; Seena Fazel, MD



Remarkable effect of methylphenidate in prisoners with ADHD

Intention-to-treat population: CAARS-O:SV total sum-score as a function of treatment group and time



- Randomised controlled trial: week 0–5; open-label extension: week 6–52

CAARS-O:SV, Conners' Adult ADHD Rating Scale – Observer: Screening Version; LOCF, last observation carried forward; NNT, number needed to treat; OROS MPH, osmotic-release oral system methylphenidate
Data from: Ginsberg Y, Lindefors N. *Br J Psych*. 2012;200:68-73.

The CIAO Project

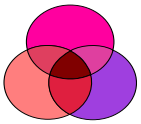
Professor Philip Asherson- Chief Investigator

Clare Evans- Research Worker/Project Coordinator

Co-investigators: Susan Young, Andrew Forester, Declan Murphy

HM PRISON SERVICE

South London and Maudsley NHS
NHS Foundation Trust



MRC Social Genetic and Developmental Psychiatry

CIAO: A pilot study of Concerta XL In Adult Offenders with ADHD

Aim: To evaluate the effectiveness of Concerta XL in reducing levels of aggression, increasing engagement with educational activities and reducing symptoms of ADHD, in young male offenders with ADHD

Method: 12-week open label study of 100 offenders with ADHD, with 6-month extension.

Drug: Concerta XL 18 – 90 mg titrated to optimal effect

Participants: Male prisoners aged 18-30 (most 18-24)

Site: The trial will take place at HMPYOI Isis.

The CIAO study

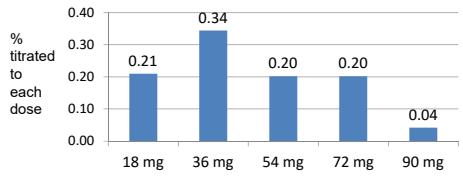
- Screened
- N = 1,922
- Screen positive
- N = 473 (25%)
- Diagnostic assessment
- 398 (84%)
- Positive assessments
- N = 278 (77%)

- **19.3%** of prison population met DSM-5 ADHD criteria
- **121** (40%) treated with OROS-MPH

CIAO: final report 2015

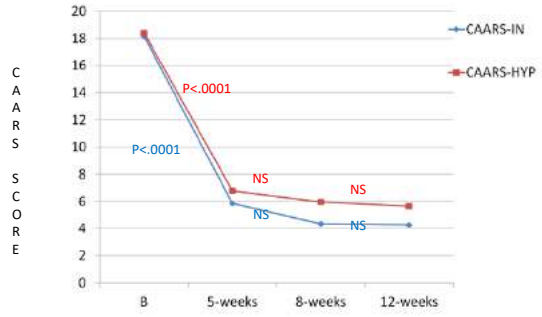
Limited drug seeking behaviour observed in the CIAO study

- Sedative drugs diverted within prisons (e.g. Mirtazapine, Quetiapine)
- Limited abuse potential unless insufflated or injected
- Preparations that are difficult to abuse: Concerta XL and Elvanse



CIAO: final report 2015

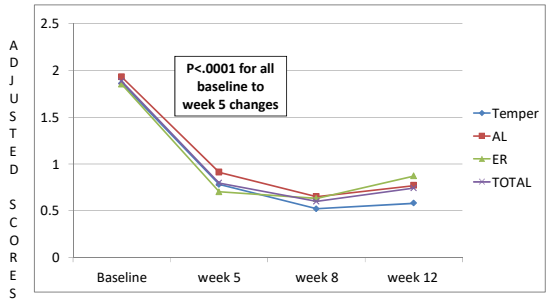
CIAO: Observer rated ADHD symptoms scores



CIAO: final report 2015

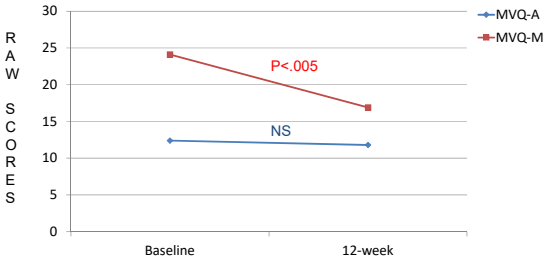
Investigator rated emotional instability

Temper control; Mood lability (AL); Emotional Reactivity (ER)



CIAO: final report 2015

CIAO: Maudsley Violence Questionnaire



CIAO: final report 2015

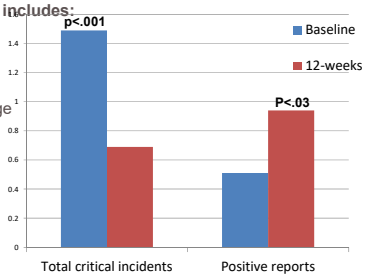
Summary of significant effect sizes from clinical rating scales (Cohen's d)

Outcome	Cohen's d ITT	Cohen's d pp
Investigator rated (I) or self-rated scales (S)		
Inattention (I)	2.27	3.00
Hyperactivity-impulsivity (I)	2.11	2.78
Emotional dysregulation (I)	1.49	1.71
Affective lability (S)	1.19	1.65
MVQ-Machismo (MVQ) (S)	0.60	0.98
MVQ-Acceptance of violence (S)	0.37	0.40

CIAO: final report 2015

Preliminary report: Number of critical incidents recorded in prison records:

- **Total critical incidents includes:**
  - Total serious assault
  - Total assault
  - Total fights
  - Total property damage
  - Total self harm
  - Total taking drugs
  - Total disobey



CIAO: Based on data 8th December 2013

Feedback from Prison Inspectorate

- **Outside unbiased perspective**
- **Inspectors highlighted the CIAO project:**

"All prisoners were offered screening for attention deficit hyperactivity disorder (ADHD) through the specialist Concerta (an ADHD treatment) in adult offenders (CIAO) trial…Some prisoners on the CIAO programme to whom we spoke were experiencing some stability of behaviour for the first time in their lives."

The HMIP report recommended continued support beyond the prison:

"There should be efforts to ensure the continued prescribing of medication and ongoing specialist support for prisoners started on the CIAO trial following their release"

Her Majesty's Inspectorate of Prisons' report carried out in February of 2014
http://www.imb.org.uk/wp-content/uploads/2015/01/isis-2013.pdf

General considerations

- ❑ Evidence for reduced offending, emotional instability and violent behaviour following treatment for ADHD
- ❑ ADHD can be treated safely and effectively in prisons
- ❑ Establish offender services for the diagnosis and treatment of ADHD
- ❑ Provide support and treatment in the community
  - Access to medication
  - Access to expert mental health advice
  - Social support: Critical time interventions
  - Social support: longer term support

Aggressotype
The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement n° 602805

DONDERS INSTITUTE

ADHD and aggression: what are the mechanisms?

biological

Barbara Franke, PhD

Departments of Human Genetics & Psychiatry
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Radboud University Radboudumc

Aggressotype

- Aggression and impulsive behaviour in ADHD and conduct disorder
- Subtyping aggression is important
  - emotionally labile, reactive impulsive aggression
  - low emotional, instrumental ('predatory') aggression
- Understanding mechanisms will lead to improved prevention and treatment options

Aggressotype The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

The Aggressotype team

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- Jan Buitelaar
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- Barbara Franke

Radboud University Nijmegen
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Maastricht University
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University of Zurich
- Susanne Walitza

concentris
- Christiana Labermaier

deCODE Genetics

iPSYCH (Aarhus)

ViewPoint

Genalice

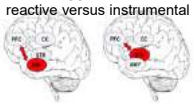
genOway

ADHD-Europe

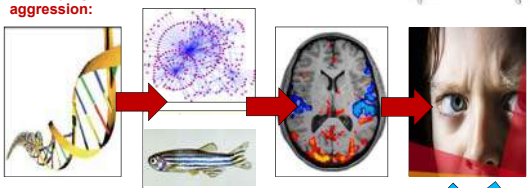
Aggressotype The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Aggressotype

Aggression: reactive versus instrumental



Mechanisms underlying aggression:



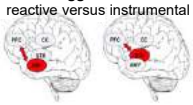
Strategies for improving treatment and prevention:

Lead development | **Predictors of aggression** | **Methylphenidate treatment of prisoners** | **Biofeedback treatment**

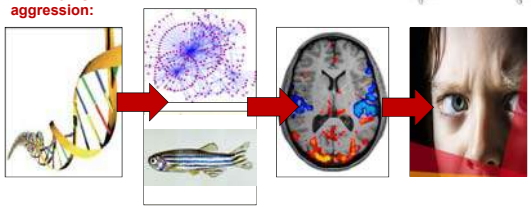
Aggressotype The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Aggressotype

Aggression: reactive versus instrumental



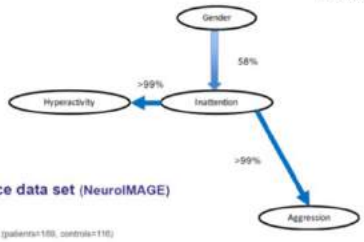
Mechanisms underlying aggression:



Aggressotype The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Is hyperactivity/impulsivity the link?

Tom Heskes Elena Sokolova



ADHD adolescence data set (NeuroIMAGE)

- Study characteristics
  - Sample size= 305 subjects (patients=189, controls=116)
  - Mean age=17.23
  - Mean IQ=97

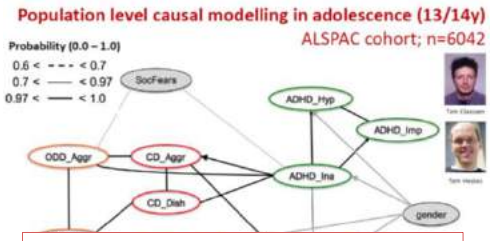
NeuroIMAGE

Aggressotype The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Is hyperactivity/impulsivity the link?

Population level causal modelling in adolescence (13/14y)

ALSPAC cohort; n=6042



Conclusion: Inattention rather than hyperactivity/impulsivity links ADHD to aggression

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Article

Developmental Relations Between ADHD Symptoms and Reactive Versus Proactive Aggression Across Childhood and Adolescence

Aja Louise Murray[1], Ingrid Obsuth[1], Jan Zirk-Sadowski[2], Denis Ribeaud[3], and Manuel Eisner[1]

Both **reactive and proactive** types of aggression are linked to ADHD (symptoms)

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Archival Report 2017 Nov 1;82(9):642-650.

NeuroIMAGE

Structural Brain Abnormalities of Attention-Deficit/Hyperactivity Disorder With Oppositional Defiant Disorder

Siri D.S. Noordermeer, Marjolein Luman, Corina U. Greven, Kim Veroude, Stephen V. Faraone, Catharina A. Hartman, Pieter J. Hoekstra, Barbara Franke, Jan K. Buitelaar, Dirk J. Heslenfeld, and Jaap Oosterlaan

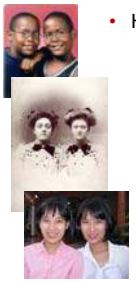
Conclusion:

- Patients with ADHD + ODD/CD have more severe alterations in regions also seen altered in those with ADHD-only
- A few alterations are specific to ADHD + ODD/CD
- No work yet on distinguishing subtypes of aggression

The link between callous-unemotional traits and neural mechanisms of reward processing: An fMRI study

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

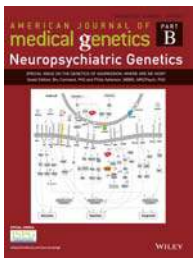
Aggression heritability



- Heritability aggressive behaviour: 50-70%
  - Relative influence of genetics increases with age (Burt et al., 2009)
    - 55.2% (1-5 years)
    - 62.7% (6-10 years)
    - 62.9% (11-18 years)
  - Stability across childhood 60-85% genetic (Porsch et al., 2015; Niv et al., 2013)
  - Stability from childhood to adulthood for 67% genetic (Tuvblad et al., 2011)

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Aggression (molecular) genetics



Editors: Bru Cormand & Philip Asherson

AggressoType

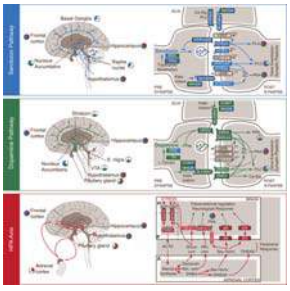
MATRICS

FemNAT CD

ACTION

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

The neurobiological basis of human aggression: A review on genetic and epigenetic mechanisms

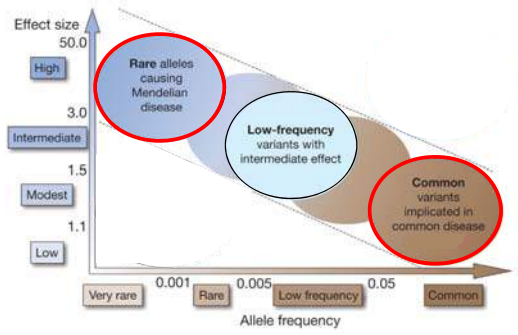


FemNAT CD

Waltes & Freitag, Am J Med Genet Part B, 2016

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Molecular genetics of aggression



Adapted from Manolio et al., Nature 2009

An integrated analysis of genes and functional pathways for aggression in human and rodent models

Yanli Zhang-James, Noelia Fernández-Castillo, Jonathan L Hess, Karim Malki, Stephen J Glatt , Bru Cormand, and Stephen V. Faraone

Molecular Psychiatry (currently responding to reviewers' comments)

1. Confirmation of known pathways: serotonin, dopamine and GABA signaling
2. Identification of novel genes and pathways: long term depression, axon guidance, synaptic plasticity, learning and memory, neuronal development, MAPK and G-protein signaling…
3. We were able to rank and prioritize 40 top-aggression genes.

Aggressotype The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Subdivision of aggression into two reactive and one proactive subtype (RPQ)

Reactive
response to external provocation/threat

or negative internal state

Proactive
premeditated, goal-oriented

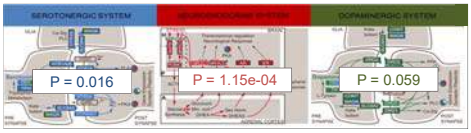
(Smeets, 2016)

Aggressotype This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602805.

Etiology of aggression subtypes: association with candidate gene-sets for aggression (BIG; N =395)

Marjolein van Donkelaar

Eur Neuropsychopharmacol. 2017 Nov 27.



Variants (MAF>1%) within (and in 100 kb flanking regions near) genes involved in serotonergic (n=43) or dopaminergic (n=77) neurotransmission and in neuroendocrine signaling (n=426)

	Males	Females
	Competitive P**	Competitive P**
Proactive aggression	0.043	0.316
Threat-based reactive aggression	0.273	0.438
Frustration-based reactive aggression	0.337	*2.275e-05**

**Significant after Bonferroni correction for multiple testing; **analysis with MAGMA*

Aggressotype This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602805.

Largest GWAS of aggression(-related) phenotype

5 large population-based cohorts (16.400 individuals):
- No genome-wide significant findings
- No genetic correlation with ADHD(?)

