Emerging Treatments for Social Disconnection in Psychiatric Illness

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“The voices get quiet during book club.”

Outline

- Social disconnection
- Social symptoms of psychiatric illness
- Social psychopharmacology: two examples
- Take-aways and future directions

How Common is Lack of Social Connection?

Feeling Lonely

About 1 in 3 adults in the U.S.

Lack of Social & Emotional Support

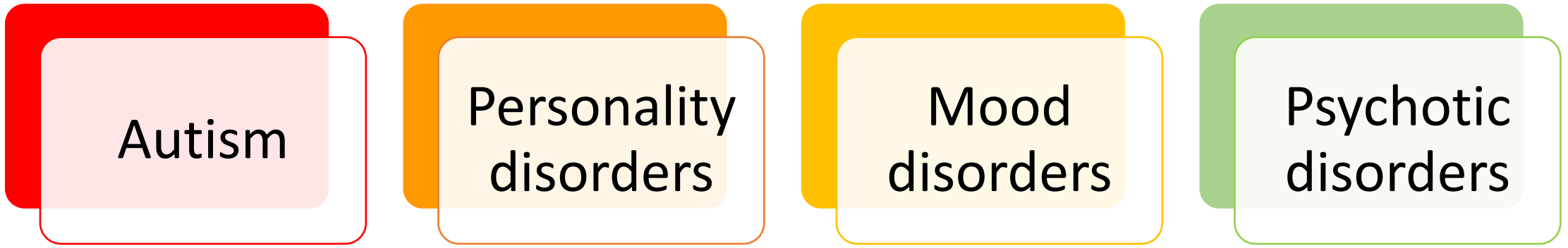
About 1 in 4 adults in the U.S.

cdc.gov

Health effects of social disconnection and loneliness

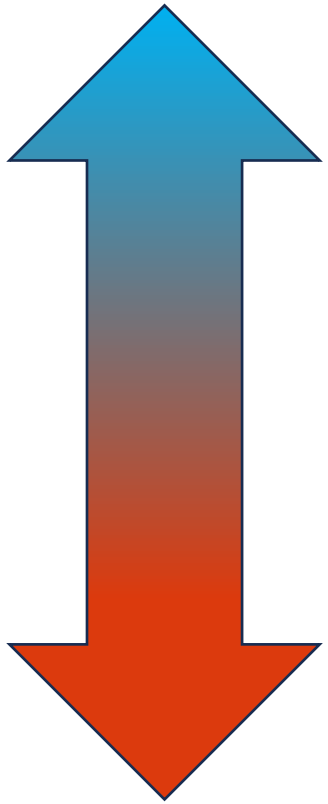
- Physical health effects (Holt-Lunstadt 2024, Na et al. 2023)
  - Cardiovascular disease
  - Weakened immune system
  - Higher mortality
- Mental health effects (Lutz et al. 2021)
  - Depression and anxiety
  - Suicide
  - Substance abuse
  - Cognitive symptoms

Problems with social function span the spectrum of psychiatric illness



Social symptoms

- Social anhedonia (lack of social pleasure)
- Asociality (low social motivation)
- Social cognitive problems
- Social anxiety
- Paranoia



Reduced reactivity to positive social input

Heightened reactivity to negative social input

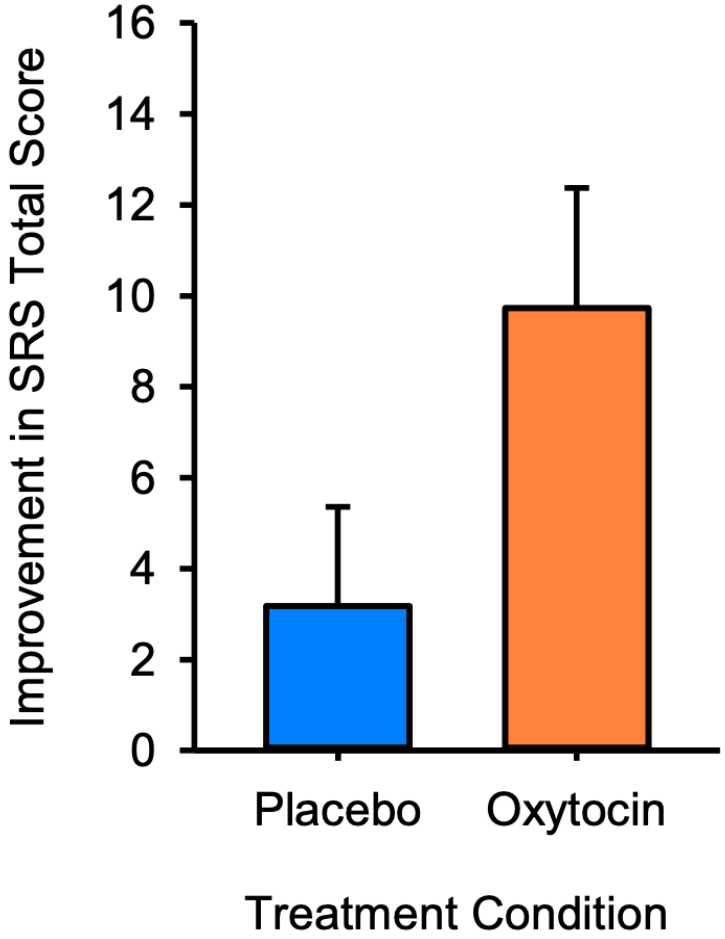
Social psychopharmacology: How can we use drugs to improve social function?

How can we measure social symptoms?

Clinical interviews	Self-report	Behavioral measures	Brain-based measures
• Symptom ratings	• Subjective ratings	• Attention bias tasks • Performance-based measures	• fMRI • EEG

Oxytocin: the “love hormone?”

Intranasal oxytocin to treat social deficits?



Parker et al. PNAS 2017

Problems with oxytocin

- Absorption
- Social context
- Personal factors
  - Personality
  - Sex
  - Menstrual cycle phase

Psychoactive drugs in the treatment of social deficits

"I felt like hugging everyone. Hugging was the most rewarding, comforting, uplifting experience."

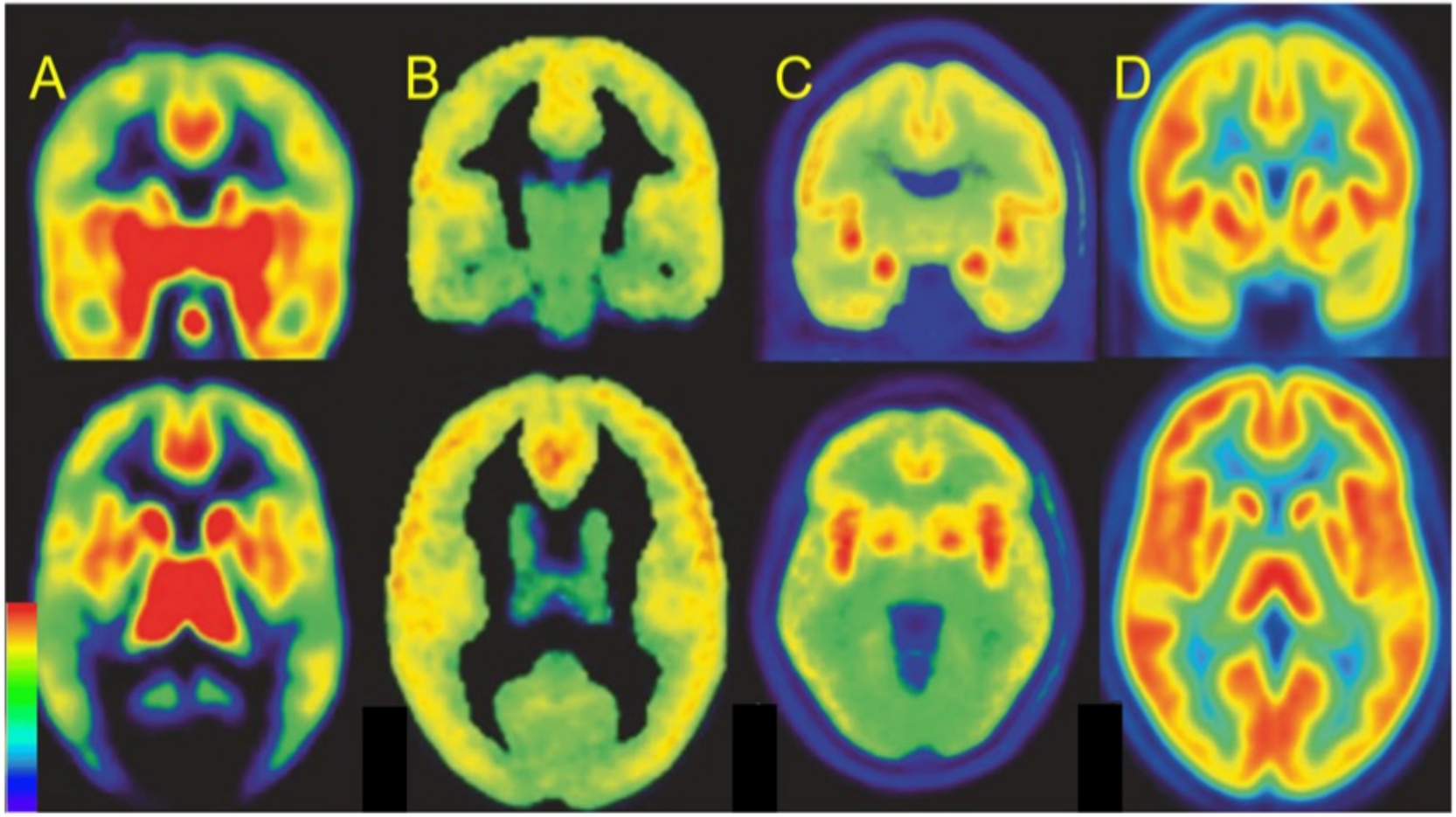
–Ecstasy experience report, www.erowid.com

