Impulsivity and Substance Use Disorders

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Conflict

DSMB member for Lundbeck – no relation to current presentation

Outline

- Relationship between ADHD and SUD
- Role of impulsivity in the development of SUD in individuals with ADHD
- Relevance to clinical management of ADHD and SUD

ADHD and SUD Co-occurrence

- Among adults with ADHD
  - 45% lifetime prevalence of SUD [1]
  - Comorbid personality/mood disorder ↑ risk for addiction vs. ADHD alone[2]
- Among adults with SUD
  - 15% to 25% are also diagnosed with ADHD[3]
- ICASA studies
  - 75% of ADHD+SUD patients ≥ 1 comorbid disorder vs. 37% of SUD patients without ADHD[4]
  - ADHD in tx seeking adults w/ SUD ranges from 5.4-7.6% to 31.3-32.6% pending on nomenclature (DSM-IV or DSM-5) and geographical region[5]

1. Jacob et al. *Eur Arch Clin Neurosci.* 2007. 2. Biederman et al. *Am J Psychiatry.* 1995. 3. 2. Wilens. *Psychiatr Clin North Am.* 2004 4 van Emmeric et al., Addiction 2014; 5 van de Glind et al., 2014 Drug Alcohol Depend,

ADHD Sx Domains and SUD

- All ADHD subtypes associated with SUD, however…

  - Hyperactive/impulsive sx ➔ stronger association – impulsivity might be a precursor of SUD

    (DeAlwis et al., Addict Behav. 2014)

  - Inattention ➔ more severe cannabis use, craving, and problem use-related outcomes

  - Hyperactivity ➔ earlier initiation of cannabis

    (Bidwell et al., Drug Alcohol Depend 2014)

Developmental Relationship Between ADHD and SUD

- If disorder A precedes disorder B, then does A cause B?
- How does the course for disorder A impact the development of disorder B?

Possible Physiologic Mechanisms for the Development of SUD

- Persistent patterns of impulsive behaviors[1]
- Altered motivation via changes in the sensitivity of the brain reward system[2]
- Persistence of negative emotional states[3]
- Sensitization hypothesis[4]

1. Tarter et al. *Am J Psychiatry.* 2003
2.. Blum et al. *J Psychoactive Drugs. 2000*
3. Koob, Kreek. *Am J Psychiatry.* 2007
4. Robinson, Berridge. *Brain Res Brain Res Rev.* 1993

Is Impulsivity a Mediator for Later-in-life SUD?

- Higher neurocognition inhibition predicts higher rates of SUD in early adulthood[1]
- Impulsivity/inhibitory control and sensitivity to rewards
  - positive correlation in controls[2]
  - inverse correlations in ADHD [3]
- Impulsivity trait may affect both behavioral inhibition and reward sensitivity

1. Tarter et al. *Am J Psychiatry.* 2003
2. Hariri et al. *J Neurosci.* 2006
3. Plichta & Scheres Neurosci Biobehav Rev. 2014

Definition of Impulsivity

- Action without foresight
- Characterized by poorly conceived and/or prematurely expressed actions that
  - Are inappropriate for a particular situation
  - Are unduly risky
  - Often result in undesirable consequences
- Response inhibition—objective measure of impaired ability to withhold inappropriate response
  - Motoric (Go/No-Go, Stop Signal tasks)
  - Cognitive (Stroop, Simon, Flanker tasks)
  - Decision-making involving risk (Gambling tasks)

Winstanley et al. *Clin Psychol Rev.* 2006;26(4):379-395.

