

# Understanding and Treating Cannabis and Tobacco Co-Use in People with Serious Mental Illness: Implications for Dual Disorders Treatment

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# Disclosures – Tony P. George

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- Co-Principal Editor, *Neuropsychopharmacology* (NPP) – **with Lisa Monteggia, Ph.D.**
- Chair, Scientific Advisory Committee, Canadian Centre for Substance Use and Addiction (CCSA)
- Advisory Boards: Drug-Free Kids (DFK) Canada, Families for Addiction Recovery (FAR), Yale-TCORS (DSMB Chair), Yale-NIDA K12 Faculty Training Program, Advisory Group



# Objectives



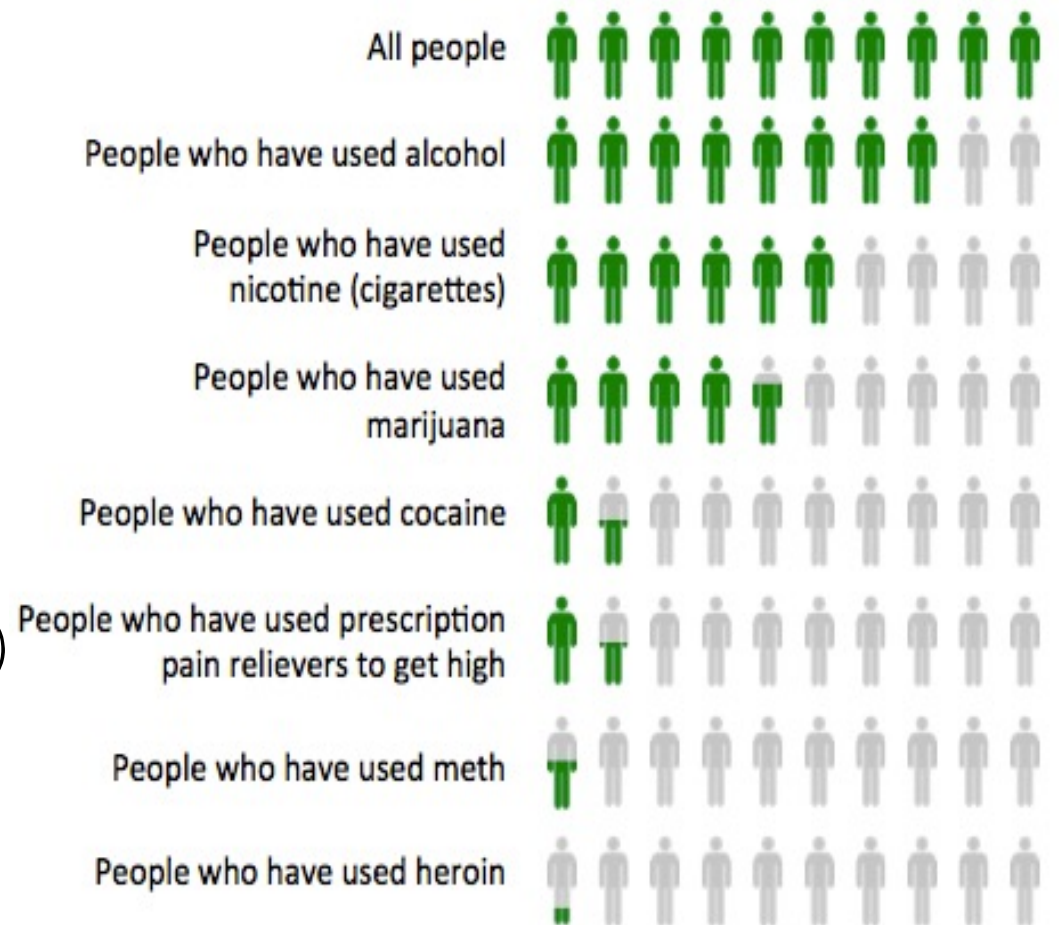
- **To understand the mechanisms for cannabis and tobacco co-morbidity.**
- **To appreciate potential treatment approaches to the co-morbidity.**
- **To apply this knowledge to a complex patient group with this frequent polysubstance co-morbidity – people with schizophrenia.**

# Cannabis Facts - 1

MS

- Rates of lifetime use  
~45%
- Derived from *Cannabis Sativa/Indica* plants.
- Prevalence of cannabis use disorder (CUD) is ~2.9% in U.S. general population (Hasin, 2018) ~4.0% in Canada, and higher in psychiatric samples (25-50%)

FIGURE 1. Lifetime use of mood-altering drugs



Hill, K.P (2015). Marijuana: The Unbiased Truth About the World's Most Popular Drug; Hasin, D.S. (2018). Neuropsychopharmacology. 43: 195-212; Lowe, D.J.E. et al. (2019). Eur. Arch Psychiat. Clin. Neurosci. 267: 107-120.



# Cannabis Facts - 2

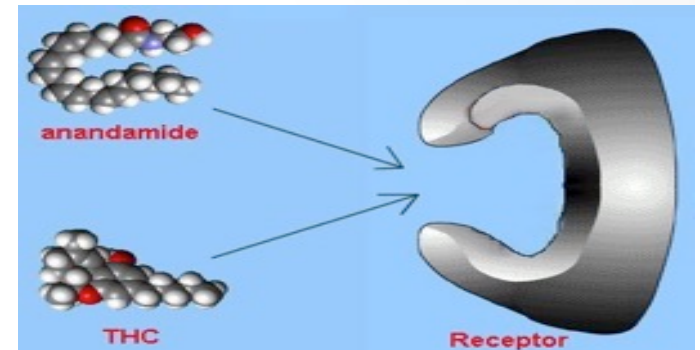
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## Contains over 400 compounds; 60 cannabinoids

- Delta-9-Tetrahydrocannabinidiol (THC), Cannabidiol (CBD)

## THC Pharmacology

- Acts at cannabinoid 1 receptors (CB1R)