<u>Two examples:</u>

- Buprenorphine
- MDMA

The endogenous opioid system

Mu (MOR) Delta (DOR) Kappa (KOR) Nociceptin (ORL1)



Cumming et al. 2019

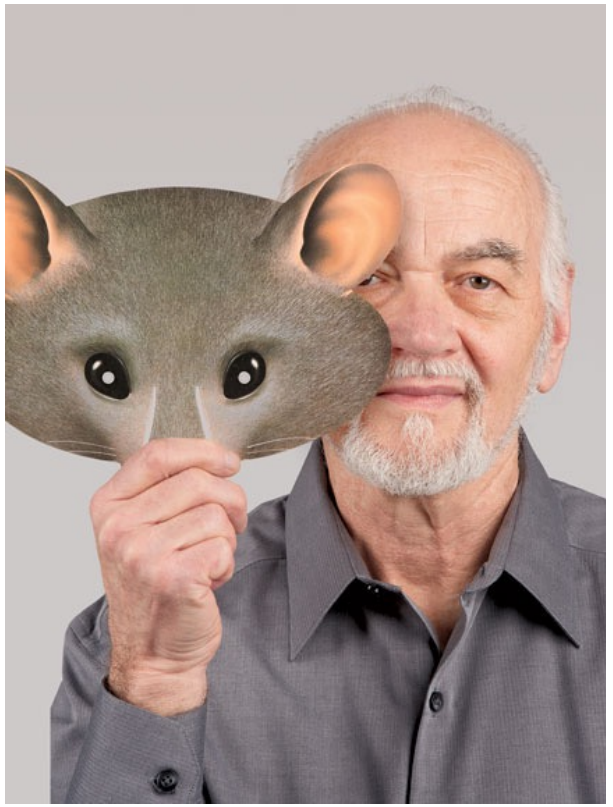
The social effects of mu- and kappa-opioids

Increased kappa opioid signaling

Increased mu opioid signaling

Negative social feelings

Positive social feelings



Jaak Panksepp
"The Brain-Opioid Theory of Social Attachment"

Buprenorphine: An opioid social buffer?

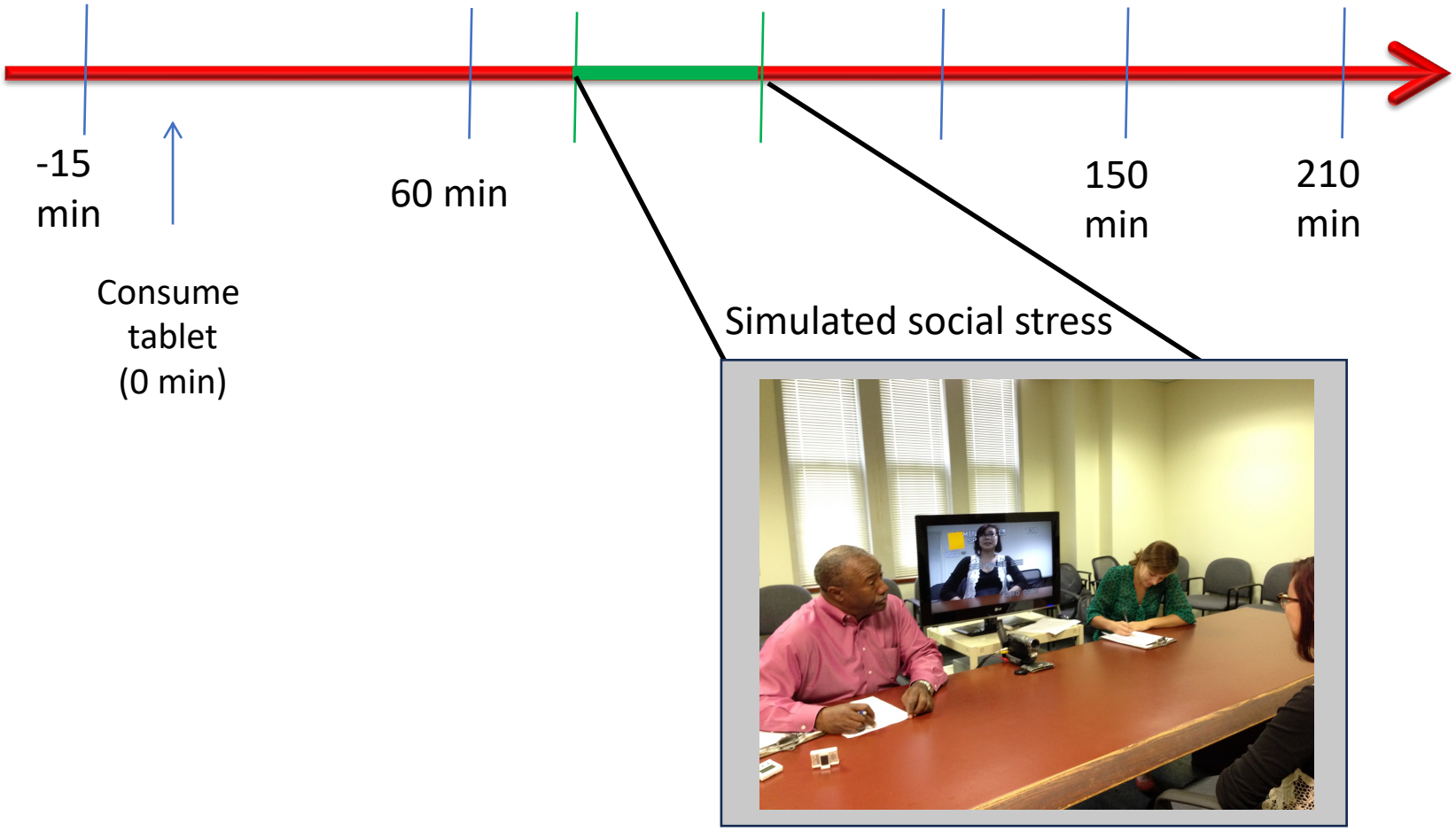
- Compound action on mu and kappa opioid systems
- Treats opioid use disorder at higher doses and suicidality at lower doses
- May increase positive social feelings and reduce negative social feelings

Does buprenorphine reduce responses to social stress?

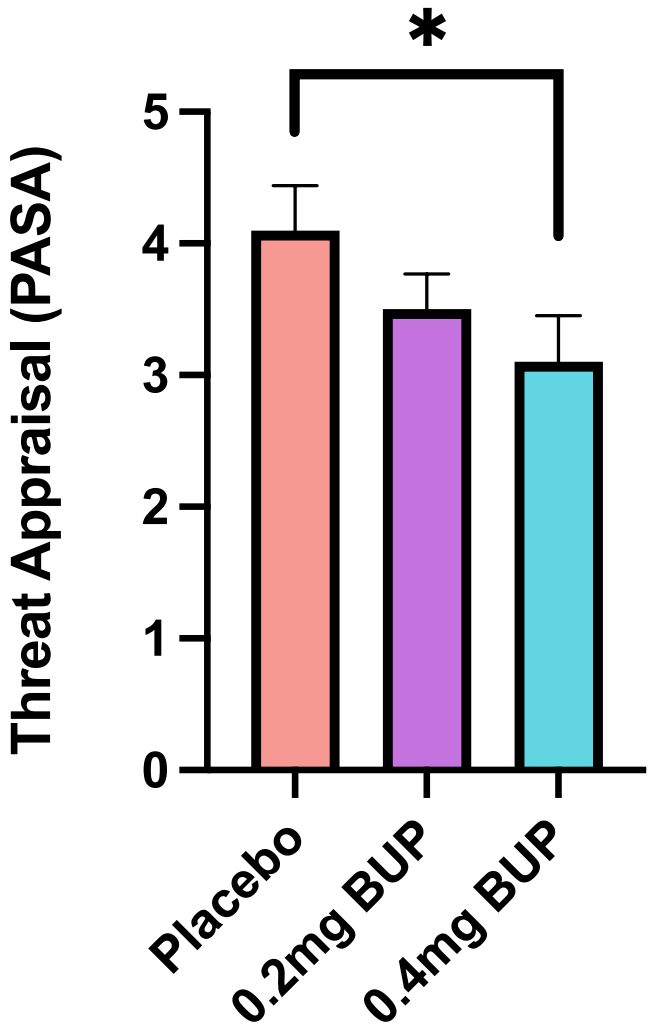
- Healthy adult participants (N=45)
- Placebo controlled, randomized
- Three groups:
  - Placebo
  - 0.2mg buprenorphine
  - 0.4mg buprenorphine
- Two sessions:
  - Trier social stress test
  - Non-stressful control task