Impulsivity in ADHD and SUD

- Impulsivity (*DSM* criteria in ADHD)
  - Blurts out answers
  - Can't wait for turn
  - Intrudes/interrupts others
- No *DSM* impulsivity criteria for SUD
- Impulsivity in adults w/ ASPD, BDPD
  - acting on impulsive urges w/out considering the consequences – loss of employment, accidents, legal difficulties, and incarceration
  - angry outbursts
  - engage in impulsive behaviors such as substance abuse, risky sexual liaisons, self-injury, overspending, or binge eating

Impulsivity in ADHD and SUD

- ADHD individuals show deficits in inhibitory control, working memory, motivation and motor control[1]

- Impulsivity variables (SST, BIS-11, comorbid impulsivity disorders) ↑ risk for alcohol use d/o in both in men and women[2]

1. Barkley. *Psychol Bull*. 1997
2. Rubio et al. *Alcohol Clin Exp Res*. 2008

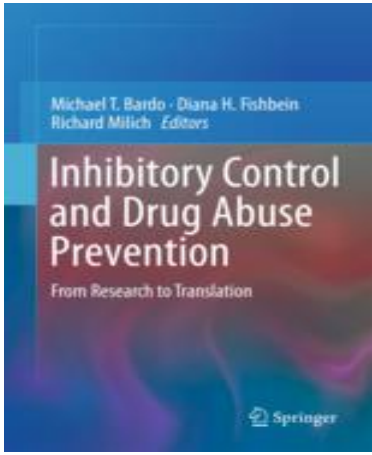
Impulsivity Concepts

- Distinction between self reports vs. objective measures of behaviors on tasks (Ivanov et al. 2008)

- Independent forms of behavior (Romer 2010)
  a) acting without thinking (no deliberation or attention to the environment) - Go/No GO, Stop Signal, Interference tasks
  b) impatience - choice for immediate/small vs. larger/delayed reward - Delay Discounting Task
  c) sensation seeking - the tendency to pursue and try new/exciting experiences

- Processes underlying impulsivity (Dick et al., 2010)
  a) positive and negative urgency;
  b) tendency to act without deliberation;
  c) lack of perseverance/inability to filter out distractions
  d) tendency to seek out novel/exciting stimulation

Variety of the above are observed in ADHD and SUD
But also in CD and ASPD/BPD



Impulsivity Facets, ADHD and SUD

- ADHD sx clusters and forms of impulsivity
  - UPPS-P Impulsive Behavior Scale w/ 5 components:
    negative urgency (NU), lack of premeditation (PRE), lack of perseverance (PERS), sensation seeking (SS), positive urgency (PU)

- Alcohol
  - **PRE** related to HI sx and alcohol use (e.g. lack of foresight and poor planning (as in ADHD) may contribute to elevated alcohol use)

- Tobacco/marijuana
  – **NU** (i.e. failure to inhibit strong impulses while experiencing strong negative emotions) related to HI sx and nicotine/marijuana use as coping w/ negative emotions

(Roberts et al., Addict Behav. 2014)

Impulsivity Facets, ADHD and SUD

- Impulsivity facets did not account for the relations of IA sx with SUD
  - IA may increase risk of SUD through a non-impulsivity pathway (i.e. poor academic achievement, affiliation w/ deviant peers Molina et al., 2012)
  - self-medicate cognitive deficits as nicotine improves cognitive functioning in ADHD (Levine et al., 1996)

- IA and HI symptoms may lead to SU via separate pathways

(Roberts et al., Addict Behav. 2014)

ICASA Multifaceted Concept of Impulsivity

- Three processes mediate the link btwn ADHD and SUD
  - *Impulsive action*
  - *Impulsive choice*
  - *Sensation seeking*

- These impulsivity-related constructs are associated w/ distinct cognitive, developmental, and neural processes.

Slobodin et al., in submission

ICASA Multifaceted Concept of Impulsivity

- ADHD individuals vary in level/type of impulsivity and vulnerability for SUD so impulsivity components should be measured independent of ADHD dx

- Impulsive action/impulsive choice are inversely related w/ executive function whereas sensation seeking is positively related to working memory (Romer et al., 2011)

- PFC is central in both impulsive action and impulsive choice (McClure et al., 2004, Rieger et al., 2003) whereas the limbic system is central in sensation seeking (Galvan et al., 2006)