## Highly Lipophilic: Fat-soluble

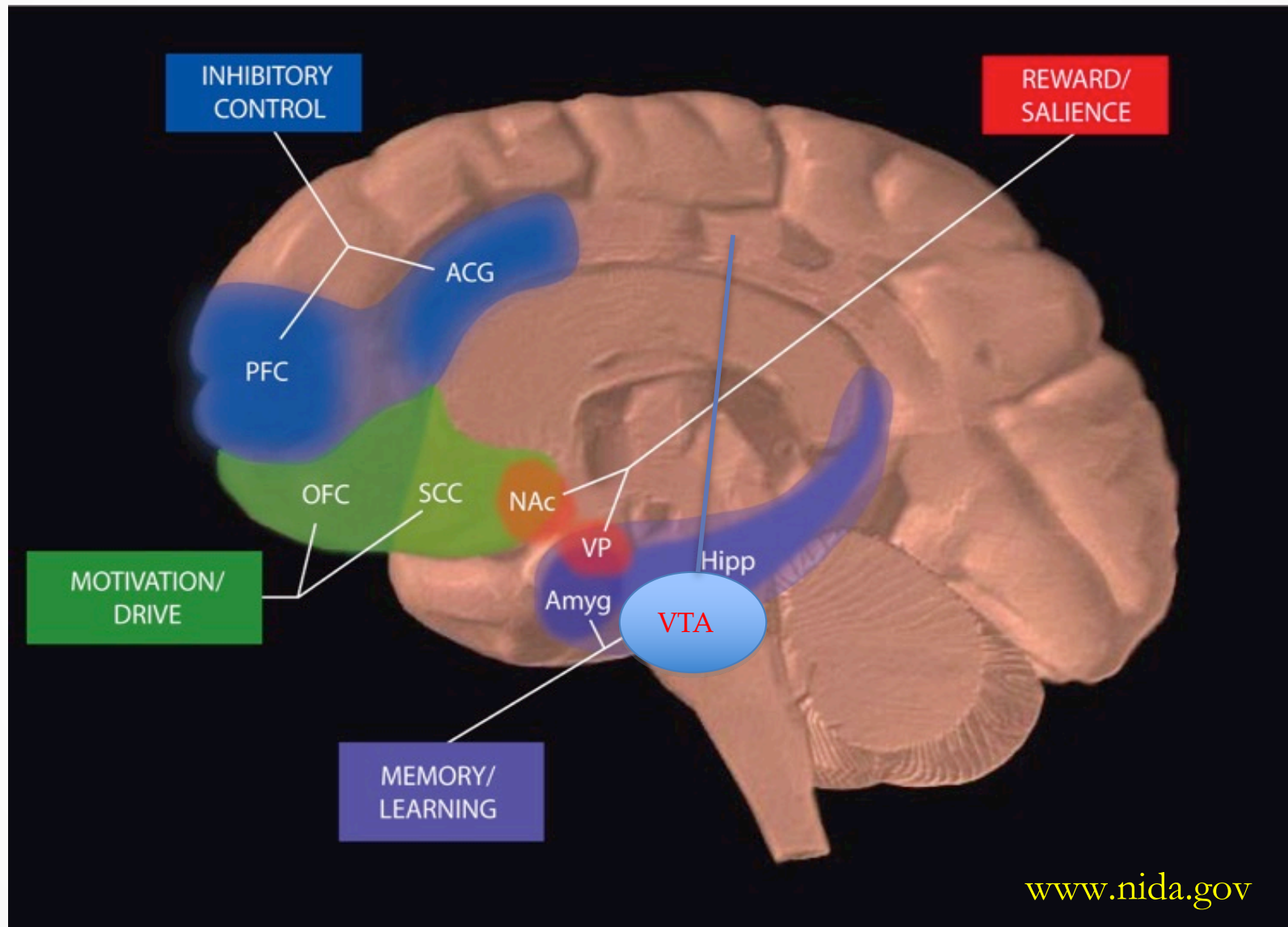
- Long half-life
- Deposits in adipose tissue and re-released into blood
- Recurrent use can lead to cannabinoid accumulation (Ashton 1999)
- Metabolized into long-acting metabolites 11-OH-THC and THC-COOH
- Complete elimination may take up to one-month (Maykut, 1985)

# Cannabis Facts - 3

TG

- THC activates CB1 receptors in mesolimbic dopamine (DA) system
  - Role of CB2 receptors is less clear
- High density in cerebellum, hippocampus - responsible for psychomotor and memory impairment
- Endogenous ligand: **anandamide**

# The Brain Basis of Addictions



**Table.** Comparison of Properties of THC and CBD<sup>4,12,14-16</sup>

Property	THC	CBD
Cannabinoid 1 receptor	Partial agonist	Low affinity
Cannabinoid 2 receptor	Partial agonist	Low affinity
5-HT <sub>1A</sub> <sup>14</sup>	No activity	Partial agonist
Psychosis	↑	↓
Anxiety	↑	↓
Short-term memory impairment	Yes	No
Distortion of time	Significant	None
Antiemetic	Effective	Effective
Cytochrome P450 3A4	Substrate/possible inhibitor <sup>16</sup>	Substrate <sup>12</sup>
Cytochrome P450 2C9	Substrate/possible inhibitor <sup>16</sup>	Low inhibition <sup>12</sup>
Cytochrome P450 2C19	No activity <sup>16</sup>	Substrate/low inhibition <sup>12</sup>
DEA status	Schedule 1	Unscheduled
FDA approved	No	Yes

CBD, cannabidiol; DEA, Drug Enforcement Administration; THC,  $\Delta$ -9-tetrahydrocannabinol.