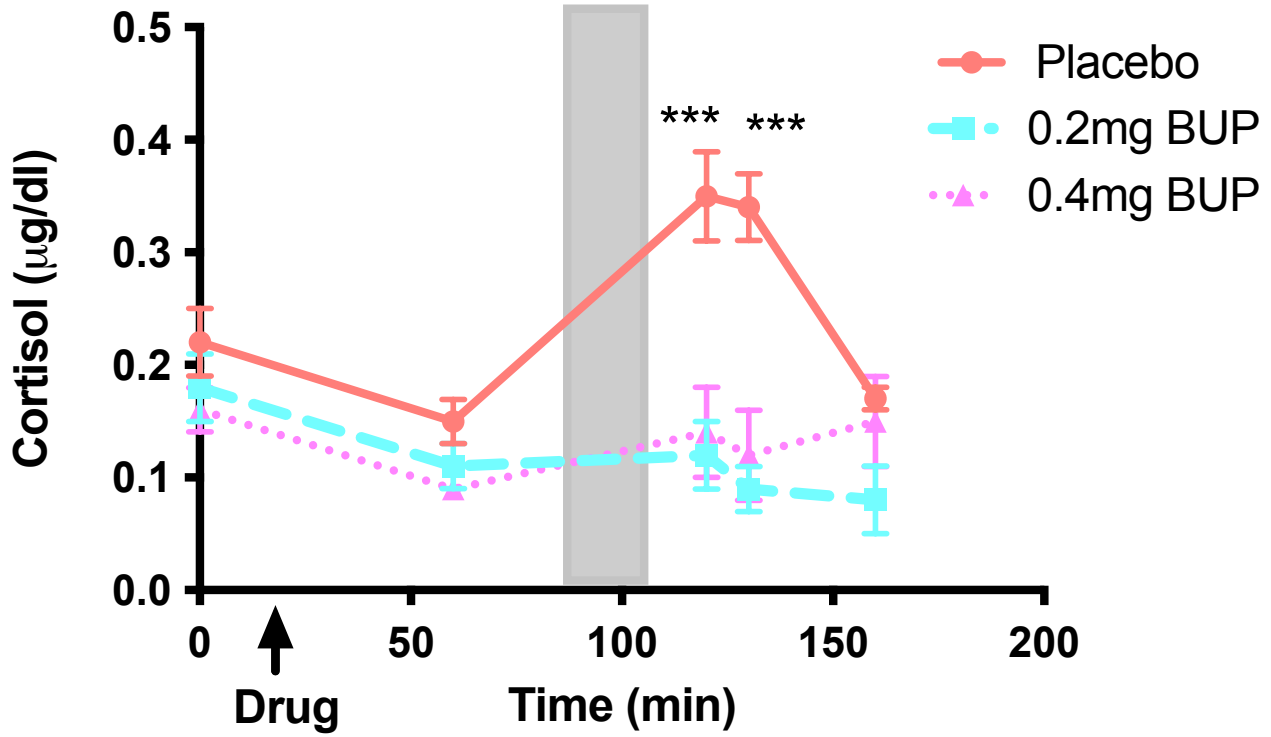
"Living room style" laboratory

Session Timeline



Buprenorphine reduces responses to social stress

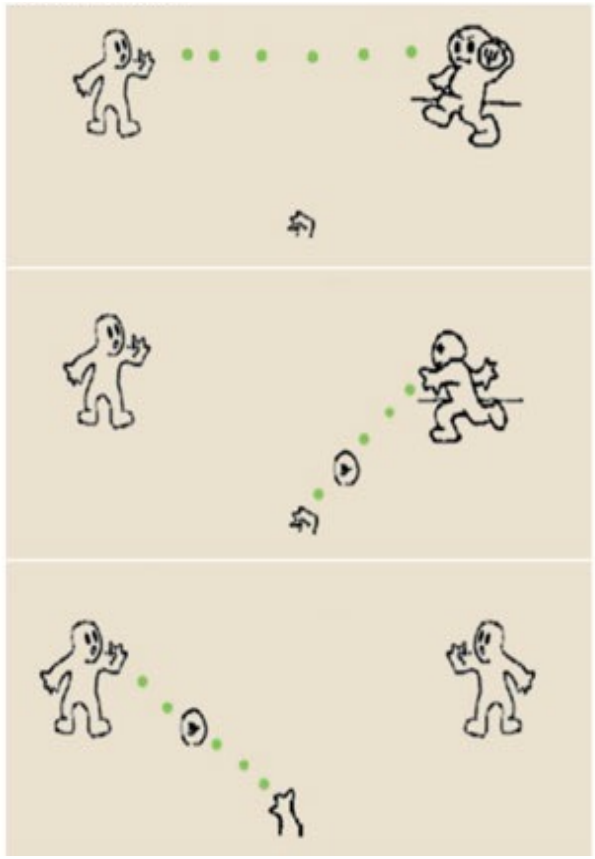




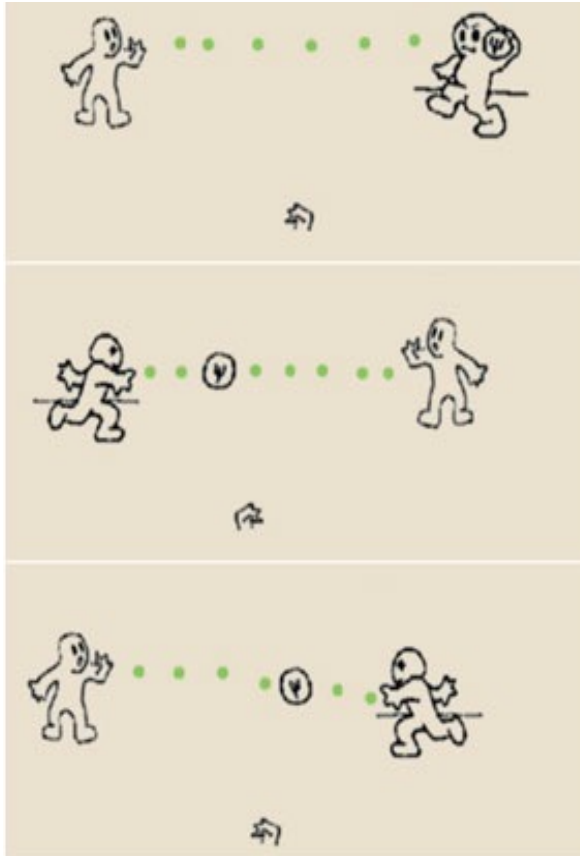
Bershad *et al.* 2016

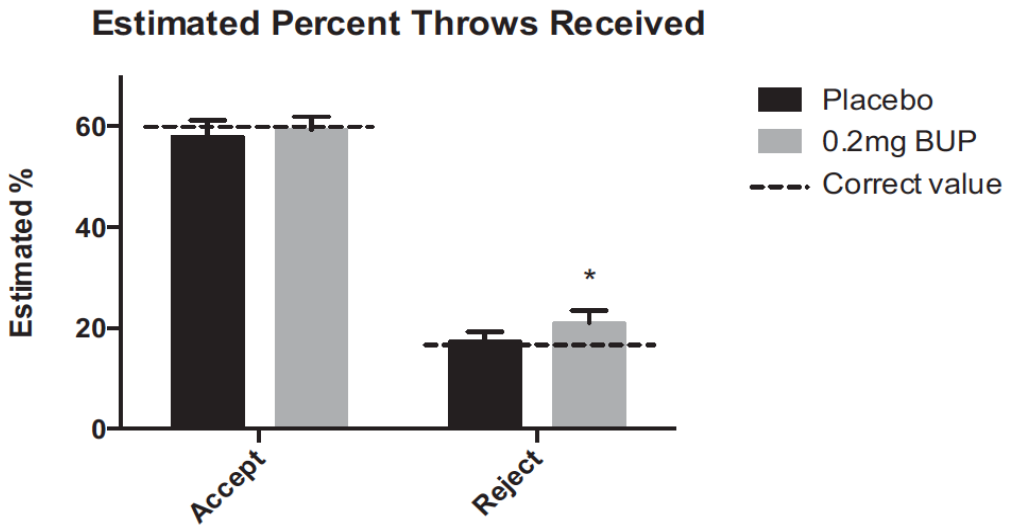
Buprenorphine reduces responses to social rejection