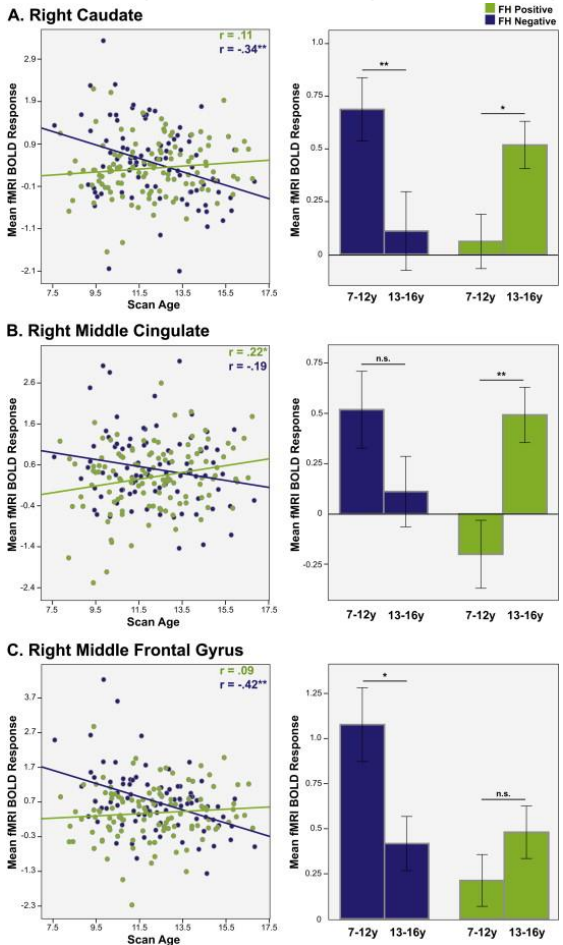
ICASA Multifaceted Concept of Impulsivity

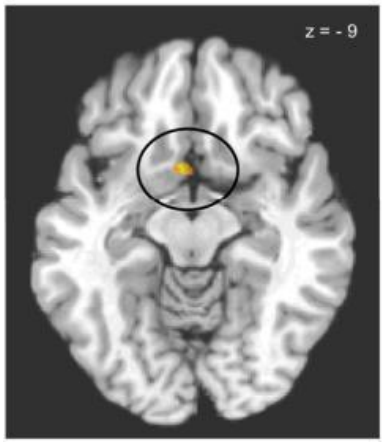
- Differences in maturation

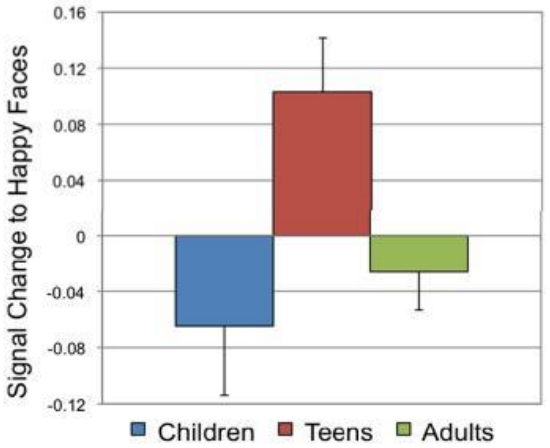
  - sensation seeking peaks in pre-/ middle adolescence then decreases

  (Harden & Tucker-Drob, 2011; Steinberg, et al., 2008, *Somerville, Hare, Casey. J Cogn Neuroscience 2011)*

  - inhibitory control gradually diminishes (Hardee et al., 2014)







ICASA Multifaceted Concept of Impulsivity

- Traditional screening for ADHD/SUD may miss individuals w/ low hyperactivity/ high impulsivity as they may not meet dx criteria for hyperactivity-impulsivity cluster