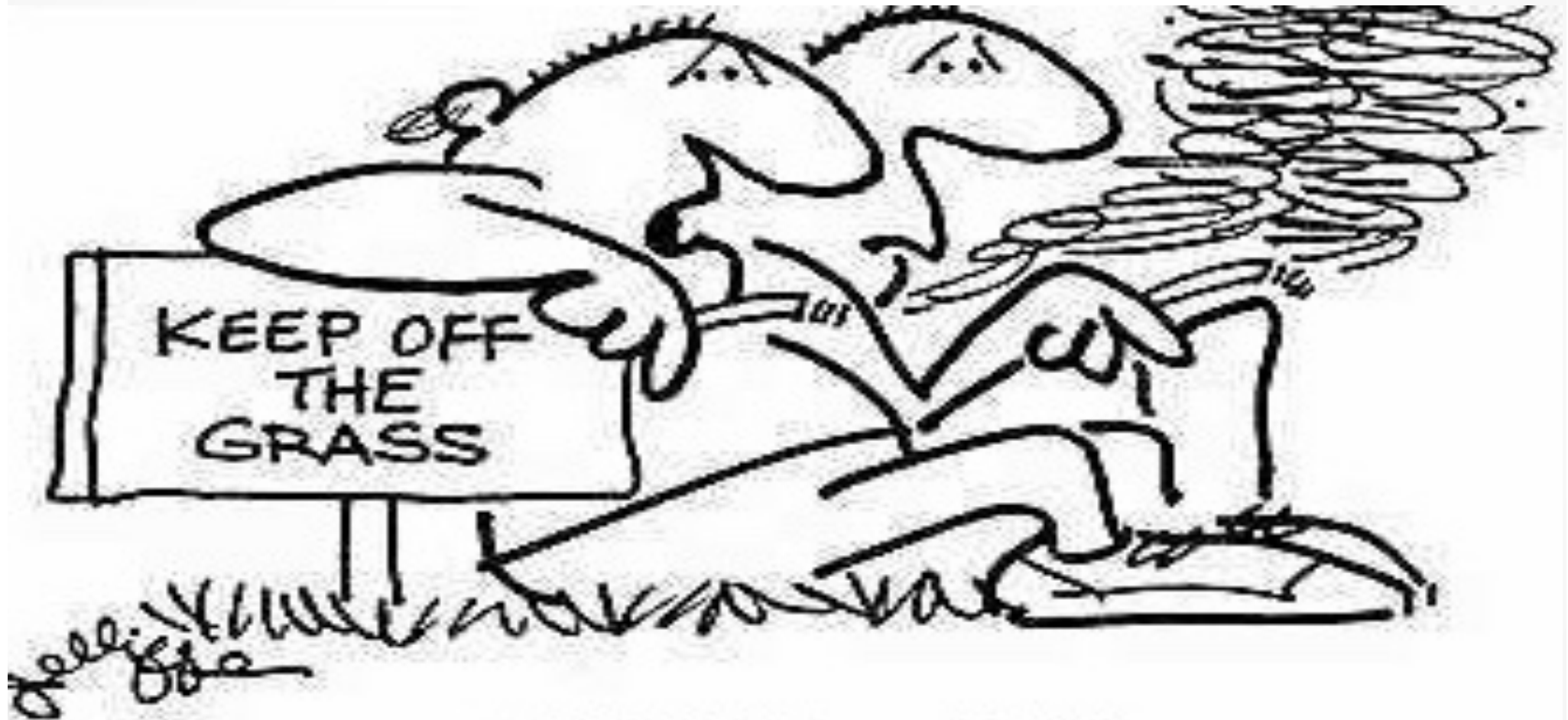
# Cannabis Intoxication and Withdrawal

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- There is a clear cannabis (THC) dependence and withdrawal syndrome (Vandrey et al., 2004)
- Intoxication – cognitive impairment, psychomotor impairment, conjunctival injection, severe anxiety.
- Withdrawal – irritability, decreased appetite/weight loss, restlessness, difficulty falling asleep, depressed mood, abdominal pain sweating (peaks within 4-7 days)

# What are the Effects of Cannabis? Is Cannabis Addictive?

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"Wish I could!"

# The Behavioral Sequelae of Cannabis Use in Healthy People: A Systematic Review

Maryam Sorkhou<sup>1,2</sup>, Rachel H. Bedder<sup>3</sup> and Tony P. George<sup>1,2,4\*</sup>

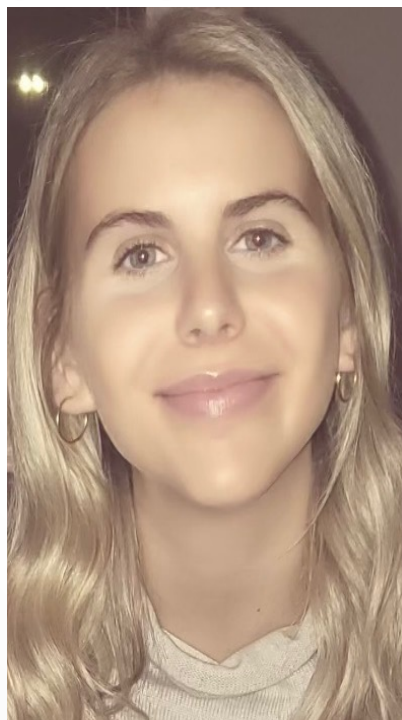
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*Sorkhou, M., Bedder, R.H., George, T.P.*

*(2021) Frontiers in Psychiatry. 12: 630247.*



Maryam Sorkhou



Rachel Bedder

Behavioral Outcome	Number of studies finding a negative impact of cannabis use	Number of studies finding no impact of cannabis use	Level of Evidence
Verbal, Episodic, and Verbal Working Memory	24	13	4 (24/37 = 64.9%)
Visuospatial Memory	1	6	1 (1/6 = 16.7%)
Attention	12	8	4 (12/20 = 60.0%)
Processing Speed	3	3	3 (3/6 = 50.0%)
Executive Function	16	8	4 (16/24 = 66.7%)
Impulsivity/Inhibitory Control	10	7	3 (10/17 = 58.8%)
Intelligence (IQ)	3	4	3 (3/7 = 42.9%)
Motivation	4	2	4 (4/6 = 66.7%)
Psychosocial Functioning	7	1	5 (7/8 = 87.5%)
Depression	16	11	3 (16/27 = 59.3%)
Anxiety	14	9	4 (14/23 = 60.9%)
Psychosis	25	2	5 (25/27 = 92.6%)

1 = 0–19% corresponds with strong evidence of no effects of cannabis use.

2 = 20–39% corresponds with moderate evidence of no effects of cannabis use.

3 = 40–59% corresponds with mixed evidence of neutral or negative effects of cannabis use.