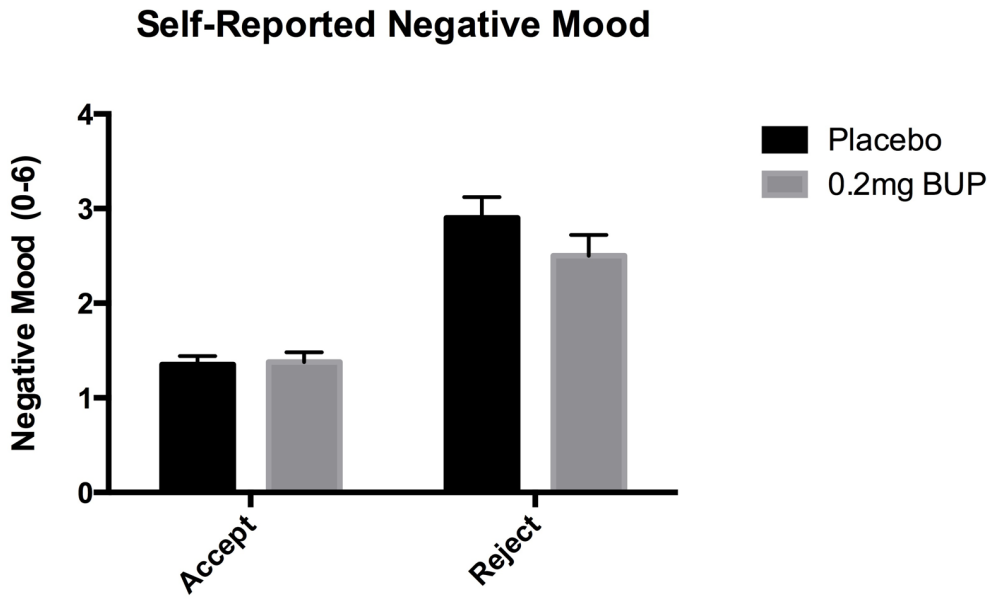
Accept condition



Reject condition



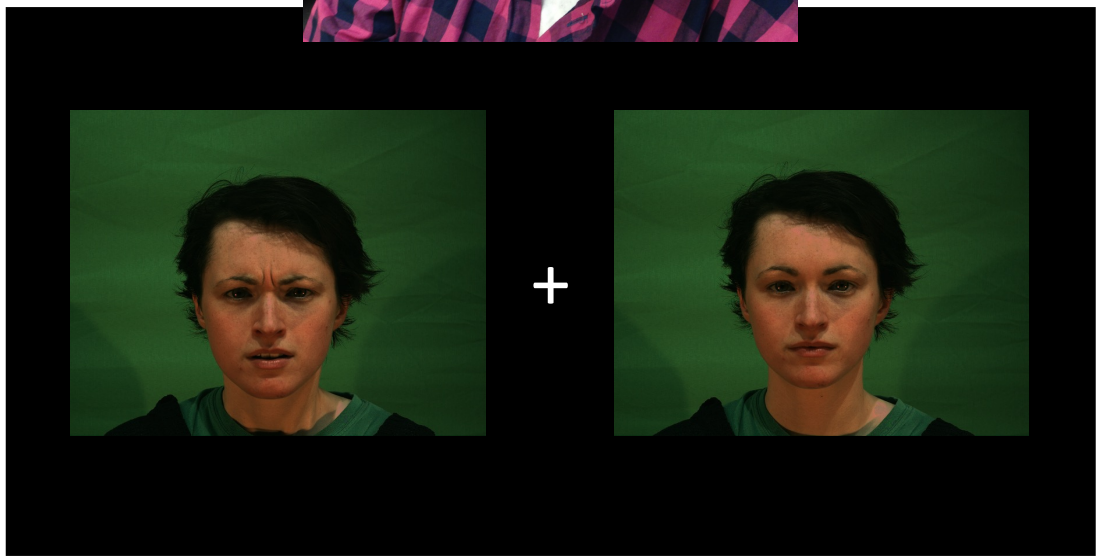




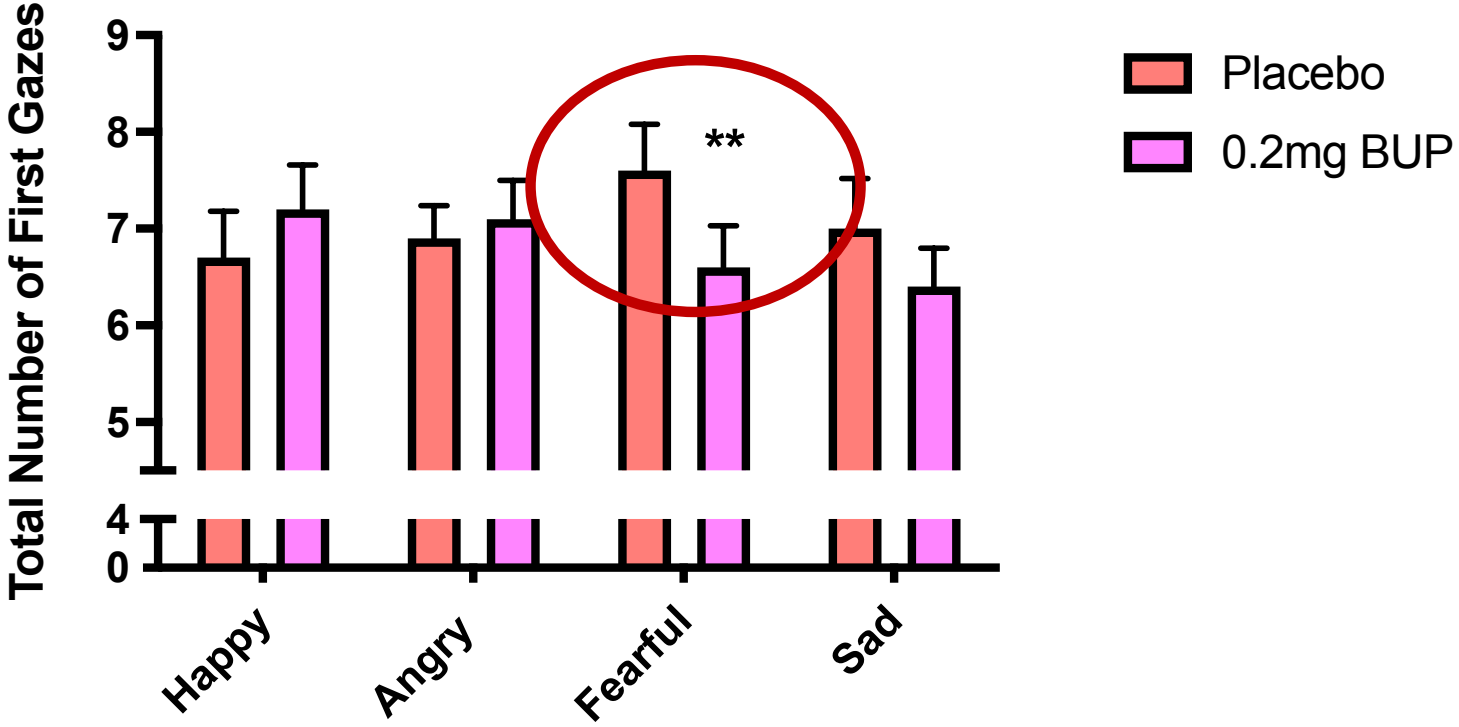
Bershad *et al*. Psychoneuroendocrinology 2016

Social Attention Bias Task

- “Social seeking”
- Emotive and neutral faces side-by-side
- Electro-oculography or eye tracking
- Measure where participant looks

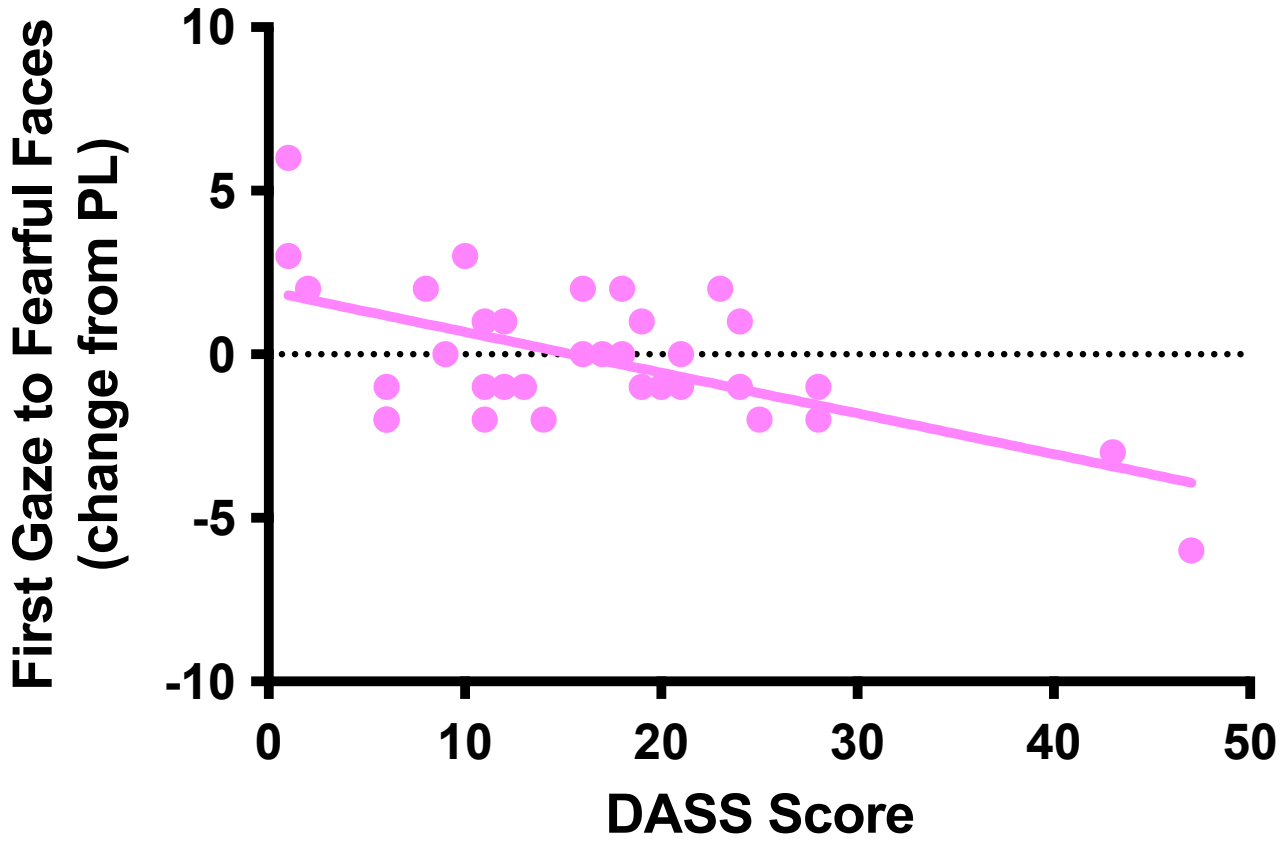


Buprenorphine reduces attention to fearful facial expressions



Bershad *et al., IJN,* 2017

Buprenorphine more effective in patients with symptoms of depression and anxiety



Bershad *et al.* 2016

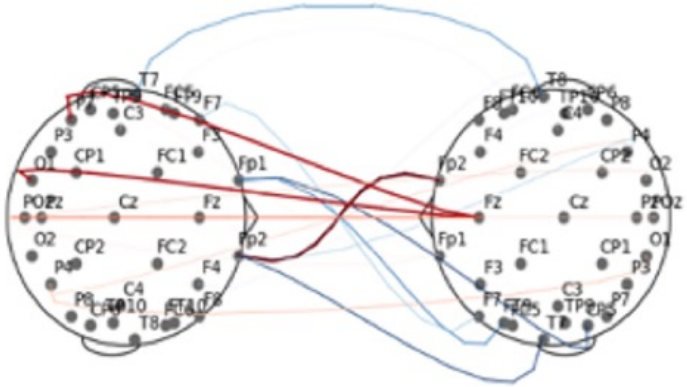
Does buprenorphine facilitate social connection in individuals with schizophrenia?