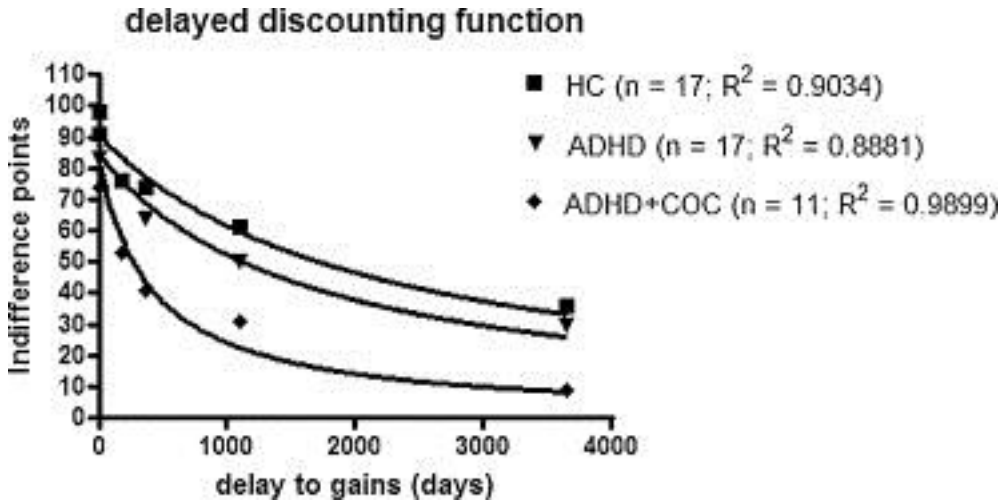
- Precise evaluation of impulsivity-related constructs in ADHD/SUD independently of dx may allow for identification of high risk individuals

- Different impulsivity facets may respond differently to different medications (Broos et al., 2012)

Additional Clinical Considerations

Impulsivity in ADHD/SUD

- ADHD + cocaine dep vs. ADHD - cocaine dep/controls
  - higher levels of motor and cognitive impulsivity
  - BIS self-report - significant differences on attention only



- ADHD + cocaine dep ➔ distinctly more impulsive subpopulation vs. ADHD - cocaine dep on objective impulsivity measures

Crunelle et al., Drug Alcohol Depend 2013

ADHD/SUD Co-occurrence

- ADHD + SUD and stim tx
  - 58.5 % had one or more relapses of SUD during stim tx (m - 27.9 mo)
  - Younger age and comorbid ASPD ↑ risk for relapse during stim tx
  - Cannabis abstinence >12 mo was a negative predictor for SUD relapse

- ADHD alone show no onset of SUD during stim tx (m - 41.1 mo)

- Stim treatment does not precipitate onset of SUD in adults without previous SUD

Torgersen et al., 2013, Atten Defic Hyperact Disord

Additional Clinical Questions

- Do impulsive individuals have altered sensitivity to the rewarding effects of alcohol/drugs?

- Do biological underpinnings of impulsivity/reward sensitivity suggest differential response to pharmacological agents

Impulsivity, Reward Sensitivity and SUD Risk

- Motivation

  Preference for drug rewards

  *Volkow et al., 1999; Hommer et al., 2011**

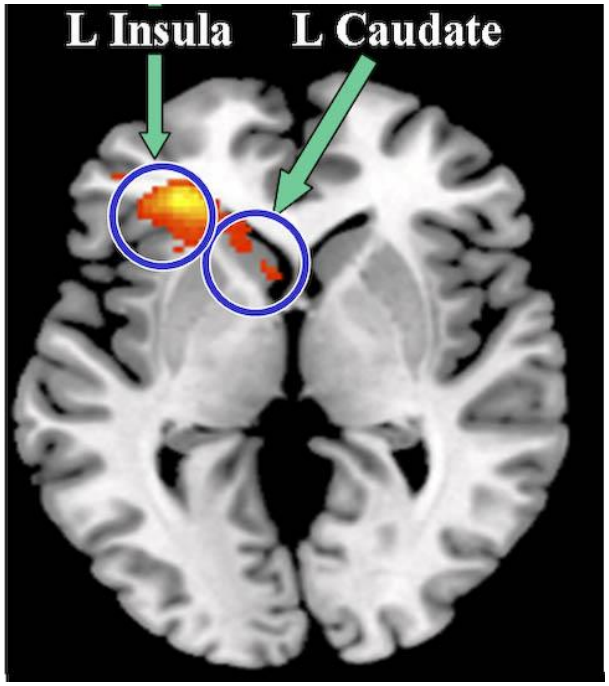
  * Majority of studies in adults exposed to drugs