Research

2017 Dec 1;74(12):1242-1250

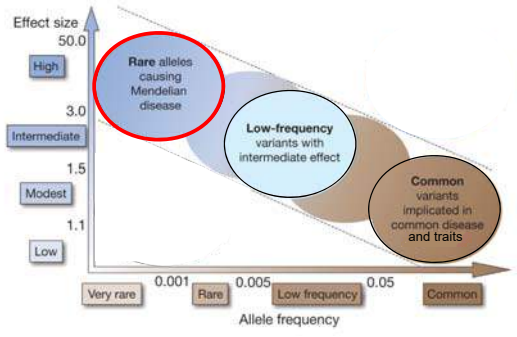
JAMA Psychiatry | Original Investigation

Genome-Wide Association Studies of a Broad Spectrum of Antisocial Behavior

Jorim J. Tielbeek, MSc; Ada Johansson, PhD; Tinca J. C. Polderman, PhD; Marja-Riitta Rautiainen, MSc; Philip Jansen, MD; Michelle Taylor, PhD; Xiaoran Tong, MSc; Qing Lu, PhD; Alexandra S. Burt, PhD; Henning Tiemeier, MD, PhD; Essi Viding, PhD; Robert Plomin, PhD; Nicholas G. Martin, PhD; Andrew C. Heath, PhD; Pamela A. F. Madden, PhD; Grant Montgomery, PhD; Kevin M. Beaver, PhD; Irwin Waldman, PhD; Joel Gelernter, MD; Henry R. Kranzler, PhD; Lindsay A. Farrer, PhD; John R. B. Perry, PhD; Marcus Munafò, PhD; Devon LoParo, PhD; Tiina Paunio, PhD; Jari Tiihonen, MD, PhD; Sabine E. Mous, PhD; Irene Pappa, PhD; Christiaan de Leeuw, MSc; Kyoko Watanabe, MSc; Anke R. Hammerschlag, MSc; Jessica E. Salvatore, PhD; Fazil Aliev, PhD; Tim B. Bigdeli, PhD; Danielle Dick, PhD; Stephen V. Faraone, PhD; Arne Popma, PhD; Sarah E. Medland, PhD; Danielle Posthuma, PhD; for the Broad Antisocial Behavior Consortium collaborators

Aggressotype The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Molecular genetics of aggression



Adapted from Manolio et al., Nature 2009

Abnormal Behavior Associated with a Point Mutation in the Structural Gene for Monoamine Oxidase A

H. G. Brunner,* M. Nelen, X. O. Breakefield, H. H. Ropers, B. A. van Oost

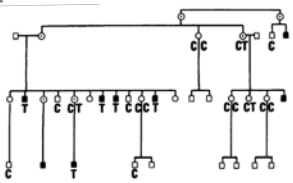
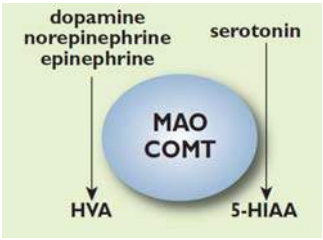


Fig. 1. Segregation of a mutation in the MAOA structural gene in a family with X-linked borderline mental retardation and prominent behavioral disturbance. All affected males and obligate carriers have a C to T mutation at nucleotide position 936. In 12 normal males, only the normal C is present.

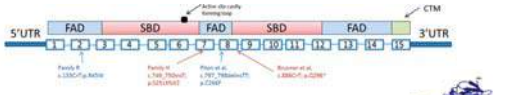
Brunner et al., Science 1993

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805



Aggressotype
The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Brunner Syndrome: point mutations in MAOA



FAD: Flavin adenine dinucleotide binding domains
SBD: Substrate-binding domain
CTM: C-terminal membrane region

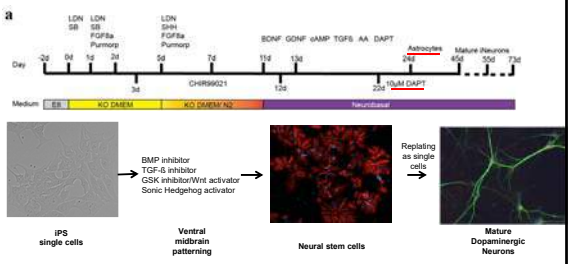
R: Arginine/W:Tryptophan
C: Cysteine/F:Phenylalanine

- Brunner et al, 1993;
- Piton et al, 2014,
- Palmer et al, 2016

Aggressotype
The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Differentiation of functional human iPSC-derived dopaminergic neurons

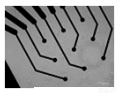
Yan Shi

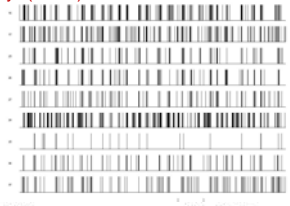


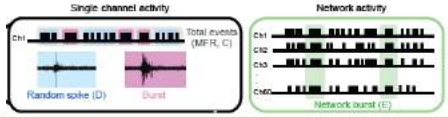
Aggressotype
The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Studying electrophysiological differences between cells in a systematic, development-sensitive manner:

- Multi-electrode arrays (MEAs)



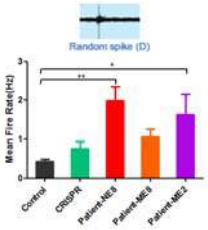


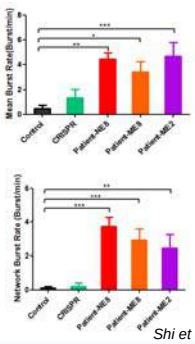


Aggressotype
The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Increased neuronal network activity in patient iNeurons

Yan Shi





Shi et al., in preparation

Aggressotype
The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007- 2013) under grant agreement n° 602805

Conclusions

- Aggression may be linked to inattention more than hyperactivity / impulsivity in ADHD
- *Both reactive and proactive aggression is linked to ADHD*
- Comorbidity with ODD/CD increases severity of alterations in the ADHD brain and also has some specific substrates; work on aggression subtypes is currently lacking
- Aggression is moderately heritable
- Identification of genes involved in aggression is ongoing; serotonergic, dopaminergic and neuroendocrine mechanisms are involved
- Genetic factors appear to act differentially and in a gender-specific manner on aggression subtypes
- Aggression-related genetic variants can work by altering cell-cell communication in the brain

Aggressotype

The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007 – 2013) under grant agreement n° 602805

ADHD in Justice

as witnessed by a public defender

JEFFREY STEIN, J.D.
SUPERVISING ATTORNEY
PUBLIC DEFENDER SERVICE FOR THE DISTRICT OF COLUMBIA

Impulse Crimes

- Fights
- "Robberies"
- Butt-grabbing
- Trash-talking
- Murder

Impulse Crimes

- Crime Lab

Source: Hidden Brain, NPR (Feb. 1, 2017)

Plea offers

- Getting
- Understanding

Jail

- Wellbutrin & Strattera
- No therapy/behavioral mod.
- Discipline

Court Supervision

Delivery Deserts

- In school
- After school
- Court system
- Poor communities

Worlds That Never Collide

- Joshua's world
- Clients' world

JStein@pdsdc.org

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UT HEALTH SCIENCE CENTER™
SAN ANTONIO

Treatment of ADHD and Comorbid Conditions in the Juvenile Justice System

Steven R. Pliszka, M.D.
Dielmann Distinguished Professor and Chief
Department of Psychiatry
The University of Texas Health Science Center at San Antonio

Disclosure (past 3 years)

Source	Research Funding	Expert Witness	Consultant
Shire	X		
Astra-Zeneca		X	
Ironshore		X	X

Juvenile Justice System in Texas

- Each major county has a "Department of Juvenile Probation", operates local facilities (Juvenile Detention, Residential and Non Residential Programs)
- In San Antonio, University Health System contracts with Division of CAP to provider psychiatric services to both Detention and Local Long Term facility
- State run Department of Juvenile Justice for serious offenders, committed to larger institutions, then placed on parole, return to communities

"The System"

- Many youth cross the mental health and juvenile justice system, have histories of psychiatric hospitalization, outpatient mental health care as well as involvement with juvenile justice
- High degree on non-compliance with meds, "on and off medication" when not in custody
- Management issues
  - Self harm
  - Aggression
  - Poor school performance
  - Sleep

Diagnoses in TJJD

- Cross section of Psychiatric diagnoses in EMR in Nov 2009.
- Sample = 835 youth treated with at least one psychiatric medication that month.
- EMR system encourages multiple diagnoses, often duplicative due to use of both DSM and ICD-9
- Diagnoses collapsed into major categories

Diagnoses in TJJD

Diagnosis Group	Number of Youth with DX	Percent of Youth with DX (out of 835)
BP	492	58.85%
MOOD NOS	478	57.18%
ADHD	468	55.98%
CD	367	43.90%
DEP	324	38.76%
PTSD	266	31.82%
IED	218	26.08%
SUICIDE ALERT	199	23.80%
MDD	125	14.95%
NP MENTAL HEALTH	90	10.77%
ANX	83	9.93%
PSYCHOTIC	82	9.81%
SUBABUSE	51	6.10%
Child abuse	43	5.14%
SCHIZOPHRENIA	39	4.67%
CANNABIS	36	4.31%
MALINGER	36	4.31%
BORDERLINE	18	2.15%
OCD	12	1.44%
ETOH	11	1.32%
PERDIS	11	1.32%

Snapshot Nov 2012

Number of Medications or Medication Changes:

Total on at least one Medication Nov 2012	604
Total on 1 Medication	198
Total on 2 Medication	202
Total on 3 Medication	125
Total on 4 Medication	58
Total on 5 Medication	15
Total on 6 Medication	5
Total on 7 or more Medication	1

	ADP
TYC TOTAL POP:	1347
% ON PSYCH MEDS:	44.8%

Diagnosis and Treatment

	ADHD DIAGNOSIS	
	YES	NO
	274	633
On Stimulant:	175	139
Per Cent:	63.9%	22.0%

	BIPOLAR DIAGNOSIS	
	YES	NO
	255	652
On Mood Stablizer:	159	97
Per Cent:	62.4%	14.9%

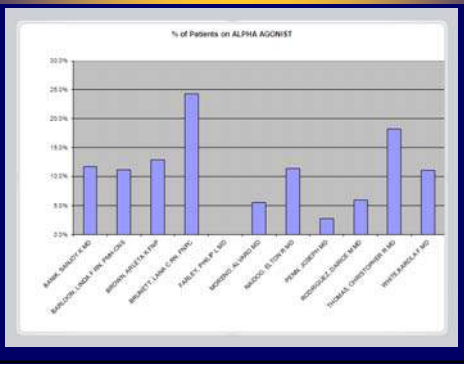
	BIPOLAR DIAGNOSIS	
	YES	NO
	255	581
On SGA:	176	318
Per Cent:	69.0%	54.7%

Diagnosis and Treatment

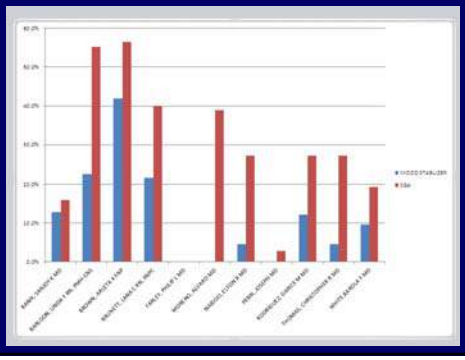
	MDD DIAGNOSIS	
	YES	NO
	214	622
On SSRI	55	88
Per Cent:	25.7%	14.1%

	NON MDD DEP DIAGNOSIS	
	YES	NO
	413	423
On SSRI	88	128
Per Cent:	21.3%	30.3%

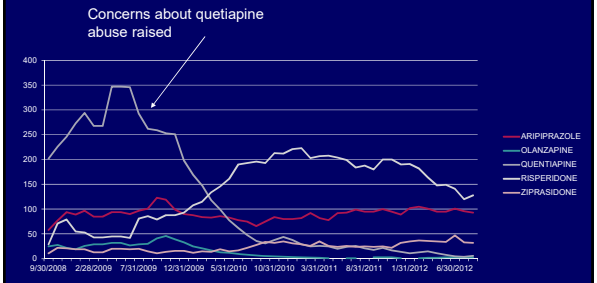
Provider Variation



Provider Variation



Changes in SGA Use



International Perspectives

Margaret Danielle Weiss
Director, Child and Adolescent Psychiatry
University of Arkansas Medical Sciences
mdweiss@uams.edu

Facts or Assumptions

- ADHD is a brain based disorder that looks the same the world over
- Cultural perceptions, comoribidities, impairment, access, therapies, medications, comorbidities, stigma, functional impairment, quality of life, guidelines, adaptive life skills and opportunities for environmental adaptations vary within and between regions

International Variation in Treatment Procedures for ADHD: Social Context and Recent Trends

Stephen P. Hinshaw, Ph.D.
Richard M. Scheffler, Ph.D.
Brent D. Fulton, Ph.D.
Heidi Aase, Ph.D.
Tobias Banaschewski, M.D., Ph.D.
Wenhong Cheng, M.D., Ph.D.
Paulo Mattos, M.D., Ph.D.
Arne Holte, Ph.D.
Florence Levy, M.D., Ph.D.
Avi Sadeh, Ph.D.
Joseph A. Sergeant, Ph.D.
Eric Taylor, M.B., F.R.C.P.
Margaret D. Weiss, M.D., Ph.D.

Global

- Spain: Cesar Sotullo
- Israel: Iris Manor
- Japan: T Saito
- Canada: Margaret Weiss
- Netherlands: Sandra Kooij
- UK: Anita Thapar
- Mexico: Freda Rubio, Juan Carlos Perez Castro Vazquez
- Europe
- Middle East
- Asia
- North America
- United Kingdon
- Australia, South America

Objective

- Take advantage of the opportunity APSARD provides to welcome the best scientists and international clinician key opinion leaders to look at intercontinental differences
- Key strengths? Challenges? Strategies to meet those challenges
- We can and do learn from each other
- Cross cultural comparison raises awareness and growth
- Within region differences we each live with within our personal locations
- Hearing the speakers, how would you answer these questions?

Quebec

- Small department with a psychoanalytic environment contributed to the first clinical trials, the recognition of the disorder and in the follow up study the growing awareness of ADHD grown up
- Recognition that the residual of ADHD in adulthood is best identified by functional impairment
- First clinical trials
- The role of family
- Modelled the paradigm of clinical research: both patients and research are well served by each other
- Virginia Douglas: put the attention in ADD, first neuroscientist to find an interest in psychopathology

Vancouver

- Provincially based, centralized centre of excellence
- Small group of dedicated physicians working together over decades to advocate, teach, advance treatment, and study ADHD
- CADDRA: one of the early networks - network the networks
- Guidelines: the process of working through of defining what we do – quality measures
- A single payer system with equal access centralized through the family physician
- Disability grants, executive training in university, responsive schools
- Child psychiatry a specialty in its own right

Challenges

- Short term medication was first line until recently
- Adult clinics are few and far between
- Access and training in ADHD/ODD evidence based therapies like PCIT or OST are poor poor
- Large rural access with care limited by telehealth of outreach
- The transition years
- Management of ADHD in the context of comorbity such as ASD, adult mood disorders is growing

Arkansas

- Reasonable and quality care for a large and indigent population
- Routine access through state wide army of trained therapists in PCIT, CPP, and TF CBT
- Wide recognition of ADHD in adults which is rather poorly treated
- No psychosocial treatment of adults
- No ABA until very recently

Challenges

- Poverty
- Trauma: ACE score over 5. Is ADHD in CDT the same? Treatment?
- Preschool ADHD treated with alpha adrenergic agonists first line
- Absence of parent management training and psychoeducation
- Autism and developmental delay not eligible for therapy
- No diagnosis ASD in adolescence
- Medicaid medication rules that make no sense
- Polypharmacy fed by expensive residential, short term admission and lack of child psychiatrists manpower
- School based care
- No lay support groups

?

- Is ADHD in the context of complex developmental trauma inevitable, how does it respond to treatment and how should those treatments be sequenced?
- What is the impact of gun violence, parental drug use, parental imprisonment, neglect, physical and sexual abuse, malnutrion, screen violence on ADHD outcome and is it preventable?
- Can we see the science and training of evidence based therapies extended to the Canadian context?
- Can common recommendations of practice guidelines or quality measures across the globe be used to influence Medicaid rules that run counter to good clinical practice?

Anita Thapar
Cardiff University
Head of Academic Child and Adolescent Psychiatry Section

ADHD assessment

- NHS: free health care to all
- GP is the first port of call for everyone
- ADHD diagnosis made by specialist services-child psychiatry, child health
- Administrative prevalence: 0.7%-1%
- Over-diagnosis, access dependent on income are not issues
- Resources limited, longest delays to diagnosis in Europe (mean 18.3 months vs 10.8 months EU countries)
- Adult ADHD clinics expanding across the UK- but transition still a problem especially in some areas

Treatment (NICE 2018)

- Emphasis on psycho-education, environmental modifications, psychological treatments
- Brief group-based ADHD-focussed behavioural support for all
- Generic group-based parent training for those with comorbid ODD/CD
- CBT for adolescents if inadequate response or meds refusal
- Medications: MPH, LDEX, atomoxetine or guanfacine
- NICE guidance not always possible to follow fully in some geographical areas
- Stigma, public attitudes –different to autism for example

Courtesy of Hollis, Simonoff, Asherson

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ADHD International Perspective.
Progress in Spain: Challenges and Strengths

Cesar Soutullo MD, PhD
Child & Adolescent Psychiatry Unit, University of Navarra, Pamplona, Spain

CUN-Madrid
2017-

CUN-Pamplona
1962-

Unidad de Psiquiatría Infantil y Adolescente

IdiSNA

Statement of Potential Conflicts of Interest

2013-2018

Relating to this presentation, there are relationships that could be perceived as potential conflict of interests:

César Soutullo: Fulltime Contract: University of Navarra Clinic, Associate Professor.