4 = 60–79% corresponds with moderate evidence of negative effects of cannabis use.

5 = 80–100% corresponds with strong evidence of negative effects of cannabis use.



# Monitoring the Future Study (MFS) – Which Drug is Most Addictive?

Anthony, J.C. et al. (1994). *Exp. Clin. Psychopharmacol.* 2: 244-268.

Substance	Cumulative Occurrence of Drug Use (%)	Cumulative Occurrence of Drug Dependence (%)	% Capture Rate
<b>Tobacco</b>	75.6	24.1	<b>31.9</b>
Cocaine	16.2	2.7	16.7
Heroin	1.5	0.4	23.1
Alcohol	91.5	14.1	15.4
<b>Cannabis</b>	46.3	4.2	<b>9.1</b>



# THC versus CBD Content: 1975 and 2023



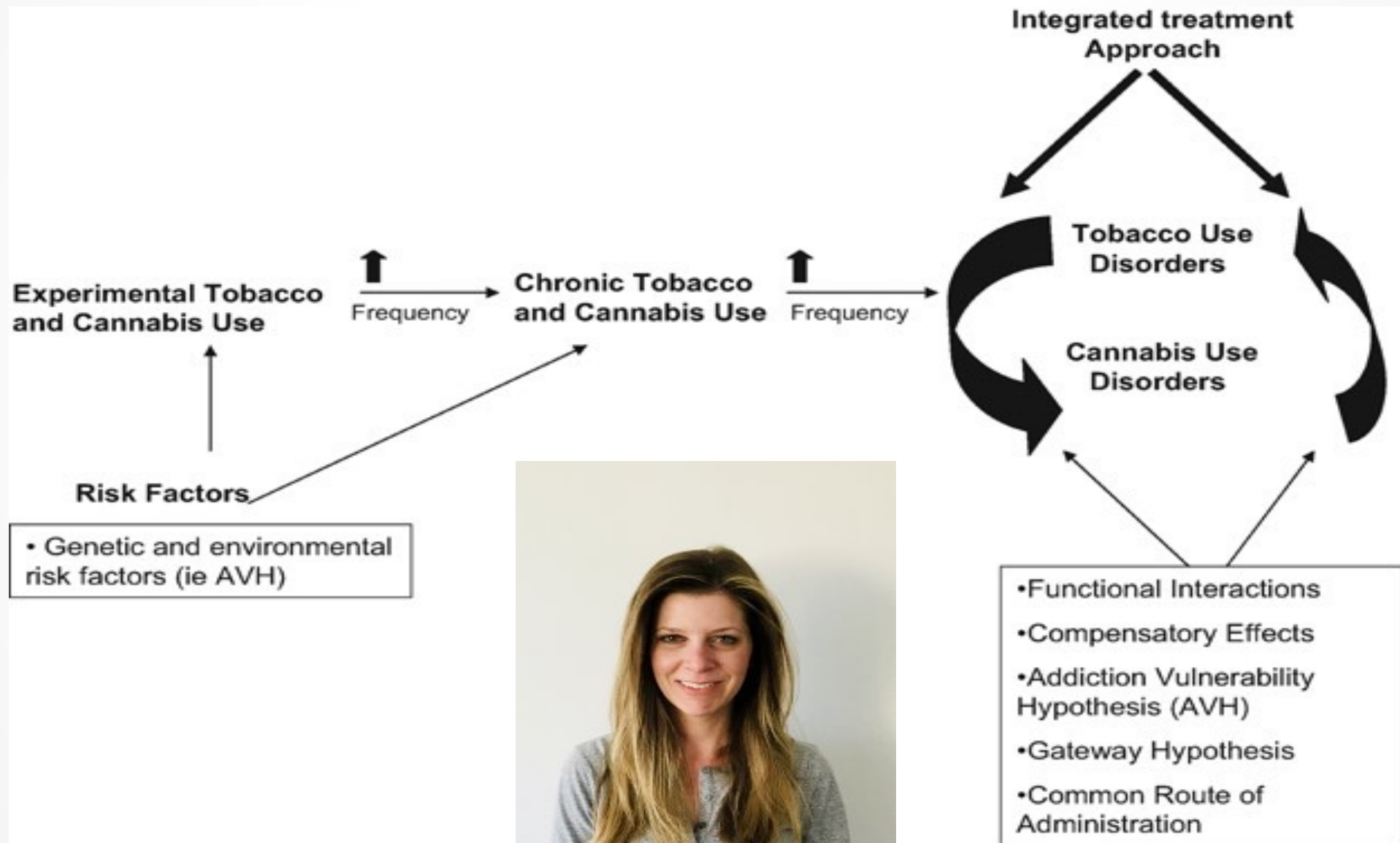
- In 1975: THC, 3%; CBD, 3%
- In 2023: THC, 25-35%; CBD <0.1%

Lowe, D.J.E. et al. (2019). *Eur. Arch. Psychiat. Clin. Neurosci.* 267: 107-120.  
Hasin, D.S. (2018). *Neuropsychopharmacology.* 43: 195-212.

# Why are Rates of Cannabis and Tobacco Co-Use So High?

- **Both are typically smoked products: cross-cuing.**
- **Substitution effects – probably common in people with clinical and cognitive symptoms, e.g. depression, anxiety, emotional dysregulation, psychosis.**
- **Cross-talk between endocannabinoid and nicotinic receptor systems** (Rabin and George, 2015, McClure et al., 2020)
- **Common social determinants: Poverty, early childhood trauma, stress, frequent combination in smoked products (e.g. Blunts).**