- Behavioral control

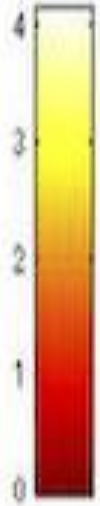
  High impulsivity = ↓ behavioral control

  Tarter et al., 2006; Ivanov et al., 2008

Activation Differences in ADHD



A.



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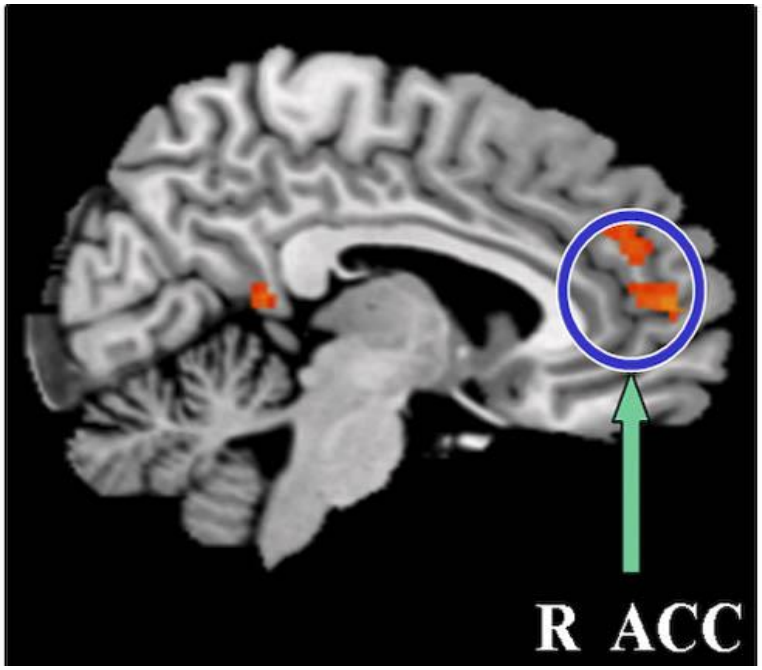


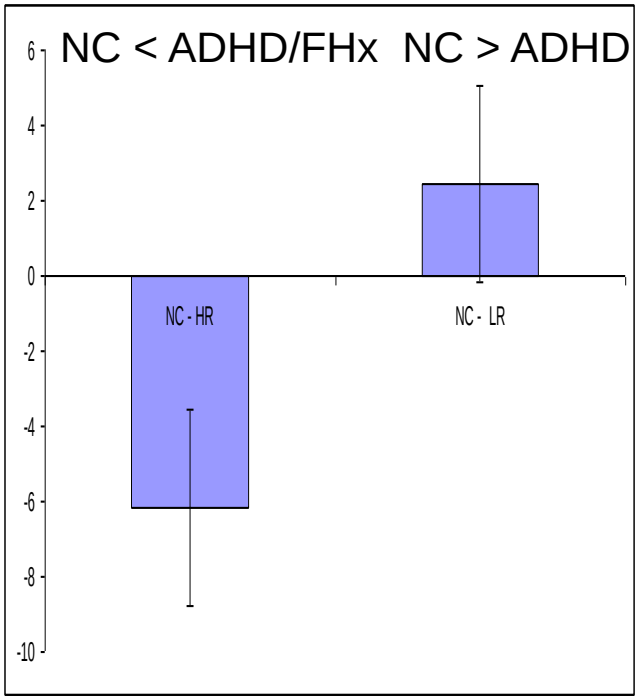
A) Reward cues/outcome activation in the left caudate/Insula HR>LR
B) Conflict activation in the Right ACC LR > HR (Ivanov et al., 2012, Psych Res Neuroimaging)