Consultant & Advisory Board: Lilly, Shire, Rubiò, Medice, NeuroTech Solutions

Research: Shire, Fundación Caja Navarra, Lundbeck, Janssen.

Speaker / CME: Lilly, Medice, Shire.

Royalties: Editorial Médica Panamericana, Mayo Eds.

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Cesar A. Soutullo, MD, PhD
Disclosure (4 years: 2013 - Jun 2017)

Fulltime contract: University of Navarra, Assistant Professor

Source	Consultant Advisory Board	Royalties (Books)	Stock >$10,000 €	Research (Department)	Speaker (Education)	Este Congreso
Lilly 2000-2015	X			X	X	
Shire 2005-	X			X	X	X
Lundbeck 2016-				X		
NeuroTech Solutions 2016-	X					
Rubiò 2012-2014	X					
TEVA 2016-				X		
Medice Group 2009-	X				X	
Fundación CAN				X		
F. A. Koplowitz 2003-16	X			X	X	
Minist. Health 2008-	X					
Ed. Médica Panamericana 2004-	X	X				
Mayo Eds 2014		X				

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Financial Relationships

Commercial Interest	Relationship
Shire	Advisory Board
Shire	Speakers Bureau
Eli Lilly	Advisory Board
Eli Lilly	Speakers Bureau
NeuroTech Solutions Ltd	Advisory Board
Rubió	Advisory Board
Editorial Medica Panamericana	Royalties
Mayo Ediciones	Royalties

4

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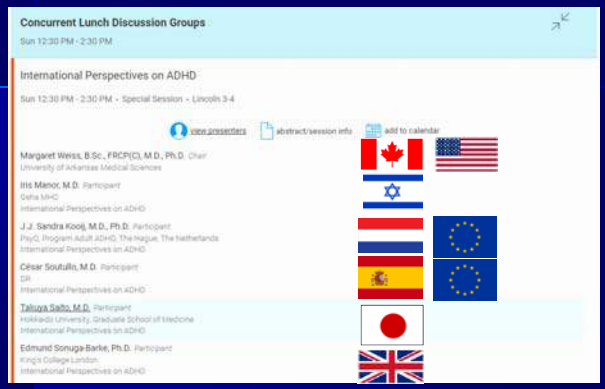
Thanks

Jeff Newcorn

Margaret Weiss

Joseph Biederman

APSARD Scientific Committee



- **Objective**: Our objective is to develop a predictive model of methylphenidate response, using a longitudinal and naturalistic follow-up study, in a Spanish sample of children and adolescents with attention deficit hyperactivity disorder (ADHD).
- **Method**: We included all children and adolescent with ADHD treated with methylphenidate (MPH) in our outpatient Clinic (2005 to 2015), evaluated with the K-SADS interview. We collected ADHD-RS-IV and CGI-S scores at baseline and at follow up, and also neuropsychological testing (WISC-IV, Continuous Performance Test (CPT-II) & Stroop). Clinical response was defined as ≥30% reduction from baseline of total ADHD-RS score and CGI-S final score of 1 or 2 maintained for the previous 3 months. Logistic regression analysis was performed for predictive analyses with SPSS-20 statistical package.
- **Results**: We included 518 children and adolescents with ADHD, mean (SD) age of patients was 11.4 (3.3) years old; 79% male; 51.7% had no comorbidities; and 75.31% had clinical response to a mean MPH dose of 1.2 mg/kg/day. Lower baseline symptom severity (lower ADHD-RS-IV scores), absence of comorbidities (oppositional-defiant symptoms, depressive symptoms and alcohol/cannabis use), fewer altered neuropsychological tests, higher total IQ and low commission errors in CPT-II, were significantly associated with good outcome and clinical response to methylphenidate treatment.
- **Conclusion**: Oppositional-defiant symptoms, depressive symptoms, and higher number of impaired neuropsychological tests is associated with worse clinical response to methylphenidate. Other stimulants or non-stimulants treatment may be considered when

7

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Agenda

International Perspective on ADHD: Spain

Early Detection

Preschool Prevalence

ADHD-RS Short Version

Awareness

Plan of Action in ADHD

Development of Parents Organization Federation

ADHD in Spain

Important role of Parents of Children with ADHD Network

ASSESSMENT

- ADHD National Guidelines available from 2010.
  - Follows NICE and AACAP Guidelines
- ADHD "shared" between Pediatric Neurology and Child & Adolescent Psychiatrty.
  - No Child & Adolescent Psychiatry Fellowships in Spain…
- DSM-5: main Diagnostic Clasification Used, ICD Codes

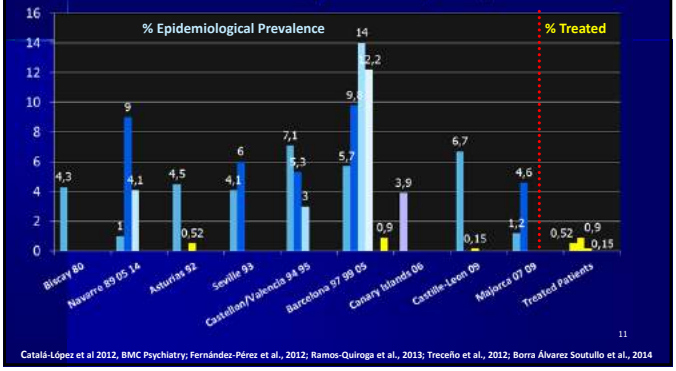
TREATMENT

- Big pockets of Psychoanalytic influence and bias against ADHD. Moderate availability of CBT.
- Growing number of medications approved

9

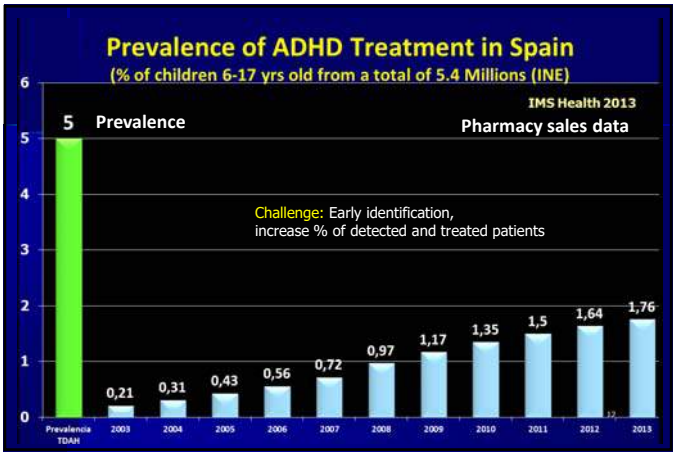
Prevalence of ADHD in Spain

Epidemiological Prevalence (BLUE) & Treatment Prevalence (YELLOW) in Spain 1980-2009



11

Catalá-López et al 2012, BMC Psychiatry; Fernández-Pérez et al., 2012; Ramos-Quiroga et al., 2013; Treceño et al., 2012; Borra Álvarez Soutullo et al., 2014



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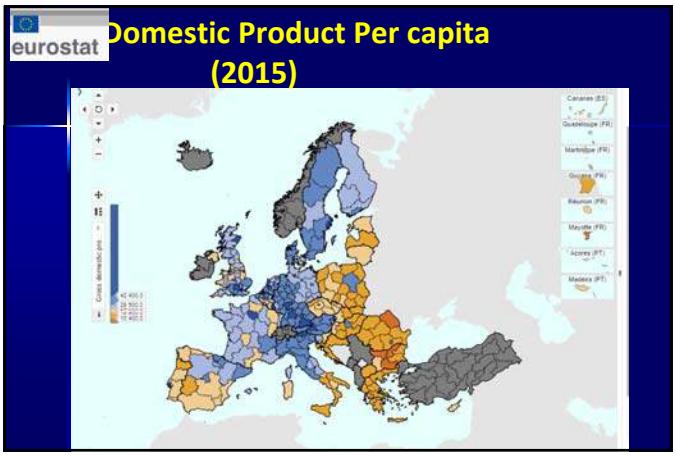
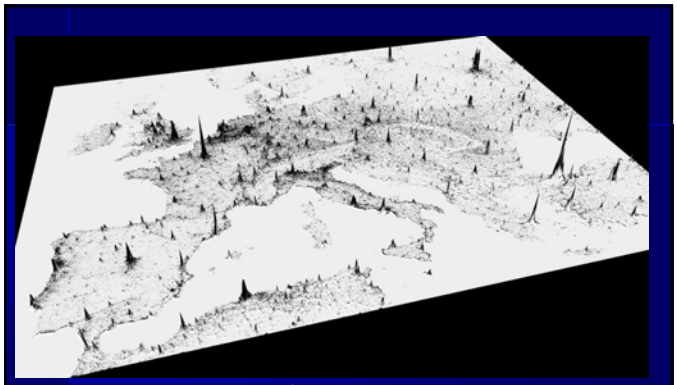
Psycopharmacology of ADHD in Spain

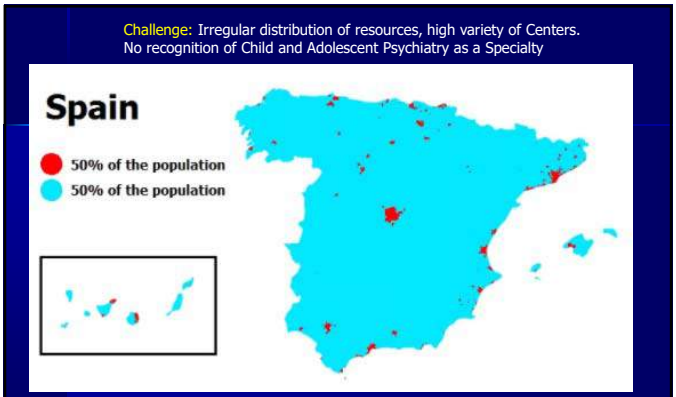
Domestic Product Per capita (2015)

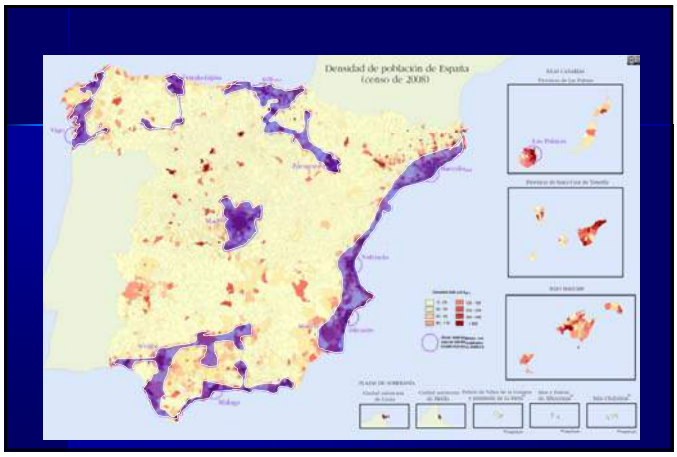


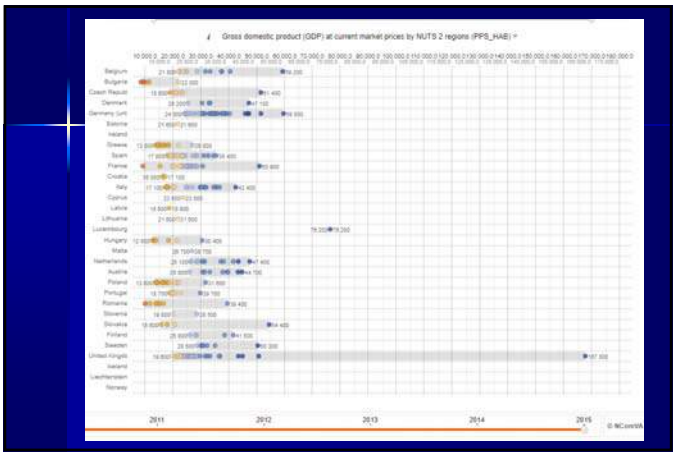


Population Density

Challenge: Irregular distribution of resources, high variety of Centers.
No recognition of Child and Adolescent Psychiatry as a Specialty

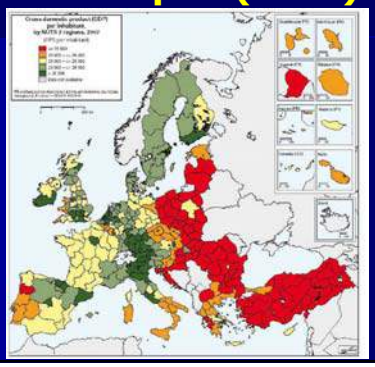






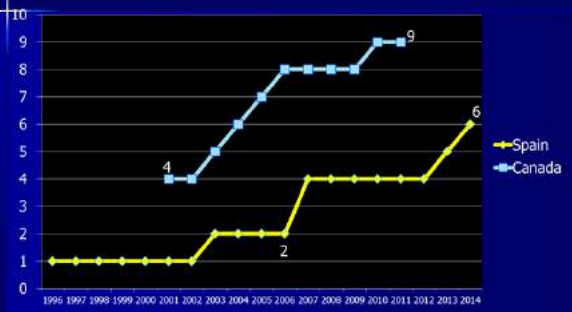
Gross Domestic Product Per capita (2007)

Source: EU Commission



Spain vs. Canada

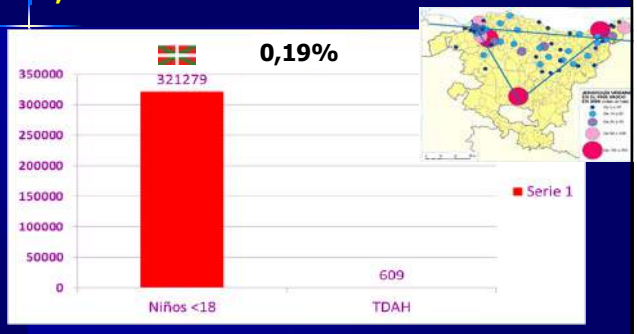
Number of medications approved for ADHD



609 Niños tratados por TDAH en el País Vasco

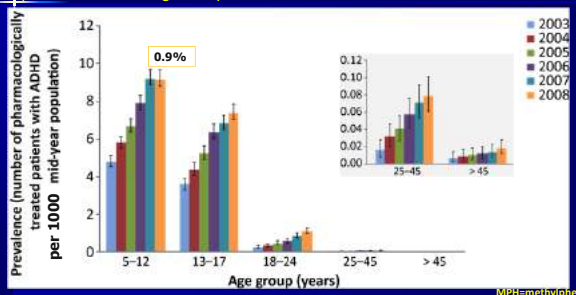
Población Total: 2,1 Millones (Censo 2007)

0,19% de los niños están tratados



Prevalence of pharmacological treatment for ADHD in the UK (2003–2008)[1]

- Prevalence of pharmacologically treated ADHD (MPH, d-AMP or ATX) in patients aged 6 years and over in UK general practice



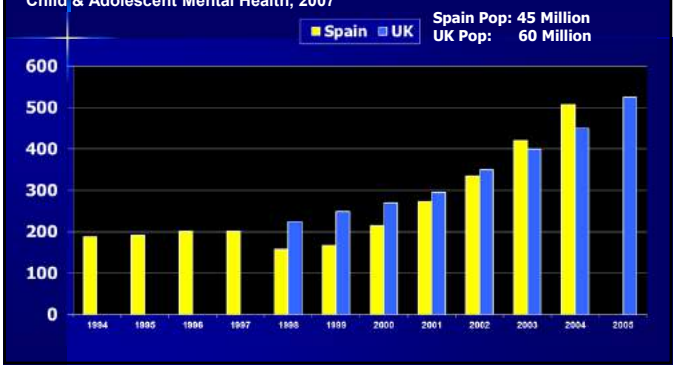
Error bars indicate 95% confidence intervals