- Participants:
  - Diagnosis of schizophrenia (N=40)
  - Socially disconnected
- Design:
  - Double-blind, placebo-controlled
  - Two sessions: Buprenorphine (0.15mg) or placebo
- Social synchrony
  - Facial affect synchrony
  - Vocal synchrony
  - Neural synchrony

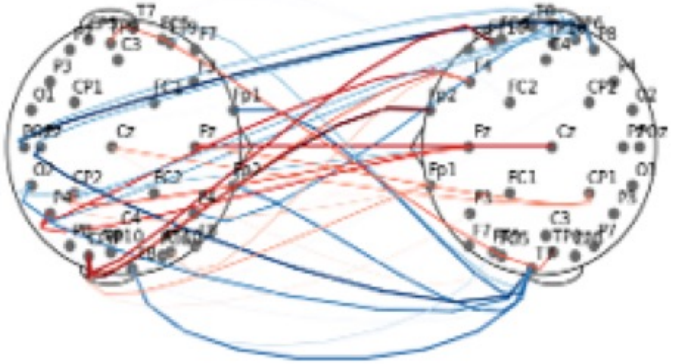
Measuring neural synchrony

- Pairs of participants interacting
- Semi-structured conversation
- Mobile electro-encephalography (EEG) units
- Relationship between activity in each scalp electrode

Placebo



Buprenorphine



Eric Reavis

Social symptoms

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- Social cognitive problems
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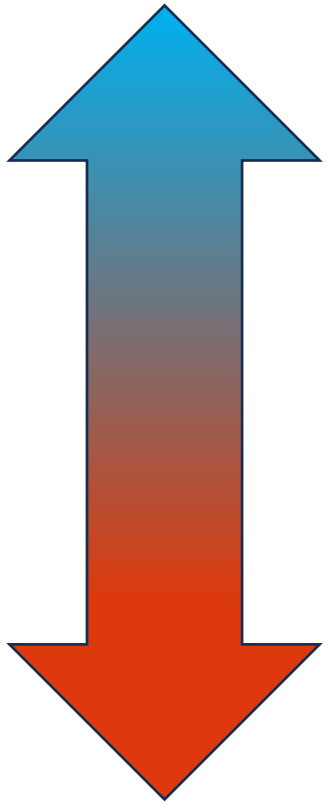


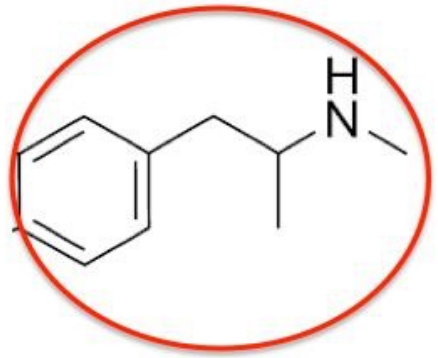
Reduced reactivity to positive social input

MDMA

Heightened reactivity to negative social input

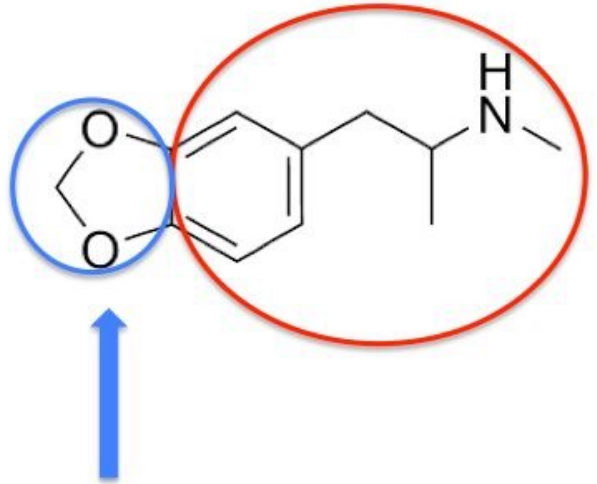
Buprenorphine

± 3,4-methylenedioxymethamphetamine (MDMA)



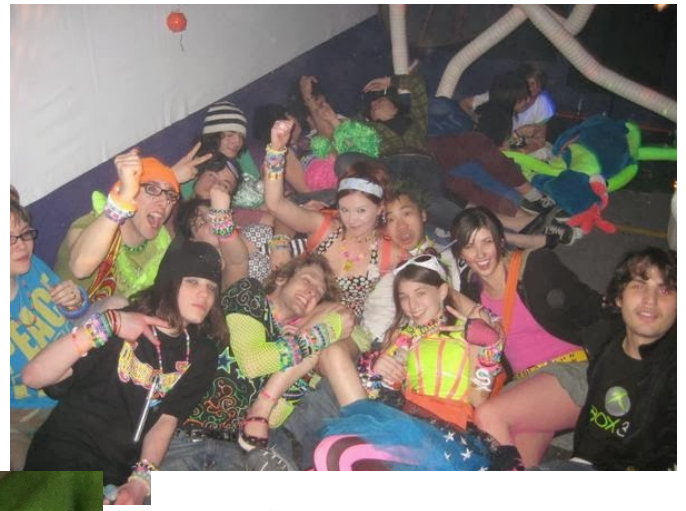
- **Amphetamine derivative**
  - Stimulant-like effects: alertness, euphoria
  - Dopamine, norepinephrine
- **Unique prosocial effects**
  - Commonly used in social settings
  - “Empathogenic” effects
  - Serotonin? Oxytocin?
- **Clinical trials of MDMA-assisted therapy for PTSD**

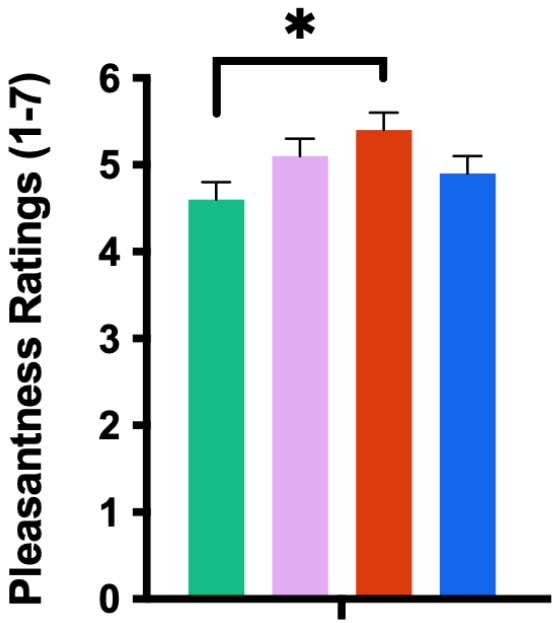
Methamphetamine
(Meth, crystal meth)

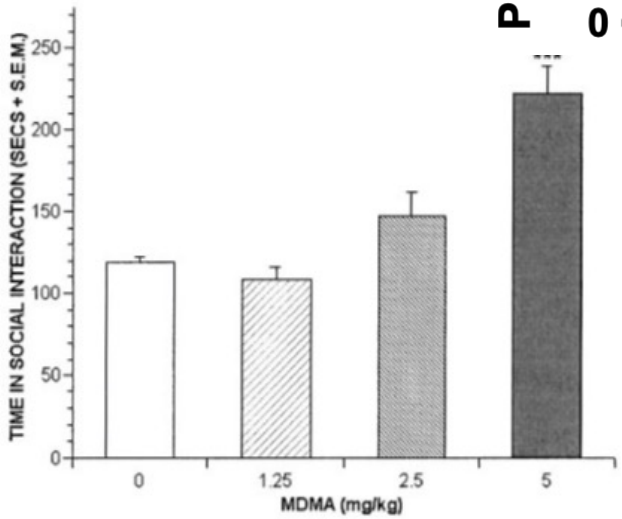


Methylenedioxymethamphetamine
(Ecstasy)