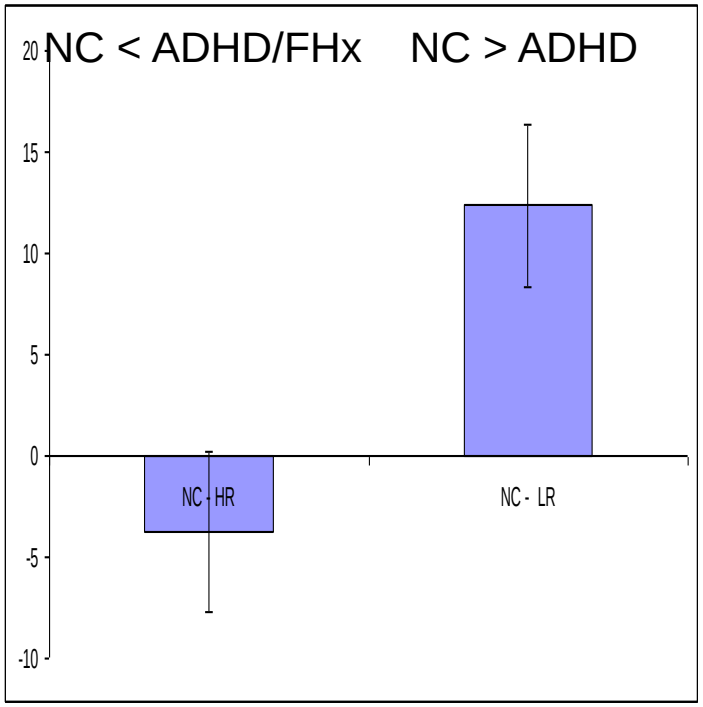
Preliminary data supporting a model of elevated reward processing with deficits in conflict resolution in children with cumulative risk for SUD (ADHD + parental SU)

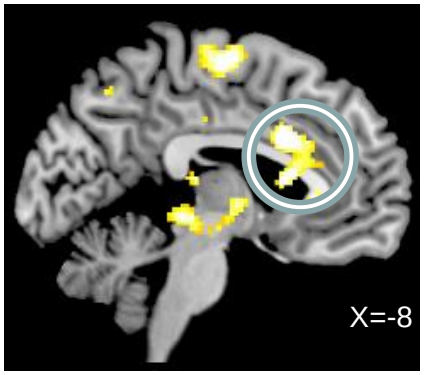
Paloyelis et al., J Am Acad Child Adolesc Psychiatry. 2012
Lemiere et al., Brain Res. 2012