1. Adapted from McCarthy S *et al. BMC Pediatr* 2012;12:78

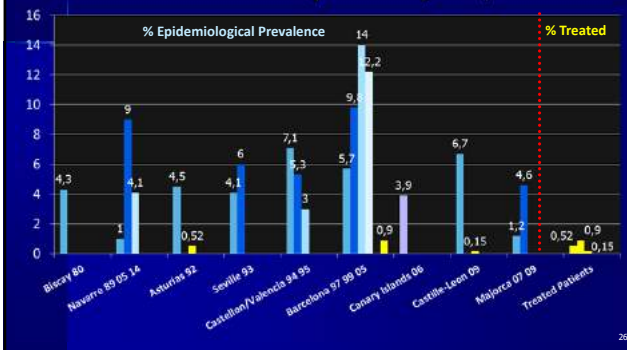
MPH=methylphenidate, d-AMP=dexamfetamine ATX=atomoxetine

Use of Stimulants in Spain vs. UK

La Razón Newspaper 18 Dec 2005 **(Thousands of units dispensed)**
Child & Adolescent Mental Health, 2007



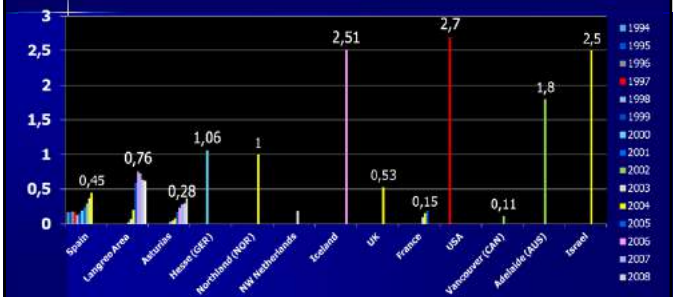
Epidemiological Prevalence (BLUE) & Treatment Prevalence (YELLOW) in Spain 1980-2009



Catalá-López et al 2012, BMC Psychiatry; Fernández-Pérez et al., 2012; Ramos-Quiroga et al., 2013; Treceño et al., 2012; Borra Álvarez Soutullo et al., 2014

% of Children (0-18) treated with MPH Internationally

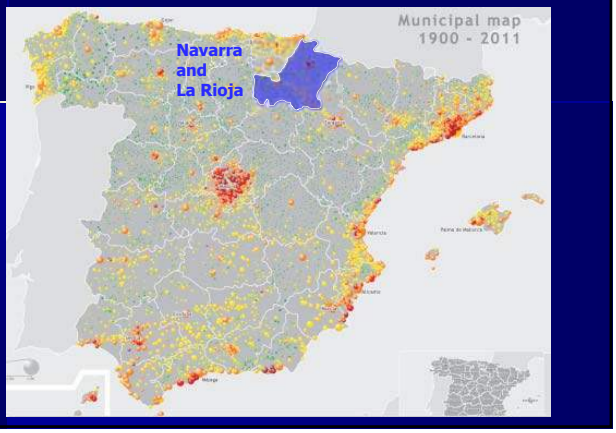
(for a Defined Daily Dose of 30 mg)



Spanish Association of Psychiatry Meeting, 2003. La Razón Newspaper Dec 2005
Fernández-Pérez M et al., 2012. Revista AEPNYA

Is the presentation of ADHD different in Spain?

(a Southern European Mediterranean Spanish-culture?)



2016

Article

Normative ADHD-RS-Preschool Data in a Community Sample in Spain

Juan-Jesús Marín-Méndez[1], María-Cristina Borra-Ruiz[2], María-José Álvarez-Gómez[3], Kara E. McGoey[4], and César Soutullo[1]

Journal of Attention Disorders
SAGE

4 to <7 y.o. Preschool children in Navarra & La Rioja
ADHD-RS- Preschool version (Parents and Teachers)

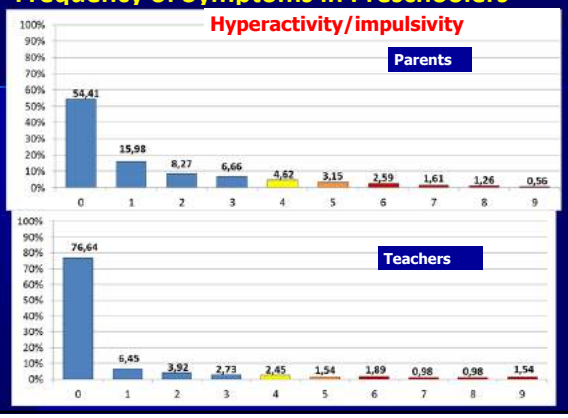
2.5% prevalence of "possible ADHD"

95 Percentile & 6 Sx Teacher+Parent questionnaire

Marín et al, 2016

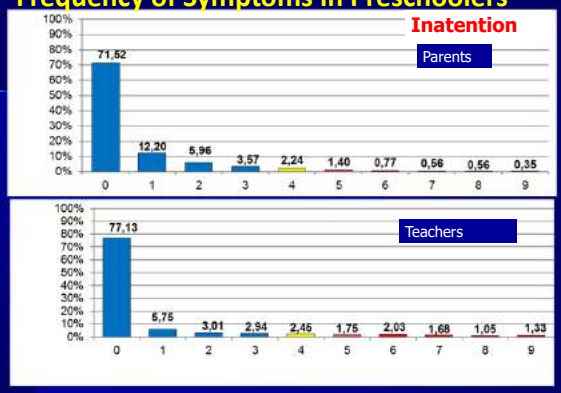
Frequency of Symptoms in Preschoolers

Marín et al, 2016

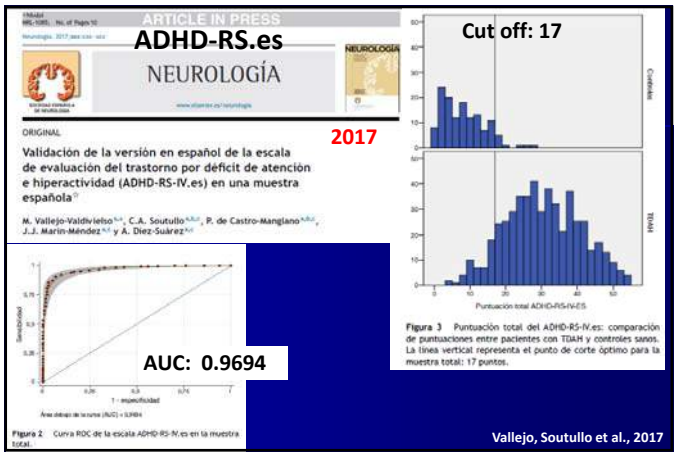


Frequency of Symptoms in Preschoolers

Marín et al, 2016



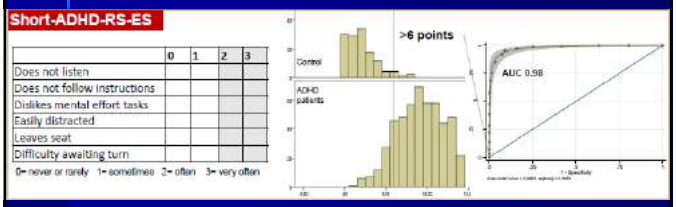
ADHD-RS.es



Vallejo, Soutullo et al., 2017

ADHD RATING SCALE: VALIDATION OF A SPANISH VERSION & PROPOSAL OF A SHORT-VERSION SCALE

Vallejo Valdivielso M., Díez-Suárez A., de Castro Manglano, P., Martín Lanas R., Soutullo Esperón C.
Child & Adolescence Psychiatry Unit. University of Navarra Clinic. Pamplona, Spain.



Vallejo, et al., 2016 EUNETHYDIS International Conference, Berlin Oct 2016

Spanish Federation of Associations for ADHD Support

37

Conclussions

- Despite the lack of CAP as a Specialty in Spain…
- Available medications include
  - MPH (4, 8, 12 hrs), LDX; ATX, GXR
- Prevalence & Presentation similar to international samples
- Awareness is increasing, but still needs to be much improved.
- Time from symptom onset to diagnosis is 4-6 years

38

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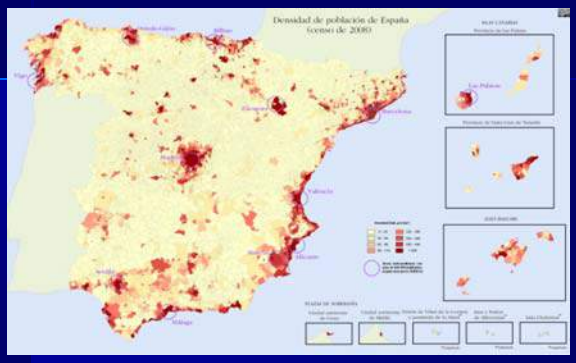
Gracias!

Karol Machiñena Azucena Díez Cesar Soutullo Arancha Díez
María Vallejo Maite Lasheras Pilar de Castro

39



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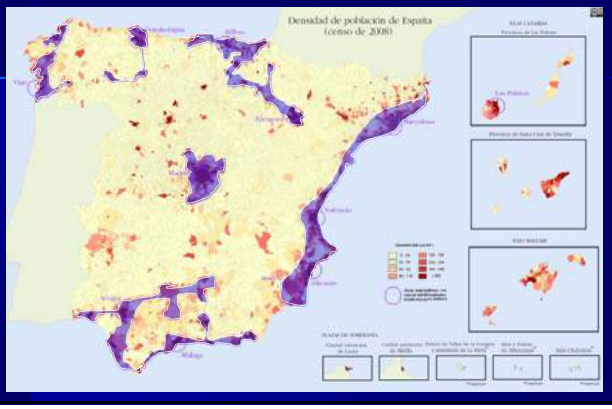
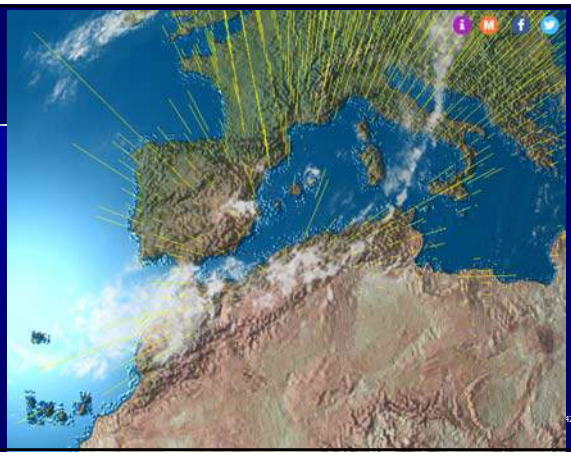
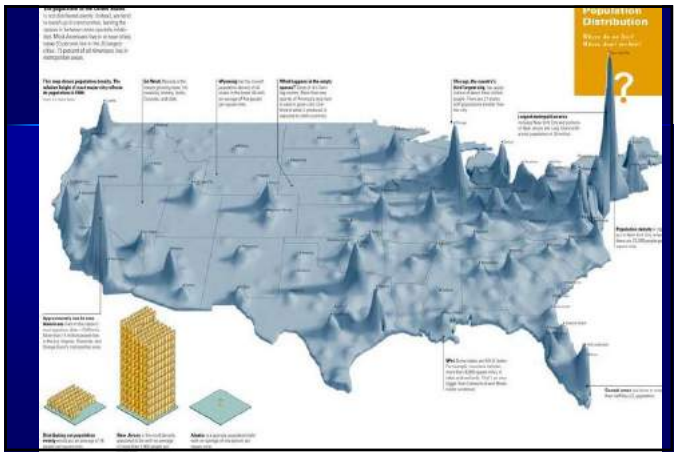
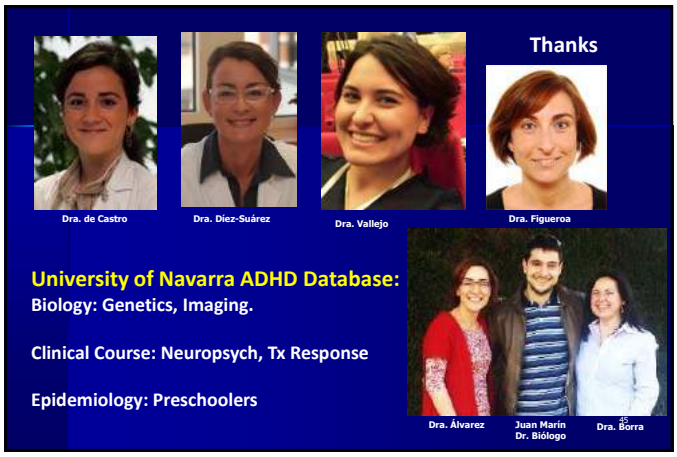


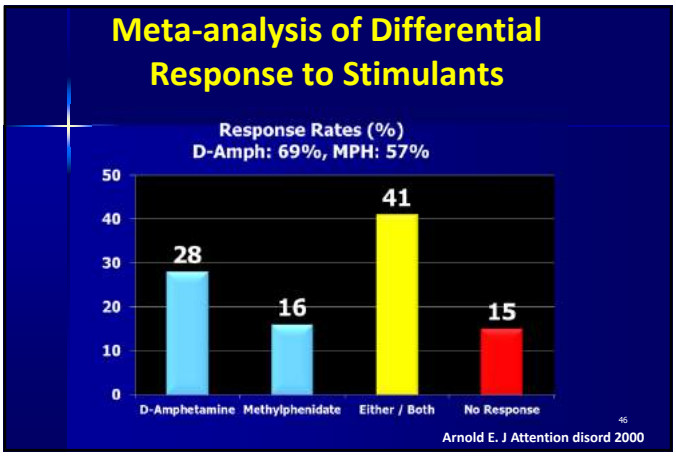


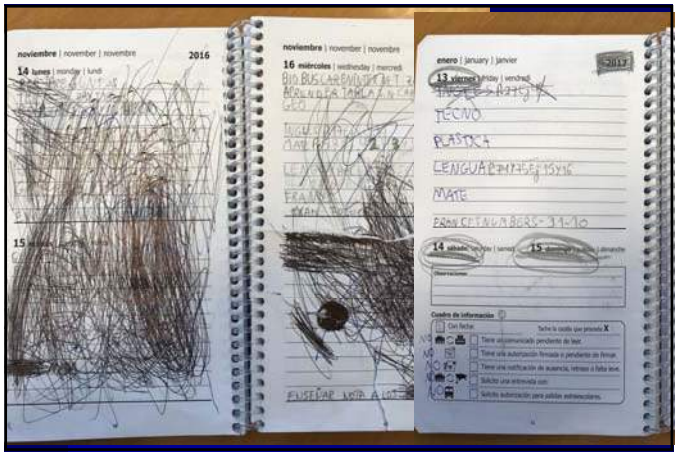
42

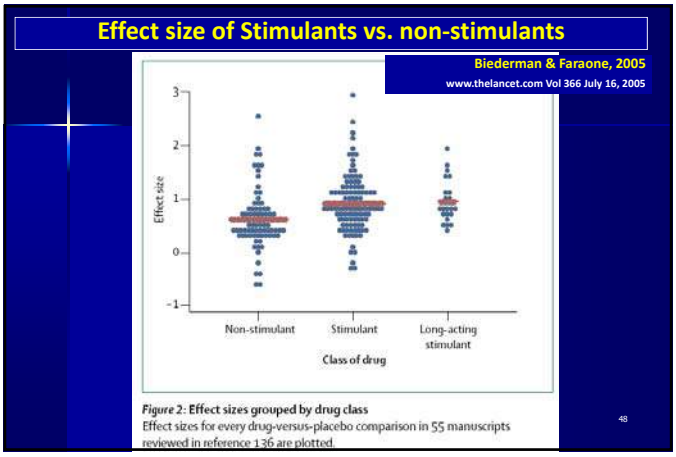

Population Distribution
?