# Tobacco and Cannabis Co-Use: Potential Mechanisms



# Potential Treatments for Cannabis and Tobacco Co-Use

**Bupropion (SR/XL)**

**Varenicline/Cytisine**

**Nicotine Replacement Therapy** (Hill et al., 2010)

**FAAH Inhibitors** (D'Souza, D.C. et al., 2019)

**Cannabidiol (CBD)** (Freeman, T. et al., 2021)

**Contingency Management** (Rabin, Dermody)

**Motivational Interviewing/Relapse-Prevention**

**Skills Training**

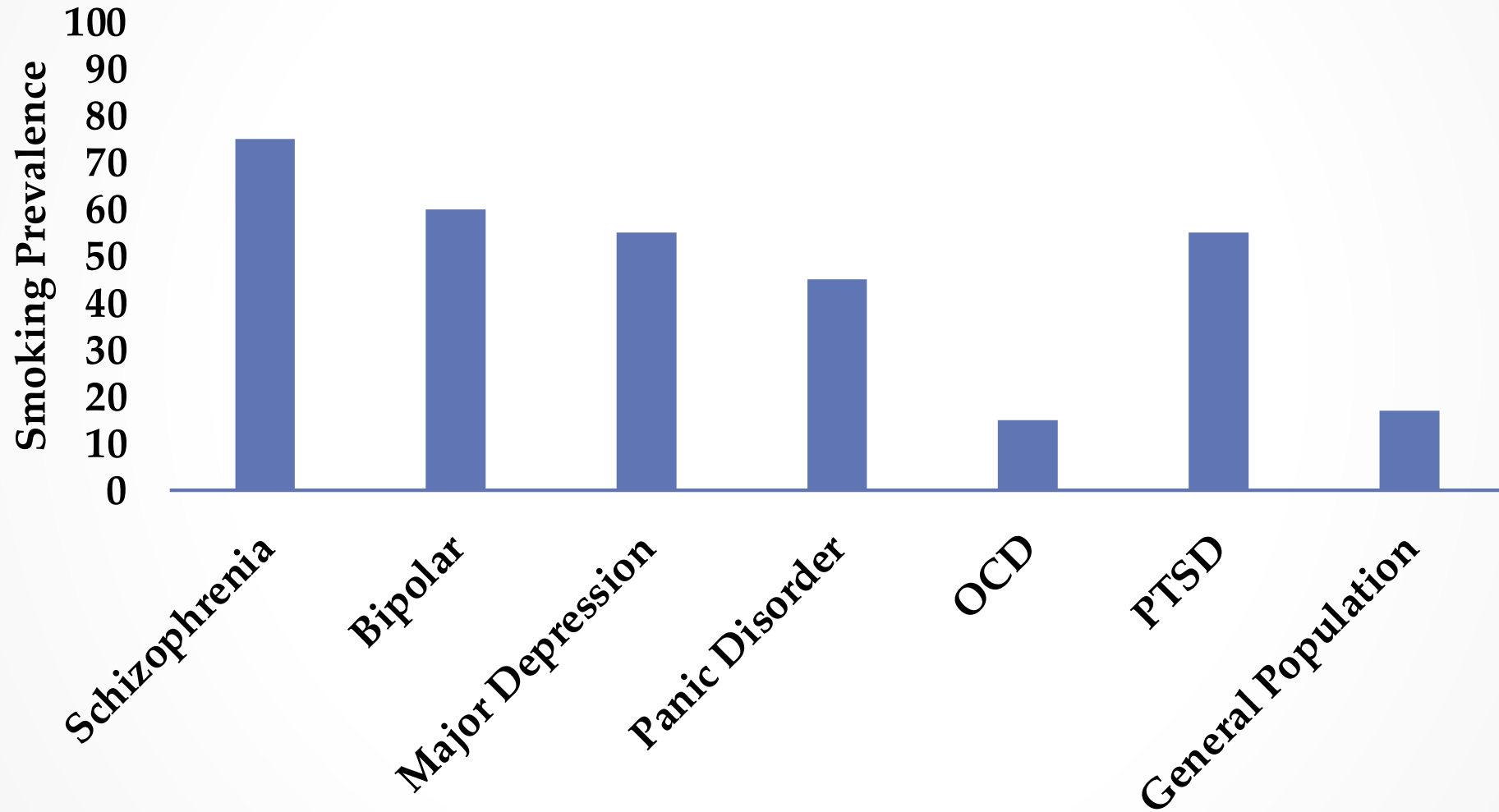


# Tobacco Smoking and Psychotic Disorders



- Higher prevalence of smoking in psychotic patients (including schizophrenia) versus age-matched controls, and more difficulty quitting (Smith et al., 2009; Morisano et al., 2009; Deruiter et al., 2013; Purcell et al., 2014)
- About 50-60% of early psychosis patients smoke tobacco, and this begins even before antipsychotic treatment (McEvoy et al., 1999).
- Patients who develop early psychosis start smoking tobacco about 5.3 years before the onset of illness (Myles et al., 2012)
- No substantive evidence that tobacco smoking is associated with the transition to psychosis (Addington et al, 2012), but this has been challenged (Gurillo et al., 2015. Lancet Psychiatry)

# Prevalence of Smoking in People with Mental Illness



Kalman, Morrissette, & George. (2005). *Am. J. Addict.*, 14: 106-123.

# Cannabis and Schizophrenia



- **Besides Tobacco, Cannabis is the most commonly used drug in people with schizophrenia**
  - **~ 25% of people with schizophrenia have co-morbid cannabis use disorder (CUD) versus ~3% in the general population** (Koskinen 2009. Schizophr. Bullet.; Hasin et al., 2015. JAMA Psychiatry).
- **Cannabis use has a negative impact on course of schizophrenia**
  - Symptom exacerbation
  - More relapses and re-hospitalizations
  - Increased treatment needs
  - Linszen et al. Arch Gen Psych 1994; Patel et al. The Lancet 2015; Zammit et al. Br J Psych 2008

# Relationship of Tobacco to Other SUDs



- Tobacco co-use is closely associated with other substance use disorders (SUDs).
- This appears to be the case with SUDs (cannabis, alcohol stimulants) in early psychosis but these relationships have not been carefully studied  
(Addington et al., 2012; Deruiter et al., 2013) .
- However, we demonstrated an unexpected relationship between cannabis use and tobacco smoking in schizophrenia (Rabin et al., 2014).