MDMA enhances rewarding social behaviors like cuddling

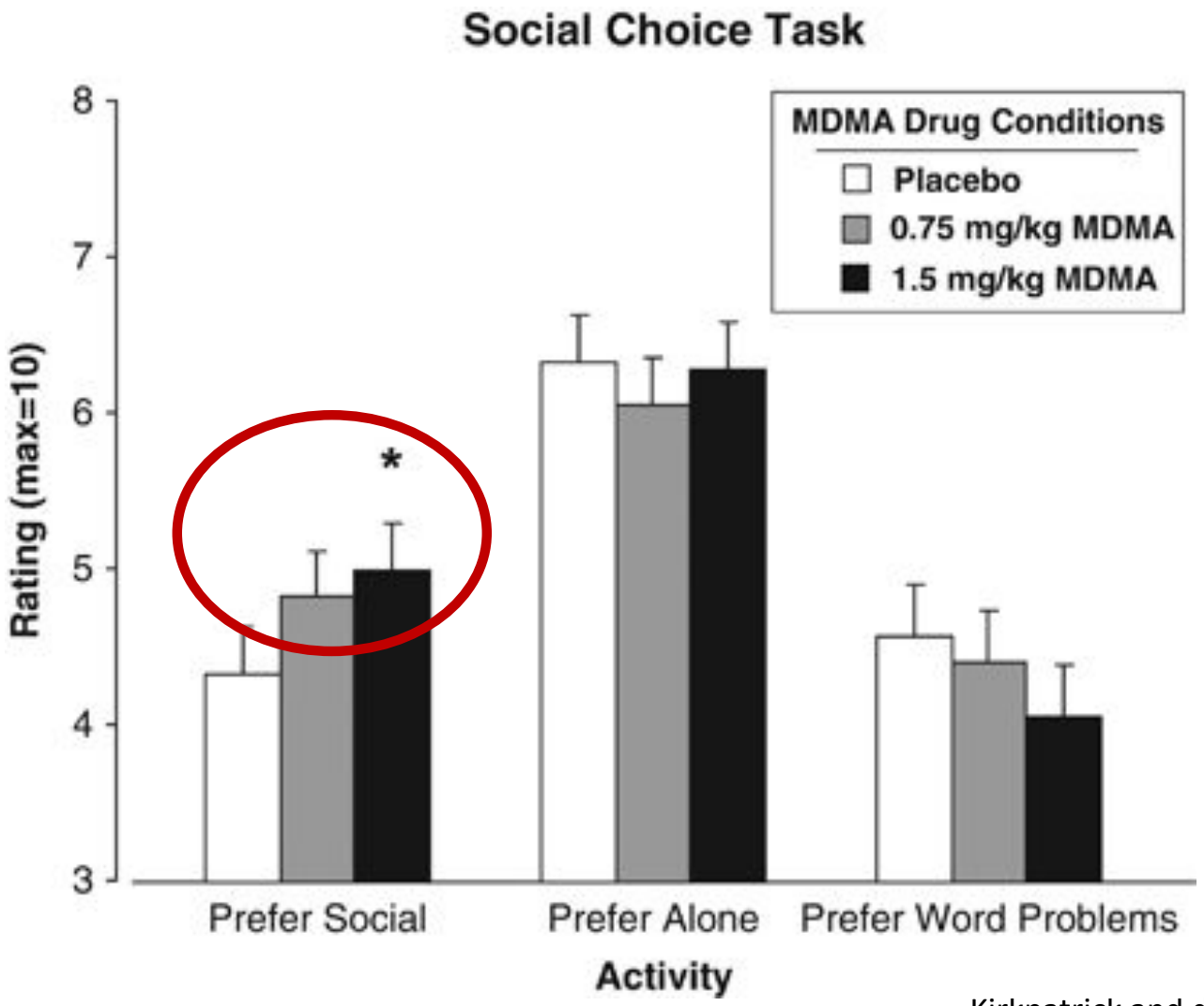






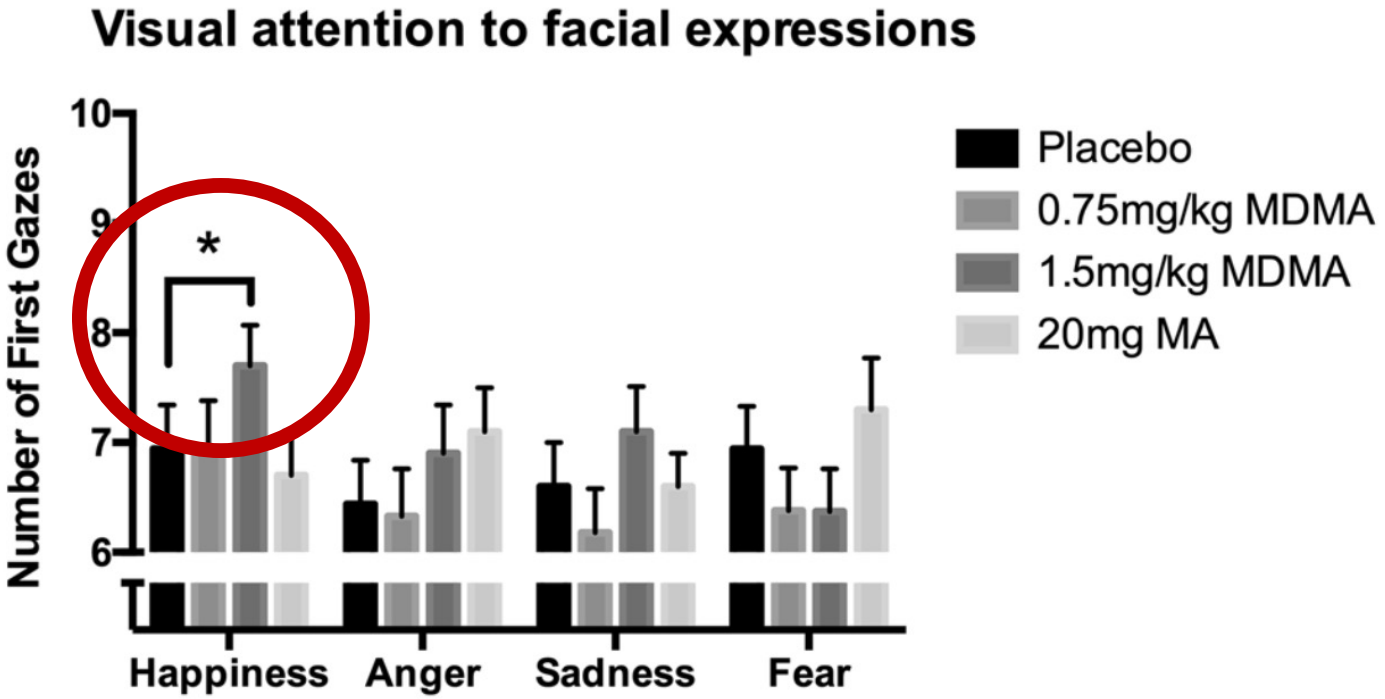
Bershad et al. 2019, Morley and McGregor 2000

MDMA increases desire to socialize



Kirkpatrick and de Wit, *Neuropsychopharmacology*, 2015

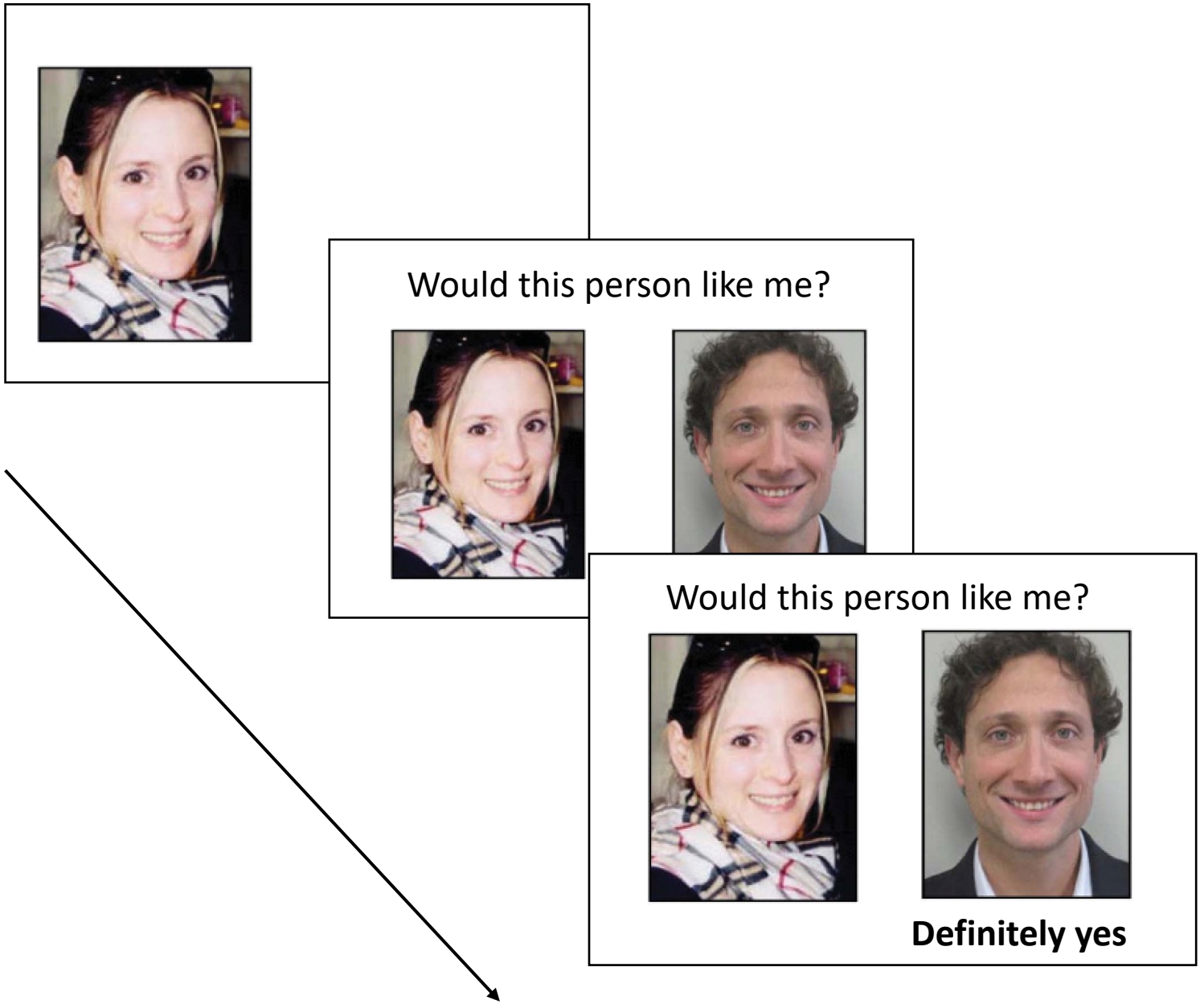
MDMA enhances attention to happy facial expressions