Pirámide de la población española
2017
Millones de hombres
Millones de mujeres
www.eumed.net


Thanks
Dra. de Castro
Dra. Díez-Suárez
Dra. Vallejo
Dra. Figueroa
University of Navarra ADHD Database:
Biology: Genetics, Imaging.
Clinical Course: Neuropsych, Tx Response
Epidemiology: Preschoolers
Dra. Álvarez
Juan Marín
Dr. Biólogo
Dra. Borra
45

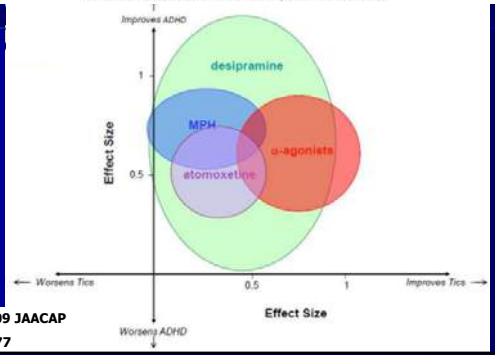

Meta-analysis of Differential Response to Stimulants
Response Rates (%)
D-Amph: 69%, MPH: 57%
50
40
30
20
10
0
28
16
41
15
D-Amphetamine
Methylphenidate
Either / Both
No Response
46
Arnold E. J Attention disord 2000




Effect size of Stimulants vs. non-stimulants
Biederman & Faraone, 2005
www.thelancet.com Vol 366 July 16, 2005
Effect size
Non-stimulant
Stimulant
Long-acting stimulant
Class of drug
Figure 2: Effect sizes grouped by drug class
Effect sizes for every drug-versus-placebo comparison in 55 manuscripts reviewed in reference 136 are plotted.
48

Meta-Analysis: Treatment of Attention-Deficit/Hyperactivity Disorder in Children With Comorbid Tic Disorders

MICHAEL H. BLOCH, M.D., M.S., KAITLYN E. PANZA, B.A., ANGELI LANDEROS-WEISENBERGER, M.D., and JAMES F. LECKMAN, M.D.



Bloch et al., 2009 JAACAP
9 Studies, N=477

49

Meta-Analysis: Treatment of Attention-Deficit/Hyperactivity Disorder in Children With Comorbid Tic Disorders

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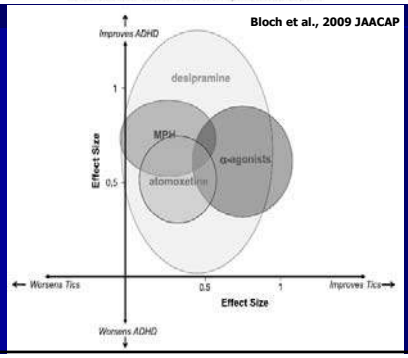
Bloch et al., 2009 JAACAP



50

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Agenda

Clinical & Neuropsychological Predictors of Methylphenidate Response

Introduction

University of Navarra Sample of Children & Adolescents with ADHD

Predictors of MPH Response

Clínica Universidad de Navarra

Objective

- 1. Describe Clinical Characteristics, course & treatment response in Children & Adolescents with ADHD in our Unit.
  - Outpatient Specialty ADHD Clinic, Tertiary University Hospital
- 2. Develope a Predictive Model of Response to treatment based on Clinical Variables and Neuropsychological Testing

52

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Method

- Observatonal study: children & adolescents (7-18 años)
- University of Navarra Clinic: (Outpatient: 2000-2014).
- Baseline and Follow-up (LOCF)
  - Inclusion: DSM-IV ADHD treated with stimulants
  - Exclusion: Neurological disorder
- Analysis: SPSS-20
  - Tests: χi^2, Student´s t for independant & paired samples.
  - ANOVA, Logistic regression for predicitive models (treatment response).
  - Items correlated c response included in Predictive Model

53

Clinical Evaluation

BASELINE EVALUATION

- Clinical Interview: family & child.
  - K-SADS-Based Template (DSM-IV)
- Perinatal data, Development
- Physical Exam:
  - Ht, Wt, BP, HR
- ADHD-RS / SNAP / CGI
- IQ Testing: Weschler (WISC-R / WISC-IV).
- Continuous Performance Test (CPT)
- (Stroop: Red, Green, Yellow)

FOLLOW-UP

- Diagnosis & Comorbidity
- Substance Use
- Physical Exam:
  - Ht, Wt, BP, HR
- ADHD-RS / SNAP / CGI
- Treatment,
  - Dose, Response

54

Soutullo et al WPA 2017 Berlin

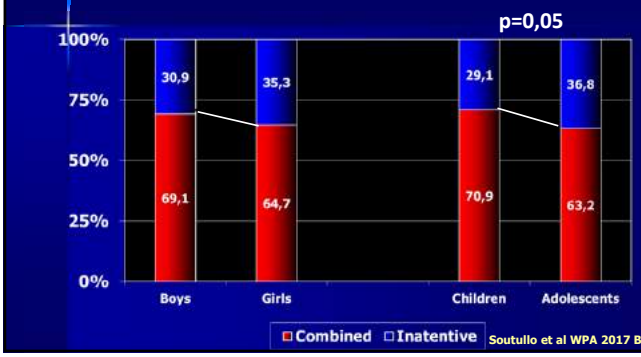
Sample Characteristics

- N=518 Children & Adolescents: DSM-IV ADHD
- Mean Age: 11.4 ± 3,3 yrs old
- 79.5 % Boys
- 68.2 % Combined (subtype/presentation)
- Follow-up period:
  - 2,75 yrs: 33 months (22.7)
- IQ: 99.3 ± 12.9

Soutullo et al WPA 2017 Berlin

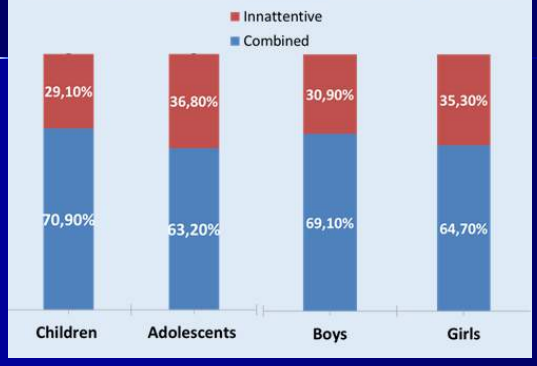
Subtype / Presentation by Sex & Age

N=518, 79.5% boys. Age 11.4 ± 3.3 years old



Soutullo et al WPA 2017 Berlin

% ADHD presentation according sex and age of onset



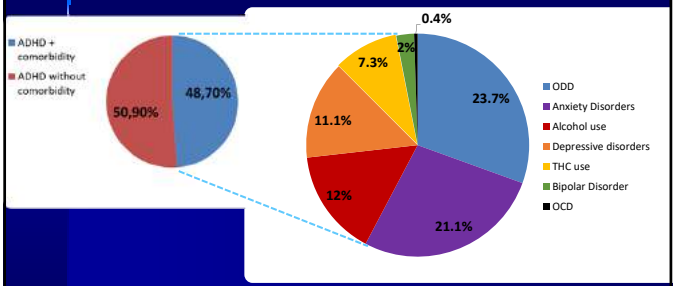
57

Sample characteristics in 518 children & adolescents with ADHD

	Total Sample	Sex			ADHD subtype			Age of onset		
		Boys	Girls	p	IA	C	p	Children	Adolescents	p
Age mean (SD) years	11.40 (3.3)	11.38 (3.2)	11.5 (3.69)	> .1	11.9 (3.4)	11.2 (3.2)	.027*	**8.9 (1.7)**	**14.6 (1.8)**	<.001
Follow-up, months	33 (22.7)	32.4 (23.2)	35.3 (20.7)	> .1	31.4 (20.8)	33.7 (23.6)	> .1	**37.7 (25.1)**	**27 (17.7)**	<.001
ADHD-RS-IV.es										
T1 ADHD-RS-IV (SD)	29.9 (10.42)	**30.71 (10.5**	**26.7 (9.6)**	<.001	28.82 (10.6)	30.4 (10.3)		31.7 (10)	27.6 (10.3)	
Inattention score	17.85 (5.47)	**18.2 (5.4)**	**16.6 (5.4)**	<.001	17.4 (5.8)	18 (5.3)	>.1	17.9 (5.4)	17.9 (5.5)	>.1
Hyperactive score	8.76 (6.0)	**12.5 (7.1)**	**10.1 (6.4)**	<.001	11.4 (7.2)	12.3 (6.9)	>.1	**13.8 (6.8)**	**9.8 (6.7)**	<.001
T2 ADHD-RS-IV (SD)	23.33 (14.19)	**24.2 (14.5)**	**20 (12.6)**	<.001	23.6 (15.7)	23.2 (13.4)		24.3 (14.1)	22 (14.2)	
Inattention score	14.60 (8.7)	**15.2 (8.9)**	**12.3 (7.6)**	<.001	14.8 (9.9)	14.5 (8.2)	>.1	15.2 (9.6)	14 (8.7)	>.1
Hyperactive score	8.76 (6.0)	**9 (6.1)**	**7.7 (5.6)**	<.001	8.9 (6.5)	8.7 (5.8)	>.1	**9.2 (6)**	**8 .1 (6)**	.045
T1-T2 ADHD-RS-IV							<.001			<.001
SNAP-IV										
T1 ODD score	10.08 (4.47)	**10.1 (4.5)**	**8.7 (4.7)**	<.001	9.3 (4.7)	10.1 (4.5)	>.1	9.9 (4.7)	9.9 (4.7)	>.1
T2 ODD score	6.36 (5.0)	**6.7 (5)**	**4.8 (4.5**	<.001	6.2 (4.9)	6.4 (4.9)	>.1	6.7 (5)	5.9 (5)	>.1
T1-T2 ODD score				<.001			<.001			<.001
CGI-S										
T1 CGI-S	3.85 (0.77)	3.9 (0.8)	3.7 (0.8)	.09	3.9 (0.7)	3.8 (0.8)	>.1	3.8 (0.8)	3.9 (0.8)	>.1
T2 CGI-S	2.71 (0.94)	2.7 (0.9)	2.6 (0.9)	.06	2.7 (0.9)	2.7 (0.9)	>.1	**2.8 (0.9)**	**2.8 (0.9)**	.009
T1-T2 CGI-S				<.001			<.001			<.001

ADHD = Attention-deficit/hyperactivity disorder. ADHD subtype presentation: **IA** (inattentive); **C** (Combined). **ADHD-RS-IV.es**: ADHD rating scale-IV (Spanish version) **ODD**: oppositional defiant disorder **CGI-S**: Clinical Global Impressions Severity Scale. T1: baseline; **T2**: end point-last follow-up visit. ***p<0.005***: statistically significant

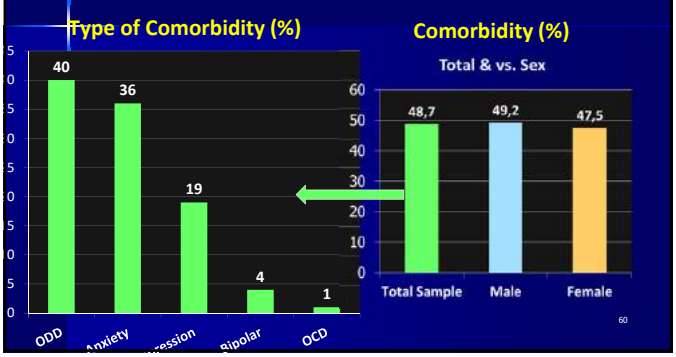
Comorbidity in 518 children & adolescents with ADHD



ODD= oppositional defiant disorder; **THC**: cannabis use; OCD: Obsessive Compulsive Disorder

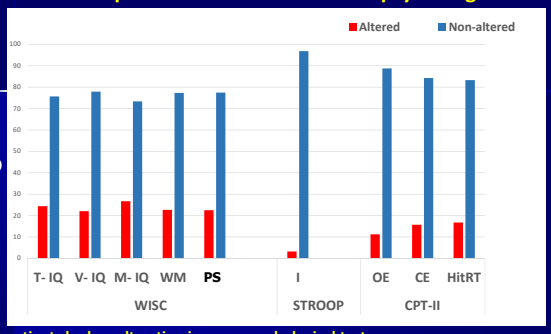
Soutullo et al., 2017, WPA, Berlin

Comorbidity in 497 Children with ADHD



60

% of ADHD patients with altered Neuropsychological Tests



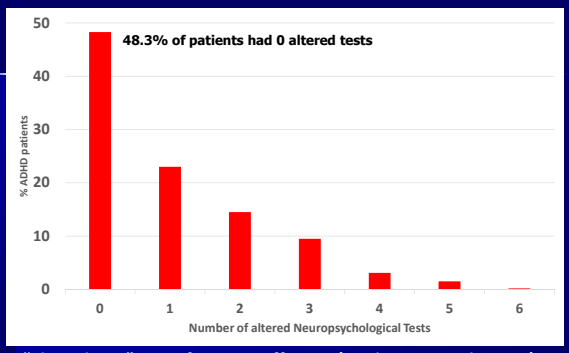
Most patients had no alteration in neuropsychological tests

(1SD away from the average value of the healthy population)

WISC= Wechsler Intelligence Scale (IQ: intelligence quotient, T-IQ Total IQ, V-IQ: Verbal IQ, M-IQ: Manipulative IQ, WM: working memory, PS: perceptual reasoning) CPT-II: Conners' Continuous Performance Test II (CE: commission errors, OE: omission errors, Hit RT: Reaction time,).
STROOP: Stroop COLOR WORD Test (I= interference)

Soutullo et al WPA Oct 2017 Berlin, Germany

% of Patients with different altered Neuropsychological Tests.

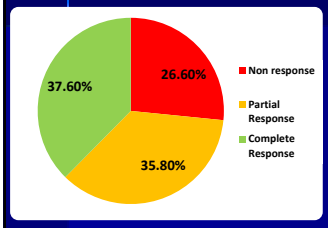


"Altered test" >1SD from cut-off score (Biederman et al., 1993)

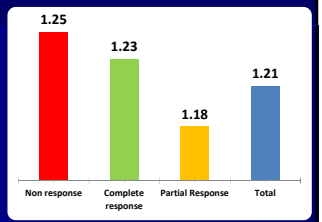
Soutullo et al WPA Oct 2017 Berlin, Germany

MPH Response in 518 children & adolescents with ADHD

Clinical response at follow-up



MPH (mg/kg/day) according to response



MPH response assessment defined as:

Complete: ≥ 30% reduction in ADHD-RS & CGI-S score of 1 or 2.

Partial: < 30% reduction in ADHD-RS & CGI-S reduction of 2 or 3 points

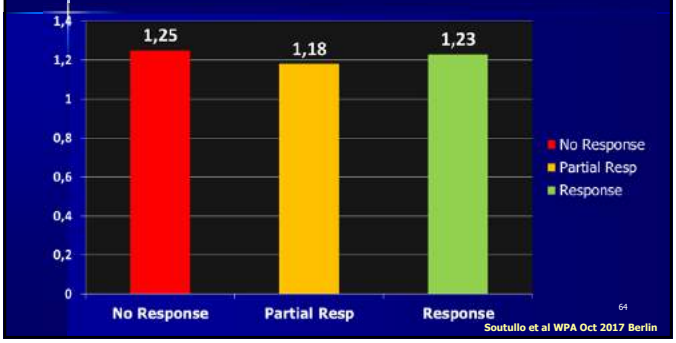
No response: no change or ADHD-RS & CGI worsening

Soutullo et al., 2017, WPA, Berlin

Mean Efficacious dose by Response Group mg/Kg/day

p=0.438 NS

ANOVA between groups



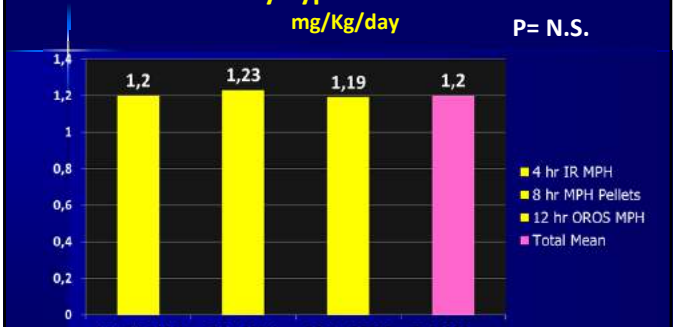
64

Soutullo et al WPA Oct 2017 Berlin

Mean Efficacious dose in responders by Type of MPH

mg/Kg/day

P= N.S.