# Cross-Sectional Study of Tobacco Smoking and Cannabis Use Status In Schizophrenia

Goal: To examine the effects of cannabis on cognitive function in SZ patients

Parsed **LIFETIME CANNABIS DEPENDENT** patients :

↙   ↘  
**CURRENT** Cannabis  
Dependent Patients  
(CD)

**FORMER** Cannabis  
Dependent (FD)  
Patients  
(remission >6 months)

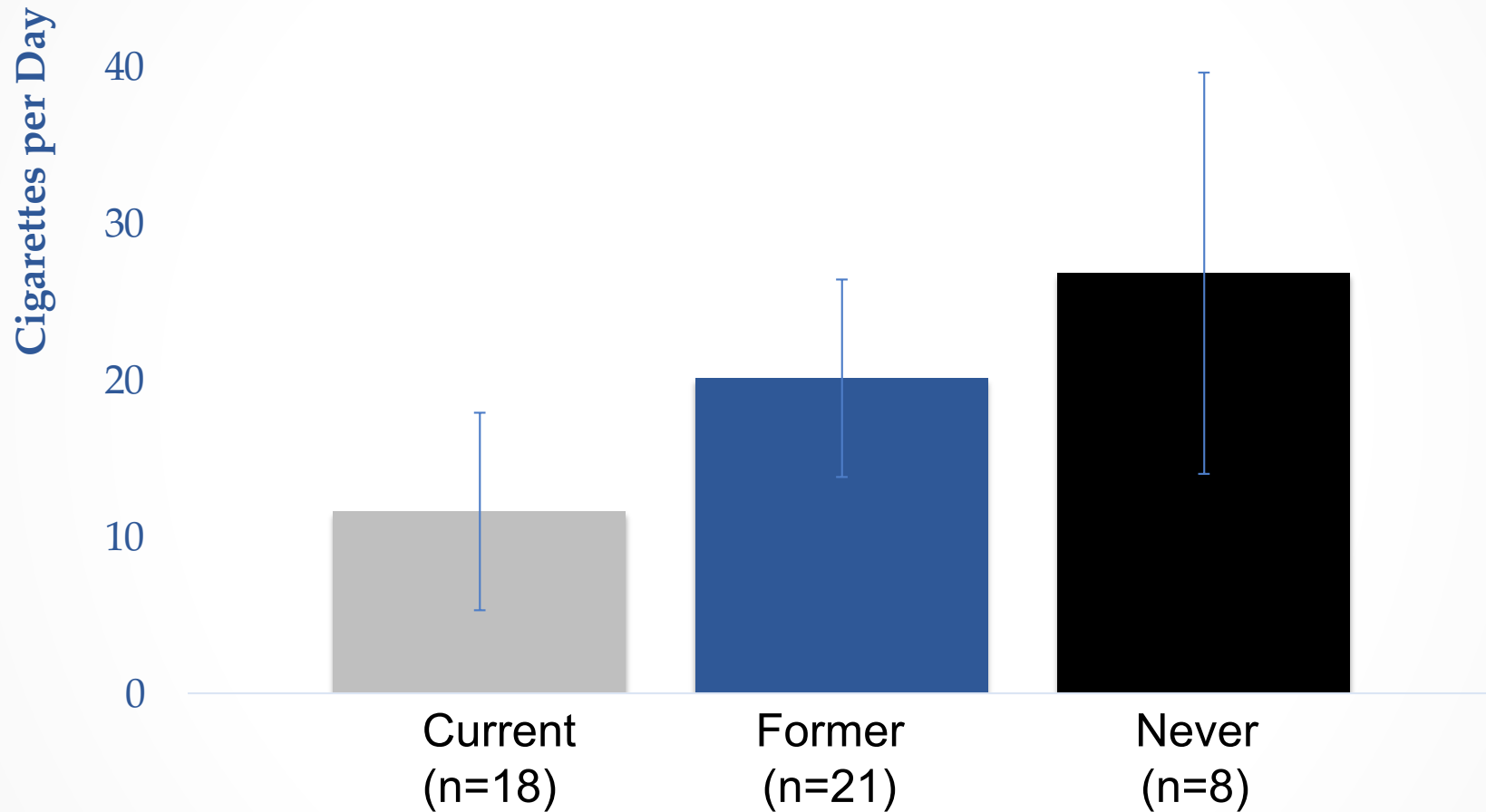


Joint years

Rabin, RA et al Psych Res 2013

Examined the effect of cumulative cannabis exposure on cognitive performance

# Cannabis and Cigarette Co-Use in People with Schizophrenia



**Cannabis Dependence History**

22

Rabin, Giddens and George (2014). Am. J. Addict. 23: 170-175.

# Prospective Study Aims

To employ the first longitudinal study design to investigate the state-dependent effects of 28-days of cannabis abstinence on cognitive symptoms in cannabis dependent SCZ patients and non-psychiatric controls