Bershad et al. *Neuropsychopharmacology* 2019

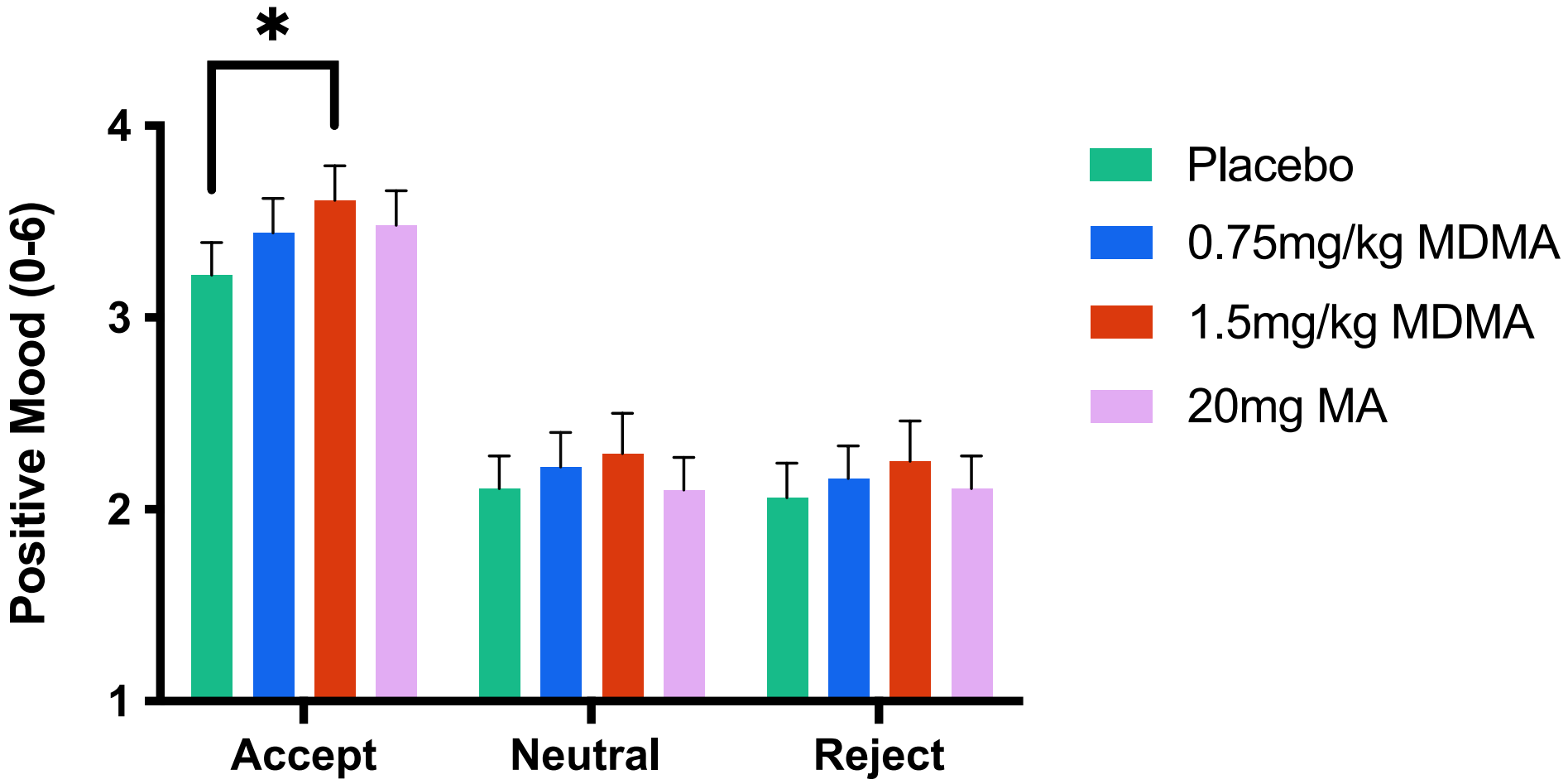
Social Feedback Task

- Subjects rate profiles 1-7
  - "Would I like this person?"
- Top 10% selected for task
- Shown each profile with feedback
- Mood questionnaire after each trial



Hsu et al. *Molecular Psychiatry* 2013

MDMA enhances affective responses to positive social feedback

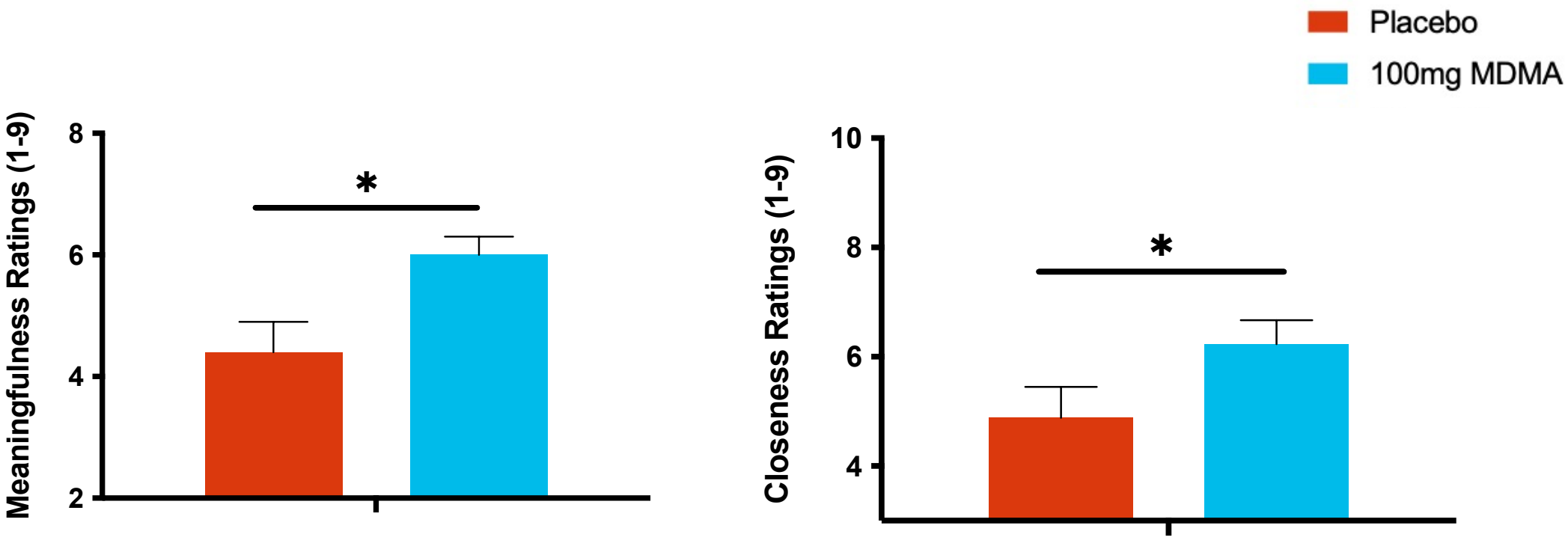


Bershad et al. *Journal of Psychopharmacology* 2023

Conversation Task

- 45 minutes of semi-structured conversation
- Laboratory confederate
- “How did you spend last Halloween?”
- Post-conversation questionnaire

MDMA enhances connectedness during a conversation

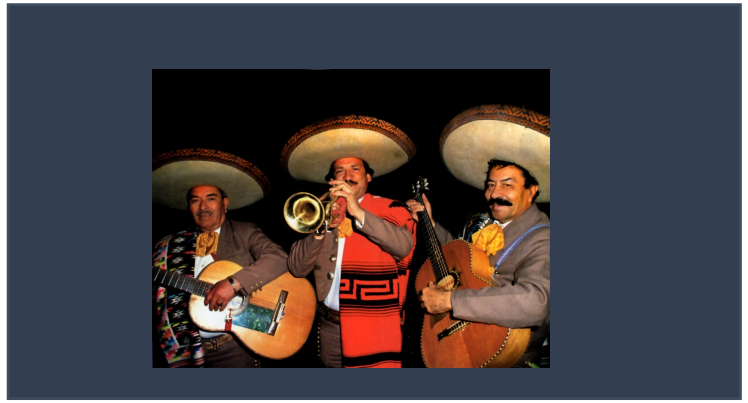


Molla et al. *Scientific Reports* 2023

What about social motivation?

Social Effort-Based Task

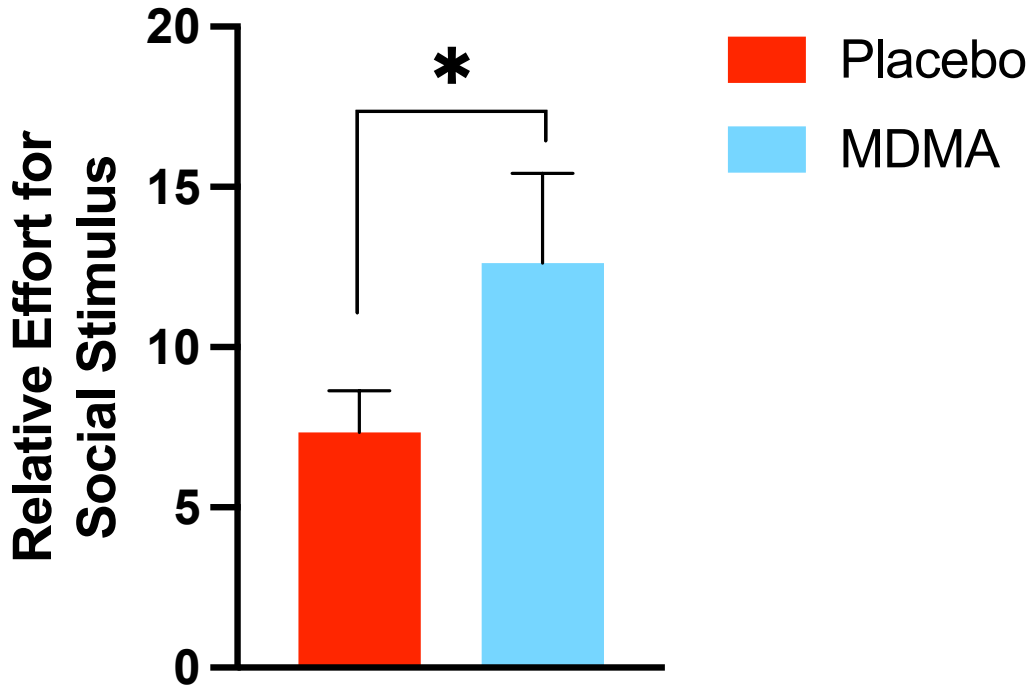
- Measures effort (button presses) to see a social vs. nonsocial stimulus
- May be an indicator of real-world social function