65

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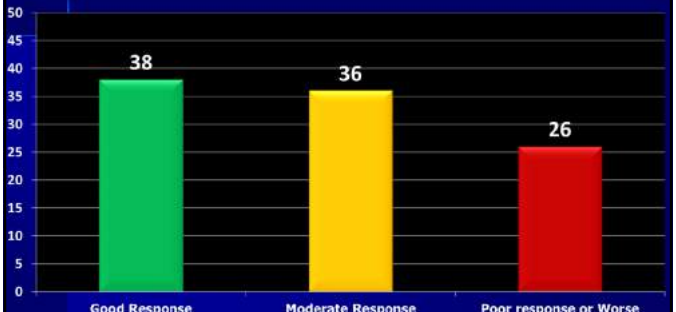
Outcome: Response (%)

Total Sample (N=518), After 3 months of Follow-up



66

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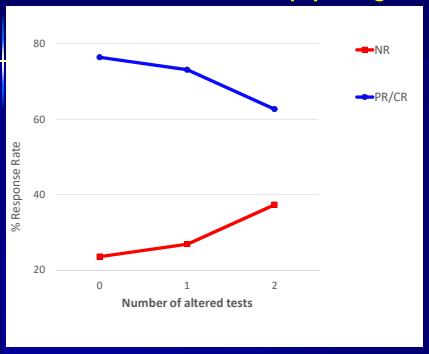
Treatment response (%) at last follow-up visit according to number of altered neuropsychological tests.



Non responders

Partial or Complete response

Soutullo et al WPA Oct 2017 Berlin, Germany

Association with response: Correlation

Predictors of response: Log Regression

Predictors of MPH complete response based on CGI-S

	B	Wald	p
Age of onset	-0.380	3.16	.076
Gender	0.142	0.338	.561
MPH (mg/kg/day)	0.165	0.309	.578
ADHD subtype	0.066	0.088	.766
T1 ADHD-RS Total	-0.020	5.35	.021**
T1 SNAP-IV ODD score	-0.553	4.58	.032**
Total- IQ (WISC-IV)	0.021	4.62	.032**
Comorbidities			
EtOH use	-1.30	6.93	.008***
THC use	-0.054	5.69	.017**
Depressive	-0.732	4.81	.026**

MPH= methylphenidate; ADHD-RS: T1= Baseline visit ADHD rating scale; ODD= oppositional defiant disorder; WISC-IV= Wechsler Intelligence Scale (T- IQ= Total intelligence quotient); THC: cannabis use; EtOH: alcohol use. B= beta coefficient Wald= Wald test

---

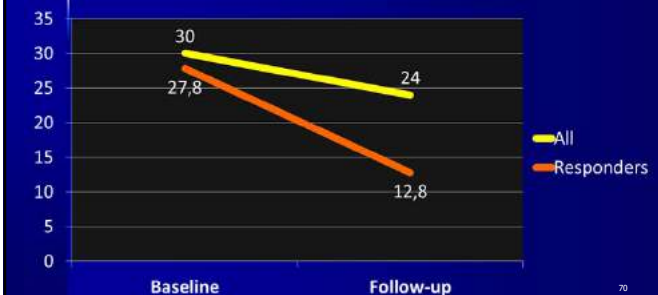
Predictors of MPH complete response based on CGI-S

	B	Wald	p
Age of onset	-0.380	3.16	.076
Follow-up, months	-0.002	0.250	.617
Gender	0.142	0.338	.561
MPH (mg/kg/day)	0.165	0.309	.578
ADHD subtype	0.066	0.088	.766
T1 ADHD-RS Total	**-0.020**	**5.35**	**.021**
Inattention score	-0.032	2.98	.084
"forgets"	**-0.38**	**7.65**	**.006**
Hyperactivity-score	0.002	0.019	.891
"fidgets"	**0.245**	**3.9**	**.048**
T1 SNAP-IV ODD score	**-0.553**	**4.58**	**.032**
"rejects rules"	**-0.376**	**4.58**	**.032**
"angry"	**-0.421**	**3.94**	**.047**
WISC-IV			
Total IQ	**0.021**	**4.62**	**.032**
CPT-II			
CE	**-0.13**	**3.87**	**.049**
SCWT			
Interference	**-0.778**	**4.61**	**.032**
Comorbidities			
OH use	**-1.30**	**6.93**	**.008**
THC use	**-0.054**	**5.69**	**.017**
Depressive symptoms	**-0.732**	**4.81**	**.026**

ADHD = Attention-deficit/hyperactivity disorder; **MPH**= methylphenidate; **ADHD-RS**: ADHD rating scale; **WISC**= Wechsler Intelligence Scale; **CPT-II**:Conners' Continuous Performance Test II (**CE**: commission errors); **OH**= alcohol use; **THC**: cannabis use. **B**= beta

---

ADHD-RS at Baseline & Follow up in all ADHD Sample (N=497) vs Responders (189; 38%)



70

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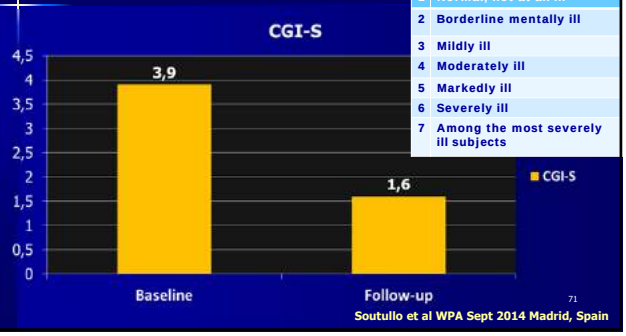
CGI-Severity: Baseline to Follow-up in Good Responders



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

71

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Results

Predictors of Response to MPH

IQ, Comorbidities, CPT items

Binary Logistic Regression

■1st Predictive Model: IQ & Comorbidities

Odds Ratio

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1ª	Total IQ	,018	,008	5,118	1	,024	1,018	1,002	1,033
	TOTALHA	-,017	,015	1,411	1	,235	,983	,955	1,011
	Sexo(1)	,348	,241	2,083	1	,149	1,416	,883	2,271
	TND(1)	-,446	,250	3,184	1	,074	,640	,392	1,045
	Depression	-,775	,360	4,634	1	,031	,461	,228	,933
	Constant	-1,943	,798	5,928	1	,015	,143		

a. Variable(s) entered on step 1: CITotalCOMUN, TOTALHA, Sexo, TND, Tr.Depresivos.

2nd Predictive Model of response based on CPT

- Negative correlation vigilance and MPH response (N=385, OR=0.98, IC: (0.97 - 1)).

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3rd Predictive Model of Response: ADHD-RS / SNAP

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Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B) Lower	Upper
Step 1[a]	Olvida	-,327	,106	9,566	1	,002	,721	,586	,887
	Interrumpe	-,159	,092	2,987	1	,084	,853	,712	1,022
	Enfadadoresentido	-,374	,154	5,880	1	,015	,688	,509	,931
	Constant	,693	,265	6,866	1	,009	2,000		

a. Variable(s) entered on step 1: Olvida, Interrumpe, Enfadadoresentido.

9. Es olvidadizo de actividades diarias
10. Mueve manos y pies o se mueve en su asiento
11. Se levanta en clase o en otras situaciones cuando no debe
12. Corre o se sube a sitios/cosas cuando se le dice que no lo haga
13. Tiene dificultad para jugar en silencio
14. Actúa como si estuviera activado por un motor/"No se le gastan las pilas"
15. Habla excesivamente
16. Contesta abruptamente/impulsivamente antes de que se termine la pregunta
17. Tiene dificultad en esperar su turno en actividades de grupo
18. Interrumpe a la gente o se mete en conversaciones o juegos
a. Hiere los sentidos
b. Discute con adultos
c. Desafía o rechaza activamente las sugerencias o normas de adultos
d. Hace cosas que molestan a los demás adrede
e. Culpa a los demás de sus errores o comportamiento inadecuado
f. Es susceptible o fácil de molestar
g. Está enfadado y resentido
h. Es rencoroso o vengativo

Forgetful OR 0.7

Interrupts / Intrudes OR 0.85

Upset & Resentful OR 0.69

Conclusions

- 37.6% of patients with ADHD treated with MPH had a good response (35.8% partial). 73.4% good of partial
- Mean MPH dose in good responders was: 1.2 mg/kg/day
- Factors that predicted good response:
  - Higher IQ, less Neuropsychological tests altered
  - Lower baseline levels of ADHD,
  - Comorbidity: Less depression & ODD Symptoms.
  - Absence of alcohol and cannabis use

74

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Conclussions

- Despite the lack of CAP as a Specialty in Spain…
- Available medications include
  - MPH (4, 8, 12 hrs), LDX; ATX, GXR
- Prevalence & Presentation similar to international samples
- Awareness is increasing, but still needs to be much improved.
- Time from symptom onset to diagnosis is 4-6 years

75

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Gracias!

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76

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Disclosure

Commercial Interest	What Was Received?	For What Role?
Alcobra Ltd.	Research Support	PI
Enzymotec Ltd.	S/P Research Support, Honoraria	S/P PI Consulting
Janssen-Cilag	Honoraria	Consulting, advisory board
Novartis Israel	Honoraria	Consulting, advisory board
Teva Israel	Honoraria	Consulting
Medison Israel	Honoraria	Consulting
UKAAN/ENAA	Travel expenses	Board member
APSARD/Pond Foundation	Travel expenses	Board member

ADHD in Israel

Dr. iris Manor
Director of ADHD Clinic, Geha MHC, Clalit
Senior Lecturer, Sackler School of Medicine, TAU
Chair of the Israeli Society of ADHD (ISA)

Evaluation and Diagnosis

- According to DSM-5
- Use of Validated scales and tests
- Not unified
- No Israeli Guidelines

Knowledge and Awareness

- A significant increase in awareness and knowledge in the past decade
- Acknowledgement of the importance of a separate professional society by the Israeli Medical Association, the approval of ISA
- Increased knowledge of the public. Many reliable sources of information are available
- Not enough knowledge especially of the primary care physicians and of adult ADHD
- The public is still fed by misconceptions and disinformation.

Medications and treatment

- Most of the stimulants exist and available, as well as Strattera
- CBT and parent education are known
- Many medications are expensive and not covered by the National Health insurance
- CBT experts are still scarce and not much available, especially in the periphery. Same problem with parent education

Expertized professionals

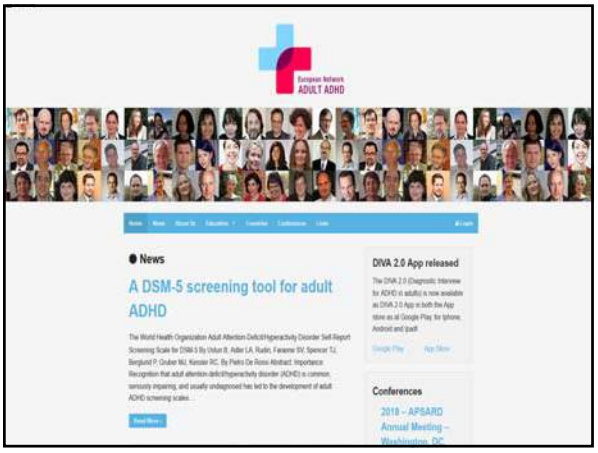
- Experts: psychiatrists neurologists, pediatricians and family physicians who have undergone special training
- Unique: in Israel most children with ADHD are diagnosed by neurologists (80%)
- Training of interested pediatricians and family physicians
- Not all psychiatrists and neurologists on the same level of knowledge
- Not enough experts, a need to train more ⟶

Thanks

Media and stigma

• The media is much more involved, largely due to our proactive work with it, and has gone from firmly negative to mildly positive while dealing with this subject	• Still – many stigmas exist • Scientology is "alive and kicking" as well as "alternative therapists"


ADHD NETWERK
HOME
NIEUWS
AGENDA
Tweets
BESTE ADHD VERZEKERING 2018
NETWERK MEETING


European Network ADULT ADHD
News
A DSM-5 screening tool for adult ADHD
DIVA 2.0 App released
Conferences

European Network
ADULT ADHD

PsyQ

PsyQ

PsyQ

DIVA
Foundation

diagnostic interview
for ADHD
in adults

PsyQ

Ongoing:
Updating DIVA 2.0 into DIVA-5, based on DSM-5 criteria

DIVA 2.0 is available in 20 languages:

DIVA-5 is available in 2 languages

Dilemma: APA requires 1500 dollar per language per printed version and app version

www.divacenter.eu

PsyQ

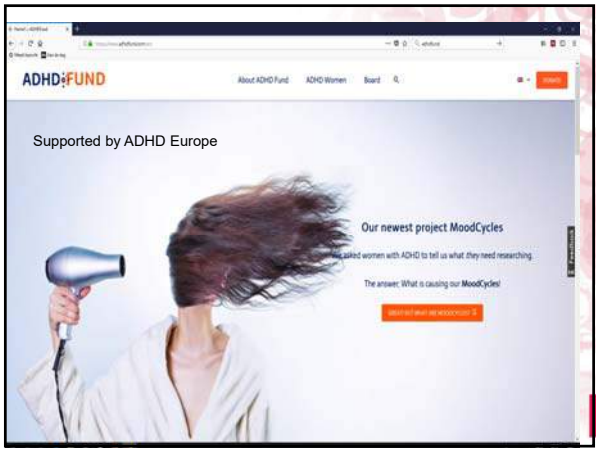
DIVA 2.0

The DIVA 2.0 App is now available in both App store and at Google Play, for Iphone, Android and Ipad! It costs 9.99 euro once, for extended use.

The DIVA 2.0 App adds the total number of DSM-IV criteria for ADHD in both child- and adulthood, and the number or areas of impairment. Data are not stored, but sent via email, both as text and as SPSS file.

PsyQ

PsyQ



APSARD 2018 Annual meeting

HOKKAIDO UNIVERSITY HOSPITAL

International Perspectives on ADHD

ADHD in Japan

Takuya Saito MD Ph D
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Hokkaido University, Sapporo , Japan

Takuya Saito
Financial Disclosures (last 3 years)

	Lecturer	Consultancy	Research Grant	Royalties
Dainippon-Sumitomo	X	X		
Janssen	X			
Shire	X	X		
Taisho	X	X		
Otsuka	X		X	
Shionogi	X	X		
Eli Lilly	X	X	X	
Mochida	X	X		
AMED			X	
Ministry of Health			X	
Ministry of Science			X	

Is there Cross cultural differences on patients with ADHD care?

- There is very limited number of studies
- Until recently much less attention for ADHD in Asia in medical fields and society general
- On the other hand over the last decade it has been increased attention to ADHD.

Japanese Health care system

The *Health Insurance Act* and The *National Health Insurance Act* established a health insurance system that covered the entire population by 1961. The *Medical Care Act 1948* and subsequent A*mendments* (1985 and 1992) form the basic law governing the Japanese health care delivery system. The health care delivery system cover all people. “Free access” is a major characteristic in the health care delivery system in Japan Both public and private sectors provide the same health care services at the same costs. Particularly in a majority of areas medical care below 15 years old is free. However, there are only three hundreds child psychiatrists for more than one hundred million people. The health care system make easier to access child psychiatrists but makes waiting list longer.

Lack of supports for children with disabilities such as development disorder

- In 2017 Act to advance the elimination of discrimination based on handicap was enacted and this law is a similar role to combination of individuals With Disabilities Education Act (IDEA) and Section 504 of the U.S Rehabilitation Act .
- Still children with ADHD can receive enough support from school system and there is lack of collaboration between medical and educational system as well. Lack of supports also includes lack of suppotrs for family.

Limited access to ADHD medication

- There are only three medications approved for ADHD included Concert (OROS-methylphenidate), Strattera (atomoxetine), Intuniv (guanfacine).
- Stimulants are under strict-use regulations imposed by the regulatory agency and prescribing stimulants requires a special permission.