**Rachel A. Rabin, Ph.D.**  
Assistant Professor of Psychiatry,  
McGill University



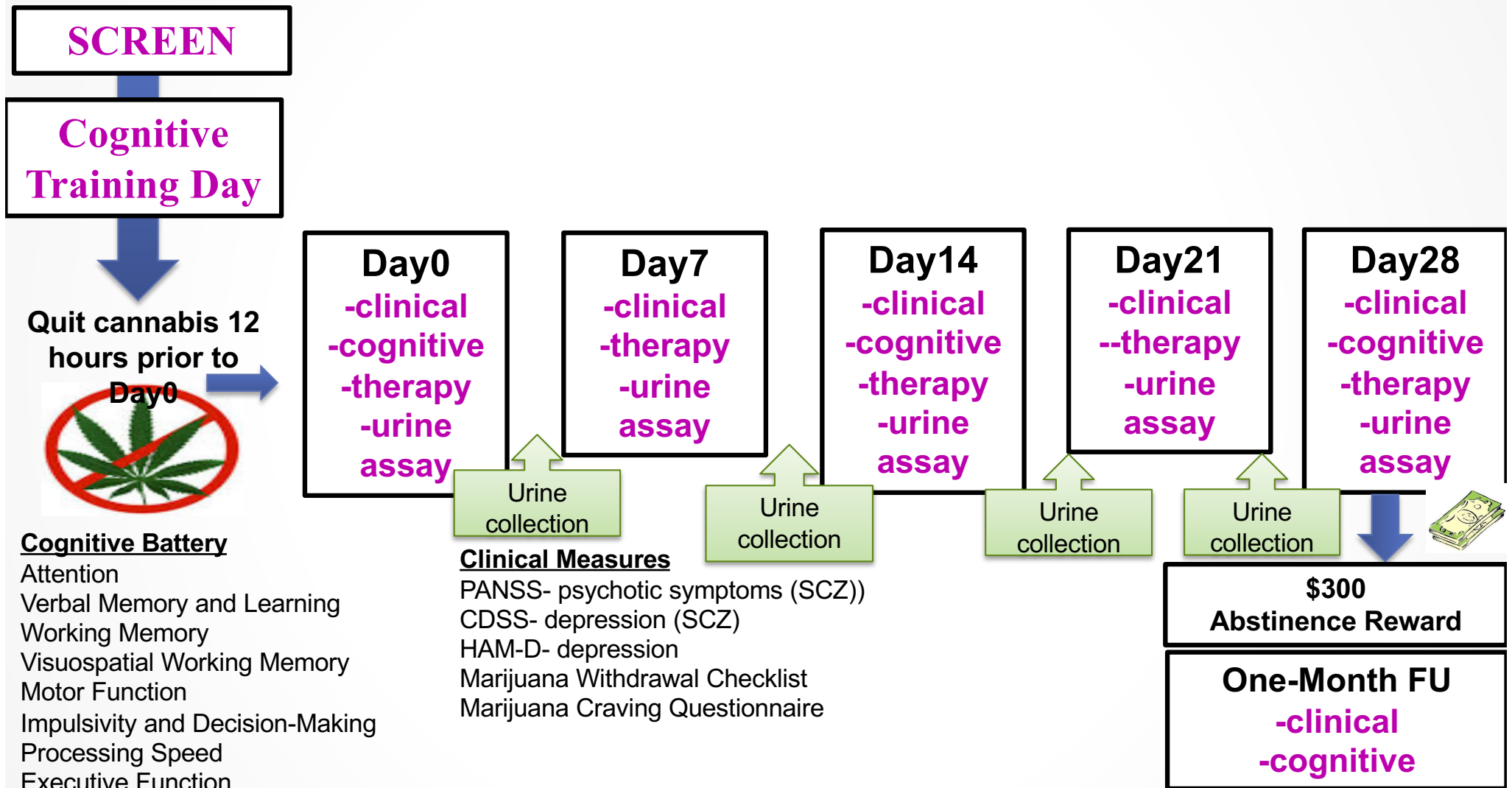
**Sarah S. Dermody, Ph.D.**  
Associate Professor of Psychology,  
Toronto Metropolitan University

# Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
<b>Participants</b>	Age 18-55	Current substance use disorder or illicit drug use or heavy alcohol use
	Males	Females
	DSM-IV diagnosis of Cannabis Dependence; Not treatment-seeking	Serious head injury w/ LOC or serious medical disorders
	Daily tobacco smoker	IQ < 80
<b>SCZ</b>	DSM-IV diagnosis of SCZ	PANSS >70
	Stable antipsychotic dose	Recent hospitalization for symptoms
<b>CTL</b>		Axis I disorder; No psychotropic medication