Activation Differences in ADHD

Parameter Estimates



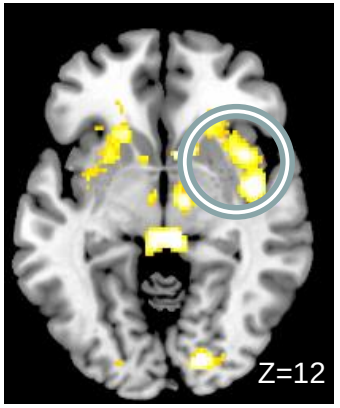




ACC

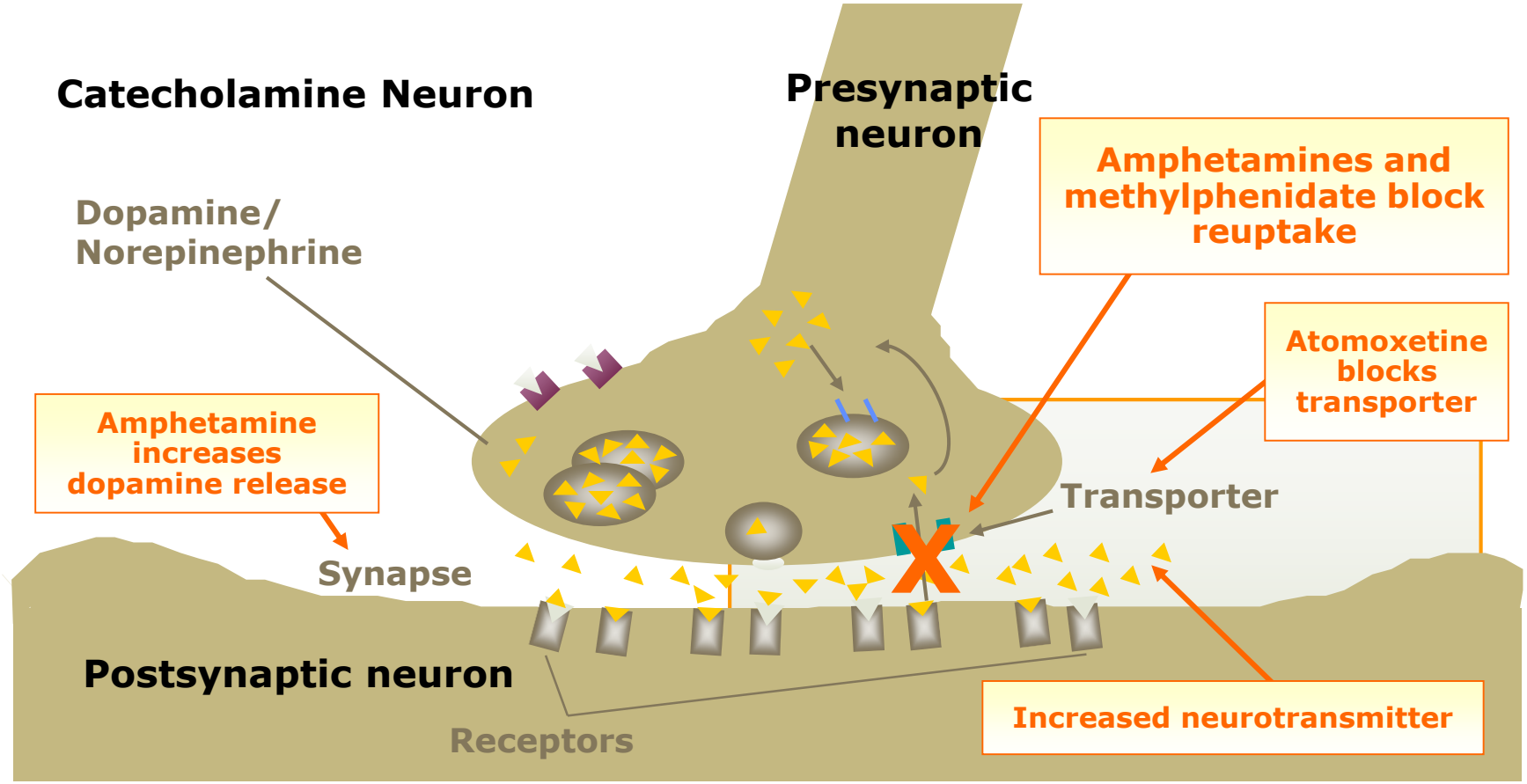
Insula

Reward cue + Incongruent Flanker



Impulsivity – Biological Correlates

Catecholamines – presumed deficits since agents that increase DA, NA improve ADHD sx and diminish impulsivity