Future direction

- Increasing global clinical trials for ADHD medication to improve access to more medications
- Improving the interdisciplinary collaboration
- Improving supports for family with ADHD

A Brief Overview of Emotional Dysregulation in ADHD

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Dr. Rostain Disclosures

Book royalties
- Routledge/Taylor Francis Group
- St Martin's Press

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Consultant honoraria
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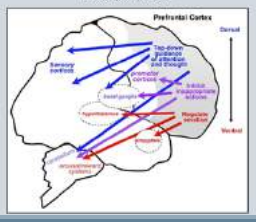
CME presentations
- WebMD, NACE and American Psychiatric Association

Regulation of Attention and Emotion



Learning Objectives

This presentation will

1. Review the prevalence of emotional dysregulation (ED) in ADHD patients
2. Discuss conceptual and measurement issues involved in defining ED
3. Consider the pathophysiology of ED
4. Review the impact of ED on functioning of people of ADHD
5. Discuss the links between ED and psychiatric comorbidity in ADHD patients,
6. Review some of the effects of ADHD treatments on ED

NOTE: This talk is based on an article submitted for publication, co-authored by Joseph Blader, Betsy Busch, Ann Childress, Steve Faraone, Jeffrey Newcorn & Anthony Rostain

Why Emotional Dysregulation in ADHD is Important

Clinical
- Many patients report difficulties with handling emotions/affect
- These difficulties have an impact on development and functioning
- This is often a focus of clinical intervention but clinical evidence to guide us is sparse

Nosologic
- There is considerable confusion and controversy regarding the role of ED in ADHD
  - e.g. - is it associated with or constitutive of ADHD?
- Boundaries between ED and mood disorders are fuzzy and often overlapping
- Need better tools for distinguishing between these constructs

Scientific
- Brain science is interested in elucidating the mechanisms of self-regulation and self-control
- ADHD offers neuroscientists an important model for understanding the inter-relationships among cognitive, behavioral and affective regulatory circuits

Prevalence of Emotional Dysregulation(ED) Among Patients with ADHD

Children: 30-40% have significant impairments
- Rage outbursts
- Irritability
- Over-reactivity
- Low frustration tolerance
- Susceptibility to anger

(Stringaris, Cohen, Pine, & Leibenluft, 2009; Barkley & Fischer, 2010; Sobanski et al., 2010; Anastopoulos et al., 2011; Spencer et al., 2011; Biederman et al., 2012; Skirrow & Asherson, 2013; Karalunas et al., 2014; Shaw, Stringaris, Nigg, & Leibenluft, 2014; Barkley, 2015; Liu et al., 2016)

Adults: over 50% report impairments

(Reimherr, Marchant, Strong, et al, 2005; Reimherr, Williams, Strong, et al, 2007; Barkley, Murphy, & Fischer, 2008; Surman, Biederman, Spencer, et al., 2011; Surman, Biederman, Spencer, Miller, McDermott, & Faraone, 2013; Barkley, 2015)

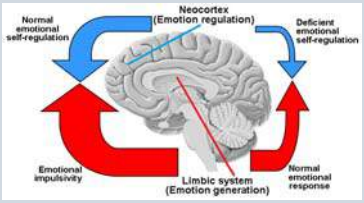
Conceptualizations of ED in ADHD

Plethora of Terms
- emotional lability
- emotional reactivity
- "over-emotionality"
- affective reactivity
- emotional impulsivity (EI)
- deficient emotional self-regulation (DESR)
- emotional dysregulation (ED)

Emotional Dysregulation (ED) is broadest term
- Includes most aspects of the other terms
- Describes the most clinically salient aspects

Two dimensions of ED
- Dysregulation of emotion generation
  - Low capacity for enjoyment (anhedonia, low hedonic tone)
  - Excessive alarm to stimuli (anxiety)
  - Excessive sadness/euphoria (depression/mania)
  - Excessive frustration to mildly noxious stimuli (irritability)
- Impaired emotion regulation
  - Difficulty exerting purposeful control over emotions
  - Emotional responses can be exaggerated in intensity, duration or form of expression
  - Autonomic, behavioral and cognitive sequelae of emotion expression exceeds developmental level

Conceptualizations of ED in ADHD



DESR

Impaired emotion regulation ("top down")
- Does ADHD serve as an "accelerant" so that emotions (strong or weak) are poorly inhibited and lead to maladaptive behavior

EI

Dysregulation of emotion generation ("bottom up")
- "To what extent do individuals with ADHD experience unusually intense emotional reactions that impel equally strong behavior?"

Measurement of ED

Review of literature found 18 instruments designed to measure ED
- No standardized tool exists
- Scales generally focus on "emotion regulation
- Some also address affective reactivity, emotional lability and emotion expression
- 8 scales are for children, 2 for adults, 8 for both
- Most have a self-report version
- 13 have been used in treatment trials
- None has been validated as a patient-reported outcome
- 11 have population norms
- Most of the scales were NOT developed for ADHD individuals
- Exceptions: Barkley, Brown, Conners, & Wender-Reimherr scales

Scale / Instrument	Reporter*	Children, Adults, or Both	Trials	Norms	Availability
Affective Lability Scale–Short Form (ALS-18) (Weibel et al., 2017)	A	Adults	Yes	Yes	Free
Affective Reactivity Index (ARI) (Stringaris et al., 2012)	Y, P	Children	Yes	Not found	Free
Barkley Deficits in Executive Functioning Scale—Children and Adolescents (BDEFS-CA) (Barkley, 2012)	Y, P	Children	None found	Yes	$
Behavior Rating Inventory of Executive Function (BRIEF or emotion control subscale) (Mahone et al., 2002)	Y, A, P, T	Both	Yes	Yes	$
Brown ADD Rating Scales for Children, Adolescents and Adults (BADDS) (Brown, 1996)	Y, A	Both	Yes	Yes	$
Conners Global Index (CGI) Emotional Lability Scale (Conners, 1997)	Y, A	Children	Yes	Yes	$
Child Behavior Checklist Dysregulation Profile (CBCL-DP) (Geeraerts et al., 2015)	Y, A	Children	No	Yes	$
Difficulties in Emotion Regulation Scale (DERS) (Gratz & Roemer, 2004)	Y, A	Both	Yes	Not found	Free
Difficulties in Emotion Regulation Scale - Brief Version (DERS-16) (Kaufman et al., 2016)	Y, A	Both	None found	Not found	Free

Scale / Instrument	Reporter*	Children, Adults, or Both	Trials	Norms	Availability
Emotion Dysregulation Scale, short version (EDS-short) (Powers, Stevens, Fani, & Bradley, 2015)	Y, A	Both	None found	Not found	Free
Emotion Regulation Checklist (ERC) (Shields & Cicchetti ,1997)	P	Children	Yes	Not found	Free
Emotion Regulation Index for Adults and Children (ERICA) (MacDermott, Gullone, Allen, King, & Tonge, 2010)	Y, A	Both	Yes	Not found	Free
Emotion Regulation Questionnaire (ERQ) (Gross & John, 2003)	Y, A	Both	Yes	Yes	Free
Emotional Lability *T*-scores on Conners Rating Scales–Revised (CRS-R) (Connors, 2001)	Y, A, P, T	Children	Yes	Yes	Free
Expression and Emotion Scale for Children (EESC) (Penza-Clyve & Zeman, 2002)	Y, A, P, T	Children	Yes	Yes	Free
State Difficulties in Emotion Regulation Scale (S-DERS) (Lavender, Tull, DiLillo, Messman-Moore, & Gratz, 2015)	Y, A	Both	None found	Not found	Free
Strengths and Difficulties Questionnaire-Dysregulation Profile (SDQ-DP) (Holtmann, Becker, Banaschewski, Rothenberger, & Roessner, 2011)	P	Children	Yes	Yes	Free
Wender-Reimherr Adult Attention Deficit Disorder Scale (Marchant, Reimherr, Robison, Robison, & Wender, 2013)	C	Adults	Yes	Yes	Free

Pathophysiology of ED in ADHD – Emotion Regulation

4 distinct parallel cortico-striatal-thalamic-cortical (CSTC) loops have been identified in the basal ganglia – skeletomotor, oculomotor, associative/cognitive and limbic

Limbic loop receives inputs from the temporal cortex and hippocampal formation; frontal lobe inputs and thalamic projects are found in the OFC and ACC

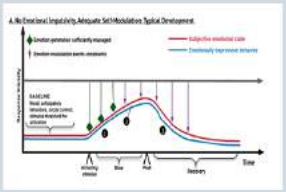
ACC has central role in linking motor planning and monitoring to emotionally significant outcomes of behavior

OFC has critical role in processing emotionally salient stimuli

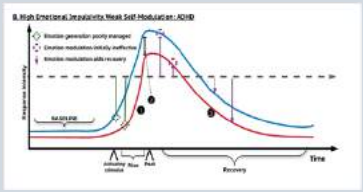
Pathophysiology of ED in ADHD – Emotional Regulation

Conceptual Model for the Time Course of Acutely Elicited Emotional Reactivity

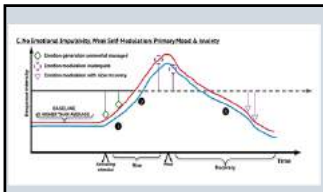
1. Baseline and generation of emotions
2. Peak levels of emotion
3. Return of emotion to baseline



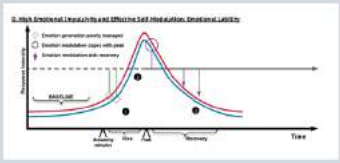
Panel A: Typical Reactivity. **Phase 1:** An activating event leads to an emotional phase in which both subjective state (red line) and emotionally expressive behavior (blue line) change gradually during the rise phase. **Phase 2:** Behavior and affect change in tandem. **Phase 3:** Emotional self-modulation skills return subjective emotionality and expressive behaviors to baseline.



Panel B: High Emotional Impulsivity and Deficient Self-Modulation – e.g., ADHD. **Phase 1:** High emotional impulsivity causes emotion generation at lower thresholds, shorter rise times and intense emotional responses. **Phase 2:** Due to poor self-modulation skills the intensity of behavioral expression is excessive for the level of emotional response. **Phase 3:** Poor self-modulation skills and high levels of emotion generation lead to slower recovery times and prolonged episodes of behavioral disturbance.



Panel C: No Emotional Impulsivity and Deficient Self-Modulation -- e.g., Mood and Anxiety Disorders. **Phase 1:** Baseline emotional intensity is higher than average. Emotion generation is gradual but reaches high levels. **Phase 2:** With no emotional impulsivity, behavioral indicators of negative emotion lag behind subjective experience. **Phase 3:** Poor self-modulation prolongs emotions and their adverse impact. Counterproductive thoughts and behaviors -- such as rumination and avoidance -- sustain and intensify maladaptive emotions.



Panel D: High Emotional Impulsivity and Effective Self-Modulation -- e.g. Emotional Lability. **Phase 1:** High emotional impulsivity causes emotion generation at lower thresholds, shorter rise times and intense emotional responses. **Phase 2:** There is a closer relationship between subjective emotional intensity and its behavioral expression. Effective self-modulation of emotions shortens the peak. **Phase 3:** Emotional self-modulation skills return subjective emotionality and expressive behaviors to baseline but high emotional impulsivity puts person at risk for another episode of extreme emotion.

Pathophysiology of ED in ADHD – Underlying Mechanisms

- Childhood temperament measures correlate "negative emotionality" and ADHD Sx
- Proneness to anger, easy frustration and low adaptability may also hinder the development of executive control processes
- Possible mechanism: "Reward Deficiency Syndrome"
  - Diminished reward signals in Ventral Striatum (VS) may contribute to drive for compensatory intensive stimulation and positive reinforcement (stimulus seeking) and greater sensitivity to reward reduction and to mild negative stimuli -- > results in "irritability" or "hyper-reactivity"
  - Explains why stimulants may alleviate reduced reward signaling in VS
- Clinical Implication:
  - High-intensity and unexpected stimuli induce highly salient rewards for those with lower sensitivity to less-rewarding stimuli.
  - Absence of highly rewarding stimuli is experienced as highly aversive –> "reactivity" to minor provocations

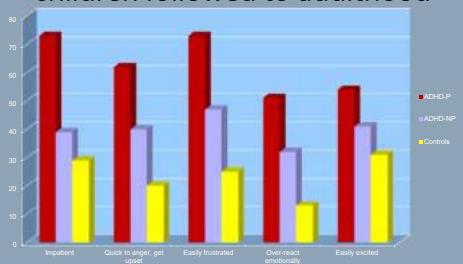
Impact of ED on ADHD

- ED is common in ADHD individuals
  - More prevalent in combined type
  - More severe in people with more severe ADHD
  - More closely associated with ODD
  - Predicts suspensions and expulsions from school
  - Associated with impaired social, daily living and adaptive skills
  - Associated with higher treatment service utilization
- Greater ED in ADHD youth predicts less likelihood of remission
- ED does not remit with age and contributes independently from ADHD symptoms to functional impairment in several areas (occupation, education, legal, financial, family life and social relationships

Impact of ED on ADHD

- ED in adults is associated with
  - Lower employment rate
  - Greater number of jobs held
  - Poorer work performance
  - Poorer peer relations
  - Greater likelihood of being fired or quitting from boredom
  - Lower likelihood of graduating high school or college
  - Higher rates of driver license suspensions & traffic tickets
  - More financial difficulties

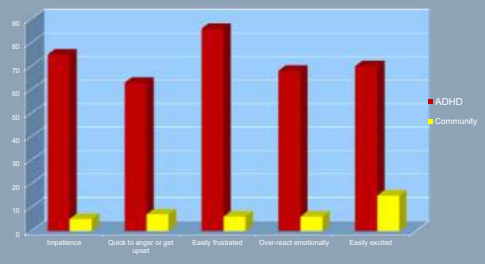
Emotional Impulsivity in ADHD children followed to adulthood



ADHD-P = Persistent ADHD, ADHD-NP = Non Persistent ADHD

From Barkley, R., Murphy, K. & Fischer, M. (2008). *ADHD in Adults: What the Science Says.* New York: Guilford

Emotional Impulsivity in adults with ADHD



From Barkley, R., Murphy, K. & Fischer, M. (2008). *ADHD in Adults: What the Science Says*. New York: Guilford

Psychiatric Comorbidity of ED in ADHD

Emotional Dysregulation is seen in psychiatric conditions other than ADHD:

- Oppositional Defiant Disorder
- Major Depressive Disorder
- Bipolar Disorder
- Disruptive Mood Dysregulation Disorder
- Conduct Disorder
- Anxiety Disorders
- Autism Spectrum Disorders
- Personality Disorders
- Intermittent Explosive Disorder

What clinical features of ED can help distinguish among these conditions?

Disorder	Clinical Feature of Emotional Dysregulation				
	Irritability	Inappropriately positive emotions	Persistent anger most of the day	Argumentative/defiant behavior and/or vindictiveness	Impulsive aggression
Attention-deficit/hyperactivity disorder	Chronic	Yes	No	No	No
Autism spectrum disorder	Chronic	Yes	No	No	No
Bipolar disorder	Episodic	Yes	No	No	No
Borderline personality disorder	Chronic	No	No	No	Yes
Oppositional defiant disorder	Chronic	No	No	Yes	Yes
Disruptive mood regulation disorder	Chronic	No	Yes	No	Yes
Intermittent explosive disorder	Chronic	No	Yes	No	Yes
Generalized anxiety disorder	Episodic	No	No	No	No
Depressive disorder	Chronic	No	No	No	No

Effects of Stimulant Treatment on ED

Study	Design	Sample Size	Results
Demirci 2016	Randomized	130	Significant improvement in RMET and BFRT after treatment with MPH or atomoxetine
Masi 2016	Randomized	144	Additional pharmacotherapy significantly improved aggression and emotional dysregulation, but not callous emotional traits
Peyre 2015	Questionnaire	173	Variables independently associated with CBCL-DP were clinical severity, internalized disorders, high emotionality, and low self-directedness
Kutlu 2017	Open label	118	Emotional dysregulation is highly prevalent in disruptive behavioral disorders that are comorbid with ADHD, and methylphenidate is effective for emotional dysregulation independently from other clinical determinants
Rösler 2010	Randomized	363	MPH was significantly statistically superior to placebo in reducing emotional symptoms with ADHD as assessed by the EDS and the ELS
Reimherr 2015	Randomized	136	Adult patients with ADHD and emotional dysregulation showed more childhood ADHD symptoms, adult symptoms of ODD, and evidence of personality disorder, with improvement of emotional domains during treatment with methylphenidate

Effects of Stimulant Treatment on ED

Study	Design	Sample Size	Results
Philipsen 2015	Randomized	419	In adults with ADHD, methylphenidate was significantly superior to placebo as assessed by change in the ADHD Index of the Conners Adult ADHD Rating Scale
Katic 2013	Open label	318	The proportion of children with behavioral impairments in executive function control of emotional response during treatment with lisdexamfetamine
Banaschewski 2013	Randomized	317	The benefits of short-term stimulant treatment in children and adolescents with ADHD extend beyond symptomatic relief and impact positively on health-related quality of life and daily functioning
Childress 2014	Open label	211	Symptoms of ADHD and emotional lability improved with lisdexamfetamine regardless of baseline emotional lability symptoms
Adler 2013	Randomized	159	Among adults with ADHD and clinically significant executive function deficits, lisdexamfetamine was associated with significant improvements in self-reported executive function ratings

RMET, Reading the Mind in the Eyes Test; BFRT, Benton Facial Recognition Test; CBCL-DP, Child Behavior Checklist-Dysregulation Profile; EDS, Emotional Dysregulation Scale; ELS, Emotional Lability Scale.