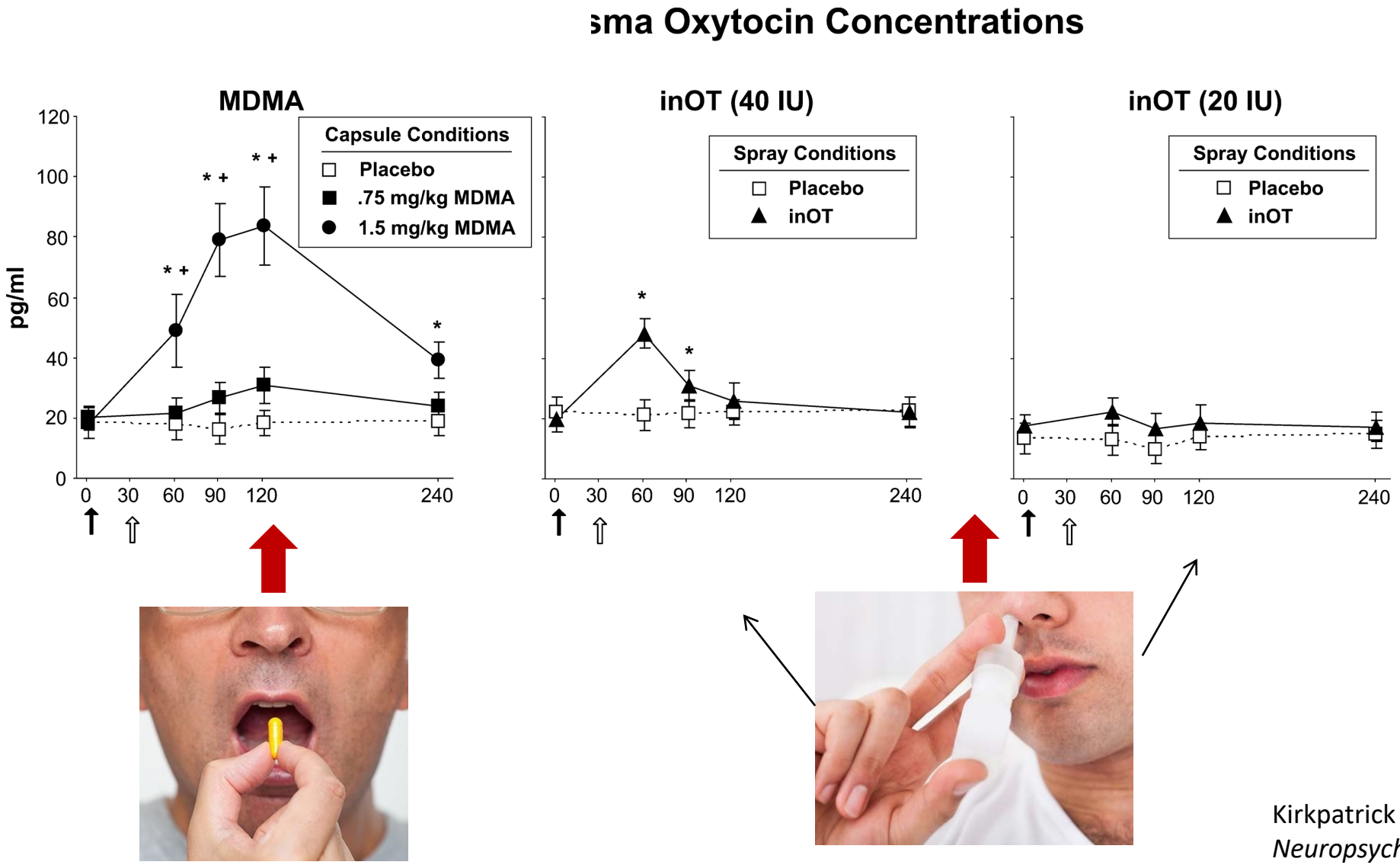
In collaboration with Eric Reavis

MDMA increases social motivation and may be useful in schizophrenia

- MDMA increases willingness to work for a social reward
- Time-limited treatment model
- MDMA in schizophrenia?



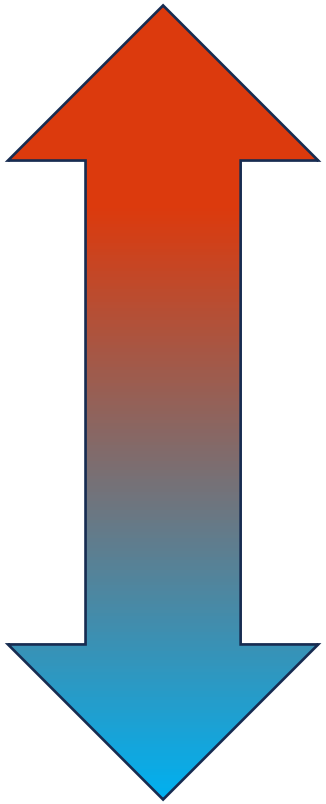
MDMA increases plasma oxytocin



Kirkpatrick et al.
Neuropsychopharmacology 2014

Two examples of psychoactive drugs in the treatment of social symptoms: summary

- Buprenorphine
  - Social stress
  - Social rejection
  - Attention to fearful faces
- MDMA
  - Desire to socialize
  - Attention to happy faces
  - Responses to positive feedback
  - Connection during a conversation
  - Social effort-based decision making

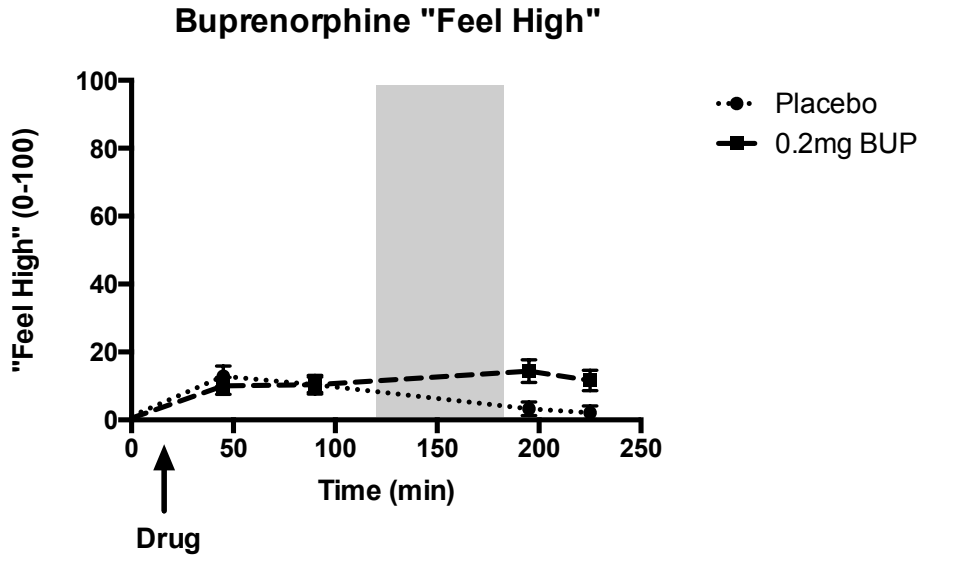


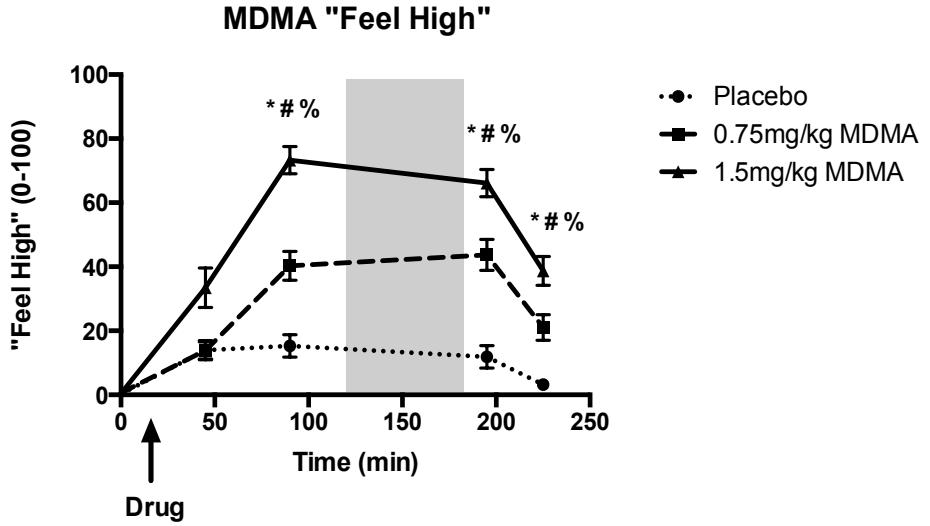
Reduces reactivity to negative social input

Enhances reactivity to positive social input

Considerations in trials with psychoactive drugs

- Psychoactive drugs are psychoactive
- Purpose of a placebo
  - Allows for the separation of expectancy effects and drug effects
- Blinding is important
  - How to maintain the blind?
    - Active comparator drugs
    - Assess blinding efficacy
      - “What do you think you received?”
      - “How confident are you?”





What about risks?

- Side effects
- Risk of abuse
- Need further research
- Risk mitigation strategies

Unknowns (there are many!)

- Effects in populations with psychiatric symptomatology
- Psychoactive drugs have risks
- Setting is important
- How long do the effects last? Lowest effective dose?
- Which psychosocial interventions are best?

Take-Aways

- The problem of social disconnection
- No current pharmacologic treatments
- Some psychoactive drugs may offer benefit, but must be studied rigorously
  - Documentation of adverse events
  - Proper control conditions
  - Proper blinding
- New treatment model

Thanks to:

- Dr. Harriet de Wit
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- Dr. Eric Reavis
- Dr. Hanna Molla
- Gerard De Vera
- Noah Moreno
- Jake Isenman
- Ioana Ciuperca
- All of you for listening!

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