Impulsivity – Biological Correlates

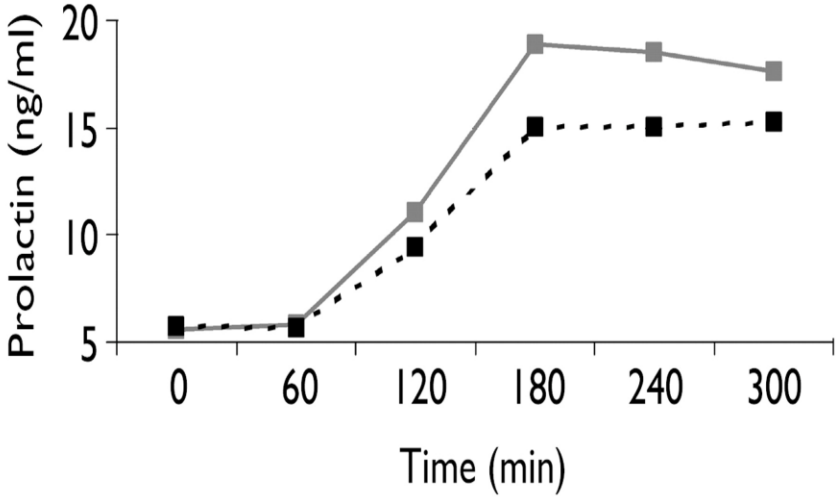
- Role of serotonin

  - Evidence for both elevated and dampened serotonergic activity (Pattij & Schoffelmeer, Eur J Pharm 2014)

  - Low prolactin response linked to ASPD/impulsive aggression in

    **adolescence* *(Flory et al., British J Psych 2007)*

    **adulthood* *(unpublished)*



Long Term Effects of MPH

- Evidence from longitudinal studies suggest mostly neutral effect of MPH/stim tx in childhood and later SUD

- Animal studies on behavioral effects of MPH vs. Atomoxetine (Jordan et al., 2014; Ansquer et al., 2014)

- One fMRI report on MPH vs. Atomoxetine tx effects in youth w/ ADHD (Schulz et al., 2012)

- Different mechanisms of action may be relevant for subgroup of individuals w/ elevated/cumulative risk for SUD

Treatment in Individuals with ADHD and SUD

- Stimulants are effective in controlling ADHD- related symptoms,[1,2] *but* have limited efficacy in controlling current SUD symptoms
- Treatment is most effective when stimulants are used with concurrent treatments for SUD (group therapy, CBT)
- Use w/ caution due to diversion/abuse potential,[3] *and* should include education on misuse and diversion[6]

1. Mariani, Levin. *Am J Addict*. 2007
2. Riggs et al. *J Am Acad Child Adolesc Psychiatry*. 2004
3. Newcorn, Ivanov. Risk-benefit considerations in ADHD pharmacotherapy. 2006.http://www.princetoncme.com/pdf/
4. Wilens et al. *J Am Acad Child Adolesc Psychiatry*. 2008;

ADHD and SUD: Clinical Considerations

- Alternative tx for ADHD sx (including impulsivity)
  - Atomoxetine (due to different neurophysiological effects)
  - Lisdexamfetamine (due to slower brain uptake)
  - Bupropion
  - Guanfacine XR
- Tx for impulsivity related to comorbid SUD &mood/anxiety
  - SSRIs/SNRIs (citalopram[1], escitalopram/reboxetine[2])
  - Mood stabilizers (depakote/lamotrigine[3], topiramate[4])
  - DA blocking agents (e.g. atypical antipsychotics[5])

1. Bezchlibnyk-Butler et al., J Psychiatry Neurosci. 2000
2. Camarasa et al., Prog Neuropsychopharmacol Biol Psychiatry 2005
3. Wang et al., Psychopharmacol Bull. 2010
4. Lane et al., Pharmacol Biochem Behav. 2009
5. Kishi et al., J Clin Psychiatry. 2013

Clinical Vignette

A Young Man with History of ADHD and Methamphetamine Use

- Referral – “recommended” by GF
- Effects of ADHD – professional (days off work, postponing licensing exam) personal
- Engagement – present both rules and options
- Discuss safe tx management – non-stim vs. stims
- Outcome

Leikauf, Ivanov Psychiatric Annals 2013

Summary

- ADHD/SUD frequently co-occur and may share common biological underpinnings
- Comprehensive assessment (as per multifaceted impulsivity construct) may allow for more precise identification of individuals at risk
- In theory

  - better control of impulsivity sx should reduce risk;

  - successful stim treatment may be protective (evidence is lacking)

- Alternative tx should be considered for individuals at elevated risk for SUD