Effects of ATX Treatment on ED

Meta-analysis of MPH and ATX for treating ED in adults with ADHD (Moukhtarian, 2017) found a moderate positive effect

Meta-analysis of all pediatric ADHD studies found small positive effects of ATX on child emotionality (Schwartz, 2014)

Reimherr (2005) studied effects of ATX for adults with ADHD in two RCTs – focused on "emotional dysregulation" symptoms from WRAADDS. ATX group improved significantly

Adler (2014) conducted 12 wk RCT of ATX in young adults and found significant improvement in Behavioral Regulation Index of BRIEF-A but non-significant improvement in Emotional Control

Asherson (2014) examined 3 pooled studies of adults with ADHD – 50% of subjects had elevated Emotional Control scores on BRIEF-A – treatment with ATX for 10-12 weeks produced small but significant improvement in EC scores for subjects with high baseline EC

Effects of Parent Behavior Management Therapies on ED in Children

Incredible Years Program

- Trillingsgaard (2014) reported significant improvements in child's emotional regulation after 16-20 weeks of program using parent reports

Parent Behavior Management Training Programs for Preschoolers

- Graziano & Hart (2016) – found that enhanced social-emotional and self-regulation training components led to better emotional regulation and overall executive functioning
- Others have found PBMT was effective for preschoolers with ADHD/ODD but these studies emphasize behavioral change rather than improvements in ED

Effects of CBT/Meta-Cognitive Therapies on ED

Sukhodolsky (2016) reviewed CBT for children and adolescents presenting with anger, irritability and aggression across diagnostic groups – benefits for ED in ADHD children was noted

Tamm (2015) tested a directed-play-based meta-cognitive executive function training in 3-7 years olds and their parents. Compared to wait list control, this intervention normalized BRIEF Emotion Regulation ratings by the end of the intervention.

Numerous group and individual CBT programs for adults with ADHD have shown improvements in ED, especially when modules like "distress tolerance" (adapted from DBT) are included

Summary and Conclusions

Emotional dysregulation is highly prevalent in ADHD patients and cannot be accounted for by the presence of other comorbid conditions

It should be considered as an associated feature of ADHD (like learning disabilities and executive function deficits)

It is linked to higher levels of impairment and predicts a more pernicious life course

It is only partially responsive to ADHD treatments (pharmacologic and psychosocial)

Central role of DA in limbic regions which subserve emotional regulation and importance of prefrontal-limbic circuits in regulation of emotion strongly support idea that ED is a core feature of ADHD

Given these putative neurobiological mechanisms, high prevalence and major impact on functioning and treatment response, ED should be part of the diagnostic criteria of ADHD

Summary and Conclusions

Major challenges remain on how to measure ED

Presence of ED in many other psychiatric conditions and *absence* of ED in many ADHD patients makes it difficult to proceed with changes in diagnostic criteria

Definitional challenges persist

- Current screening and diagnostic tools separate ADHD from "mood disorder" symptoms
- Distinguishing between ED and irritability is difficult

Need new measurement tools

Need to target ED in assessment and treatment

Need multidisciplinary approach to elucidating the neurobiology of ED

Mesolimbic circuits in ADHD

Jonathan Posner, MD
Associate Professor of Psychiatry
Columbia University
New York State Psychiatric Institute

Disclosures of Potential Conflicts

- Shire Pharmaceuticals
- Aevi Genomics

Outline

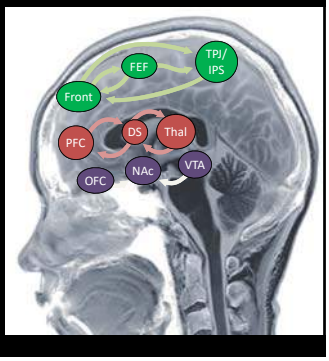
- Mesolimbic circuits in ADHD
  - Recent MRI studies
- Conceptual model
  - How does mesolimbic function relate to ADHD?
- Implications
  - Prevention

Neural Circuits & ADHD

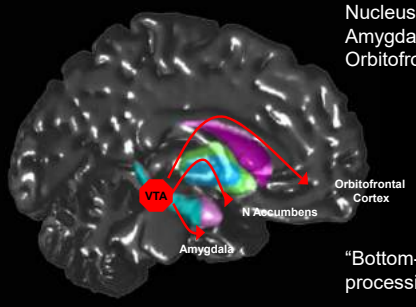
Frontoparietal circuits:
- Alerting attention
- Orienting response

Dorsal frontostriatal circuits:
- Inhibitory control
- Response selection
- Executive functions

Mesocorticolimbic circuits:
- Motivation
- Reward processing
- Frustration/aggression



Mesolimbic Circuits

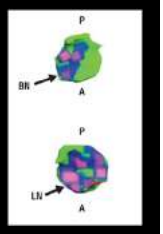


Nucleus Accumbens
Amygdala
Orbitofrontal Cortex

"Bottom-up" processing

Amygdala in ADHD youth

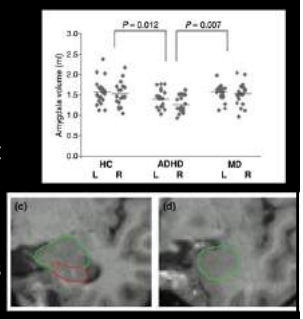
- Plessen et al, 2006
  - ADHD (n=51) vs HC (n=63)
  - 6–18 years old
  - Overall amygdala volumes did not differ
  - Reduced surface area over baso-lateral amygdala (R & L)
  - Amygdala surface area correlated with hyperactive & inattention symptoms



JAMA Psych, 2006

Amygdala in ADHD adults

- Frodl et 2010
  - ADHD vs MDD vs HC
  - 20 adults per group
  - Reduced R amygdala volumes relative to HC and MDD
  - R amygdala volumes correlated with hyperactive symptoms



Acta Psych, 2010

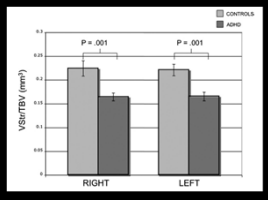
Mixed findings

- Perlov et al, 2008
  - Adults ADHD (n=27) vs HC (n=27)
  - Non-significant differences in amygdala volumes
  - *1.5 Tesla MRI*

J Psych Neuro, 2008

Ventral Striatal in ADHD Youth

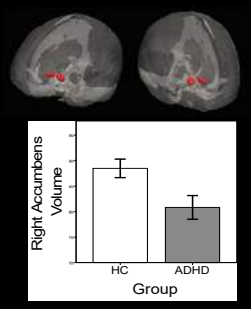
- Carmona et al, 2009
  - ADHD (n=42) vs HC (n=42)
  - Age 6-18
  - Reduced ventral striatal (accumbens) volumes
  - R ventral striatal volumes correlated with hyperactive/impulsive symptoms



Bio Psych, 2009

Nucleus Accumbens in ADHD Youth

- Cha et al, 2015
  - ADHD (n=30) vs HC (n=31)
  - 6–13 years old
  - Reduced right accumbens volumes
  - Correlated with impulsivity (measured by CPT)



Neuropsychopharm, 2015

ENIGMA study

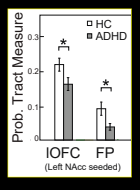
- ADHD (n=1,713) vs HC (n=1,529)
- 23 sites internationally
- Median age of 14 years (4–63 years)
- Reduced amygdala and accumbens volumes
  - Amygdala showed largest effect size of all subcortical regions

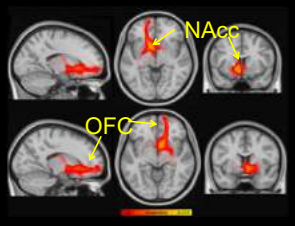
	Cases (n=799)	Controls (n=1529)	*d* (95% CI)	for diagnosis
Accumbens	776	1484	−0·12 (−0·21 to −0·03)	0·0069
Amygdala	753	1474	−0·18 (−0·27 to −0·10)	>0·0001
Caudate	777	1502	−0·10 (−0·19 to −0·01)	0·0248
Hippocampus	757	1446	−0·08 (−0·17 to 0·003)	0·063
Pallidum	776	1484	0·01 (−0·07 to 0·10)	0·74
Putamen	784	1508	−0·13 (−0·22 to −0·04)	0·0037
Thalamus	692	1253	−0·03 (0·04 to −0·12)	0·53
Intracranial volume	793	1512	−0·06 (0·04 to −0·16)	0·15

Lancet Psych, 2017

Mesolimbic structural connectivity

- ADHD (n=30) vs HC (n=31)
- 6–13 years old
- Reduced structural connectivity between the accumbens and orbitofrontal cortex

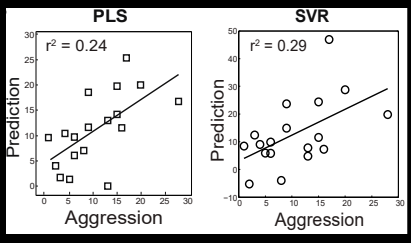




Neuropsychopharm, 2015

Mesolimbic circuit & Aggression

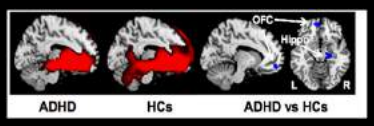
- Machine learning
- 24-29% variance in aggression accounted for by mesolimbic connectivity
- Parent reported CBCL



Neuropsychopharm, 2015

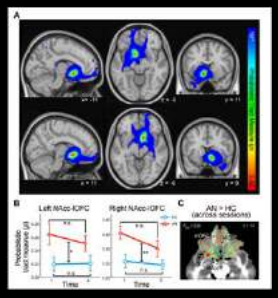
Mesolimbic – functional connectivity

- ADHD (n=22) vs. HC (n=20)
- Ages 7-12
- Reduced functional connectivity between the accumbens and OFC
- Correlated with emotional lability



Psych Research, 2013

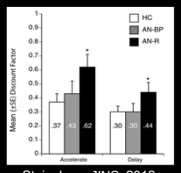
Trans-diagnostics - Anorexia



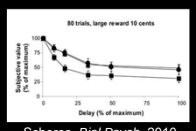
- Anorexia nervosa (AN, n=22) vs HC (n=18)
- Ages 16-25
- MRI before & after weight restoration
- Increased structural connectivity between the accumbens and OFC in AN
- Correlated with AN symptom severity

Human Brain Mapping, 2016

Delay of Gratification



Steinglass, *JINS*, 2012

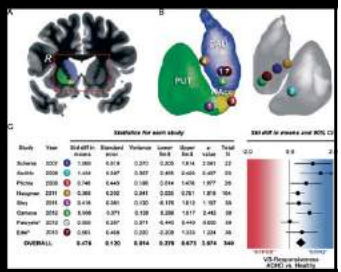


Scheres, *Biol Psych*, 2010

- **Anorexia** - Increased capacity to delay gratification
- **ADHD**- Decreased capacity to delay gratification

Task fMRI studies

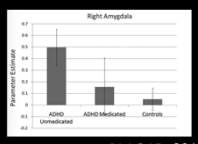
- 7 MRI studies of reward processing (MIDT) in ADHD
- Adolescents & adults with ADHD
- Hypoactivation of VS during reward anticipation in 6 or 7 studies
- Moderate effect size (d = 0·48)



Neuro & Biobeh Reviews, 2014

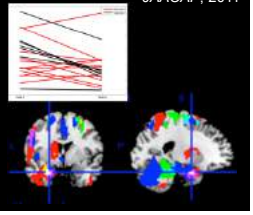
Amygdala function

- ADHD (n=15) vs HC (n=15)
- Masked fear faces
- Left amygdala hyperactivity in ADHD
- Stimulant normalized



JAACAP, 2011

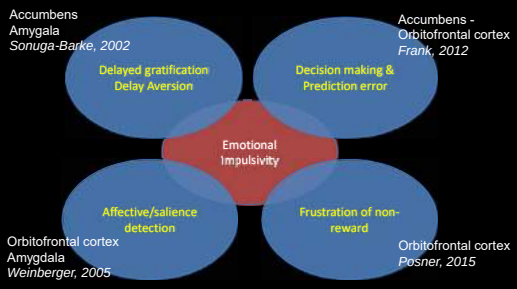
- ADHD (n=28) vs HC (n=16)
- Pre-treatment
  - ADHD shows amygdala hyperperfusion
- Post-treatment
  - Lisdexamfetamine reduces left amygdala hyperperfusion



Summary

- Abnormal mesocortical circuitry in ADHD based on:
  - Volumetrics
    - Amygdala
    - Nucleus accumbens
  - Structural and functional connectivity
    - Nucleus accumbens <–> orbitofrontal cortex
  - Function (task & perfusion)
    - Nucleus accumbens
    - Amygdala

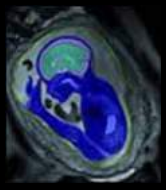
What does it mean?



Future Directions

- Mesolimbic circuit as a target for prevention
- 20-30% ADHD attributable to environmental causes

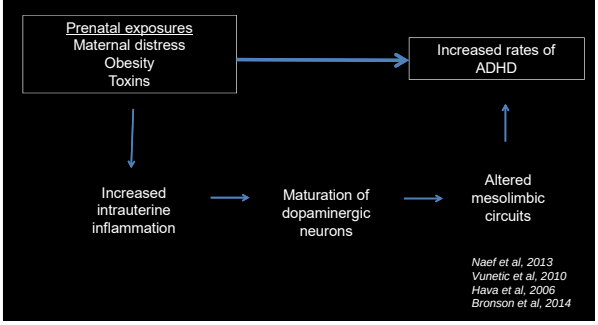
Fetal programming → Mesolimbic circuits



Intra-uterine environment

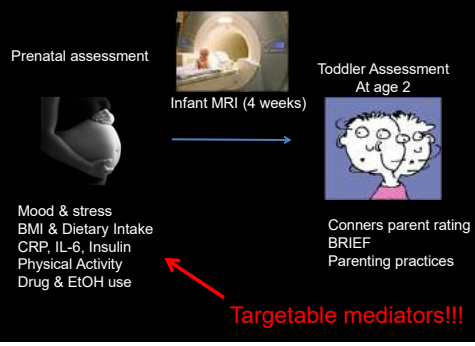
- Prenatal maternal anxiety/depression - "distress"
  - ADHD symptoms at age 6 (O'Connor et al, 2003)
  - 22% of variance in ADHD symptoms at age 8-9 (Van den Bergh et al, 2004)
  - CPT performance at age 15 (Van den Bergh et al, 2006)
- Prenatal maternal obesity
  - Increased risk for ADHD
  - Replicated across 7 cohorts & nearly 400,000 children (Fernandes et al, 2012)
- Toxins -prenatal flame retardants (PBDEs)
  - CPT performance at age 5 & ADHD symptoms at age 7 (Eskenazi et al, 2013)
  - ADHD symptoms at age 4 (Cowell et al, 2015)

Mechanisms



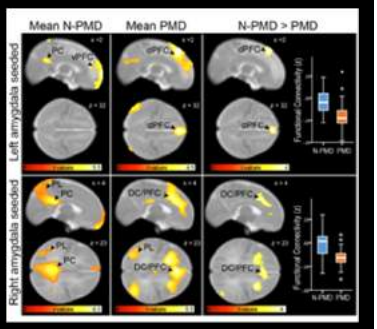
Naef et al, 2013
Vunetic et al, 2010
Hava et al, 2006
Bronson et al, 2014

Study Design



Prenatal maternal depression

- 20 infants exposed & 44 unexposed
- Non-sedated resting fMRI scans at 4-6 weeks
- Atypical connectivity with prefrontal, posterior cingulate, and parietal lobes (DMN)
- Behavioral/clinical correlates



Trans Psych 2016

Acknowledgements

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Infant studies

Jiook Cha, PhD
Diffusion tractography