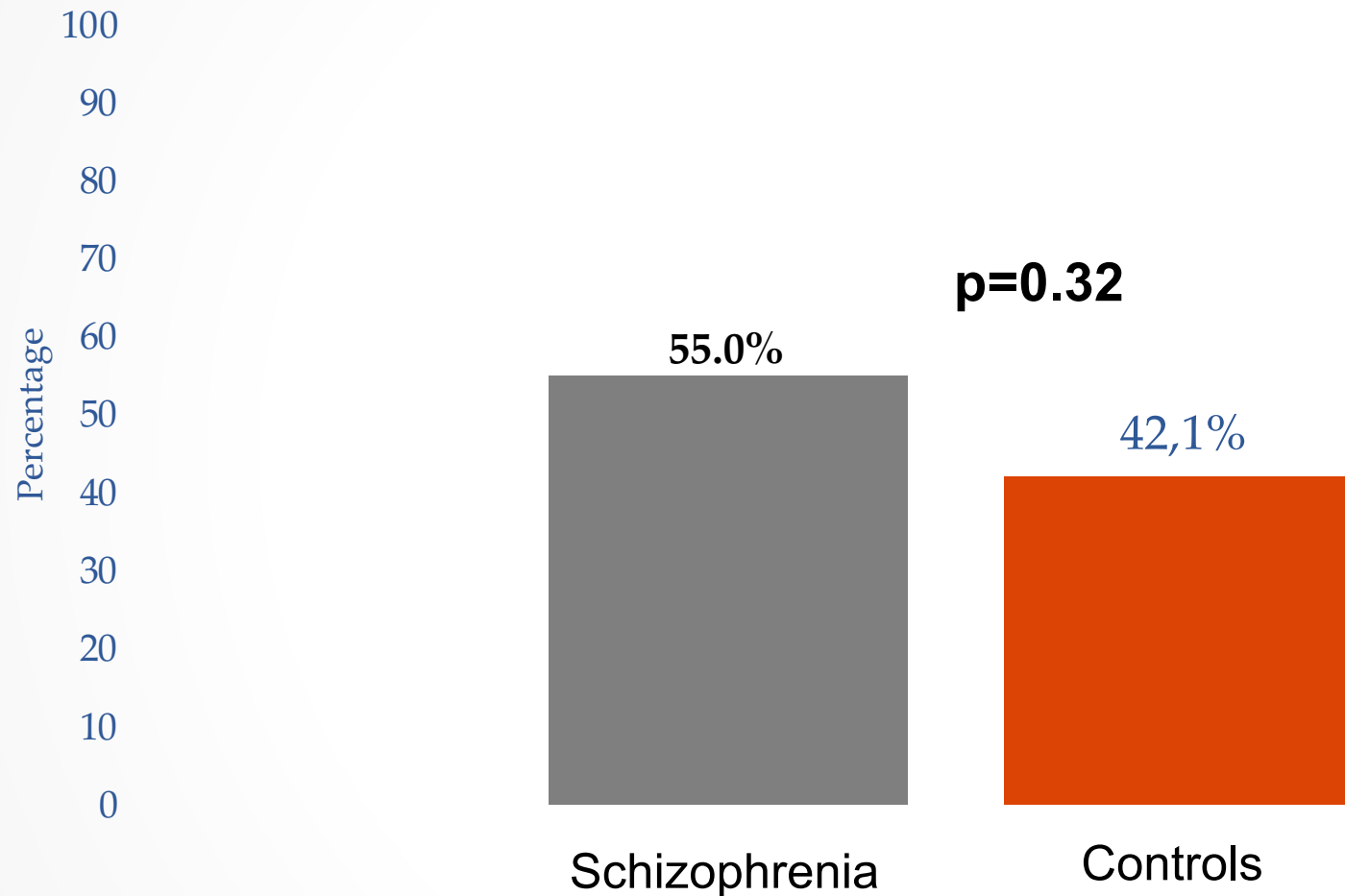
# Study Design



# Was the Cannabis Abstinence Paradigm Successful?



# Cannabis Abstinence in Schizophrenia and Control Participants

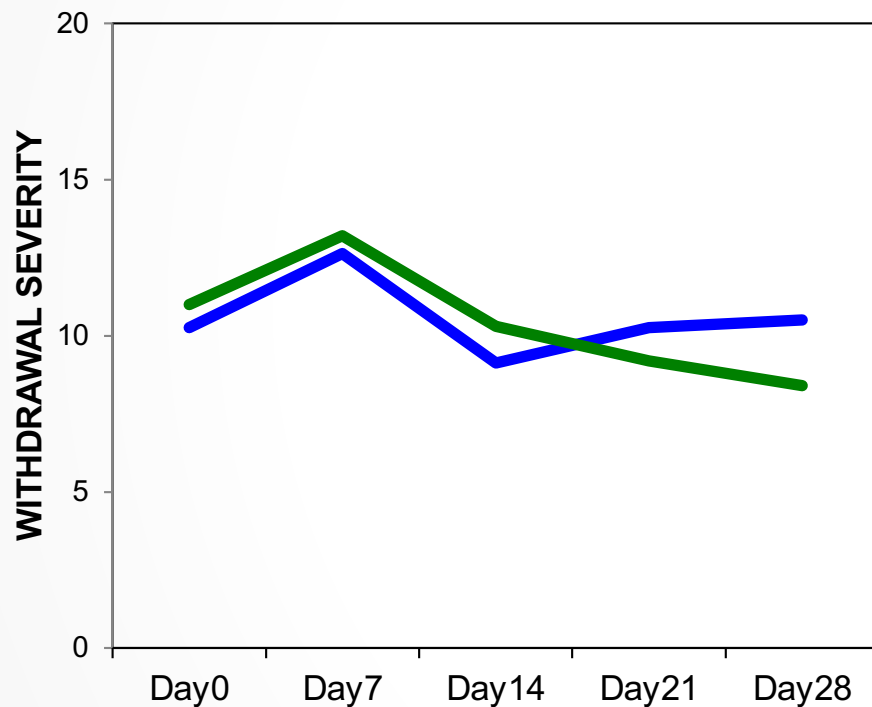


Rabin, RA et al. (2018). *Schizophrenia Research*.194: 47-54.

\*Abstinence = Urinary THC-COOH levels <20 ng/ml by GC/MS at Day 28

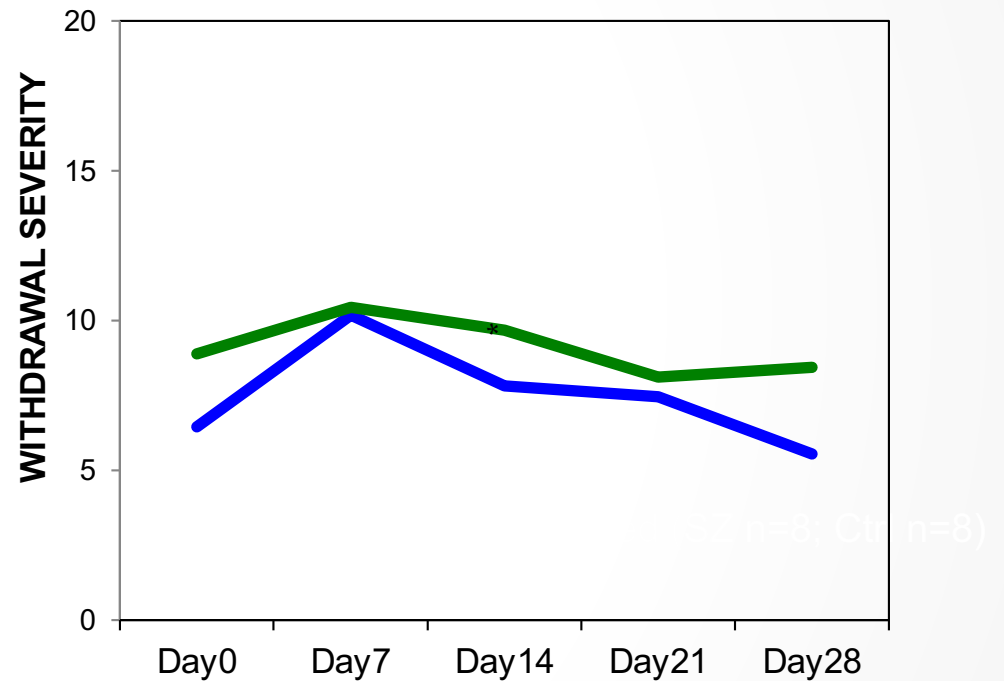
# Cannabis Withdrawal Symptoms in Schizophrenia Versus Control Participants

**SCZ** Abstainer (n=8)  
Non-Abstainer (n=11)



Time; [F(4, 68) = 1.607,  $p=0.182$ ];  
Time x group; [F(4, 68) = 0.357,  $p=0.838$ ]

**CTL** Abstainer (n=11)  
Non-Abstainer (n=9)



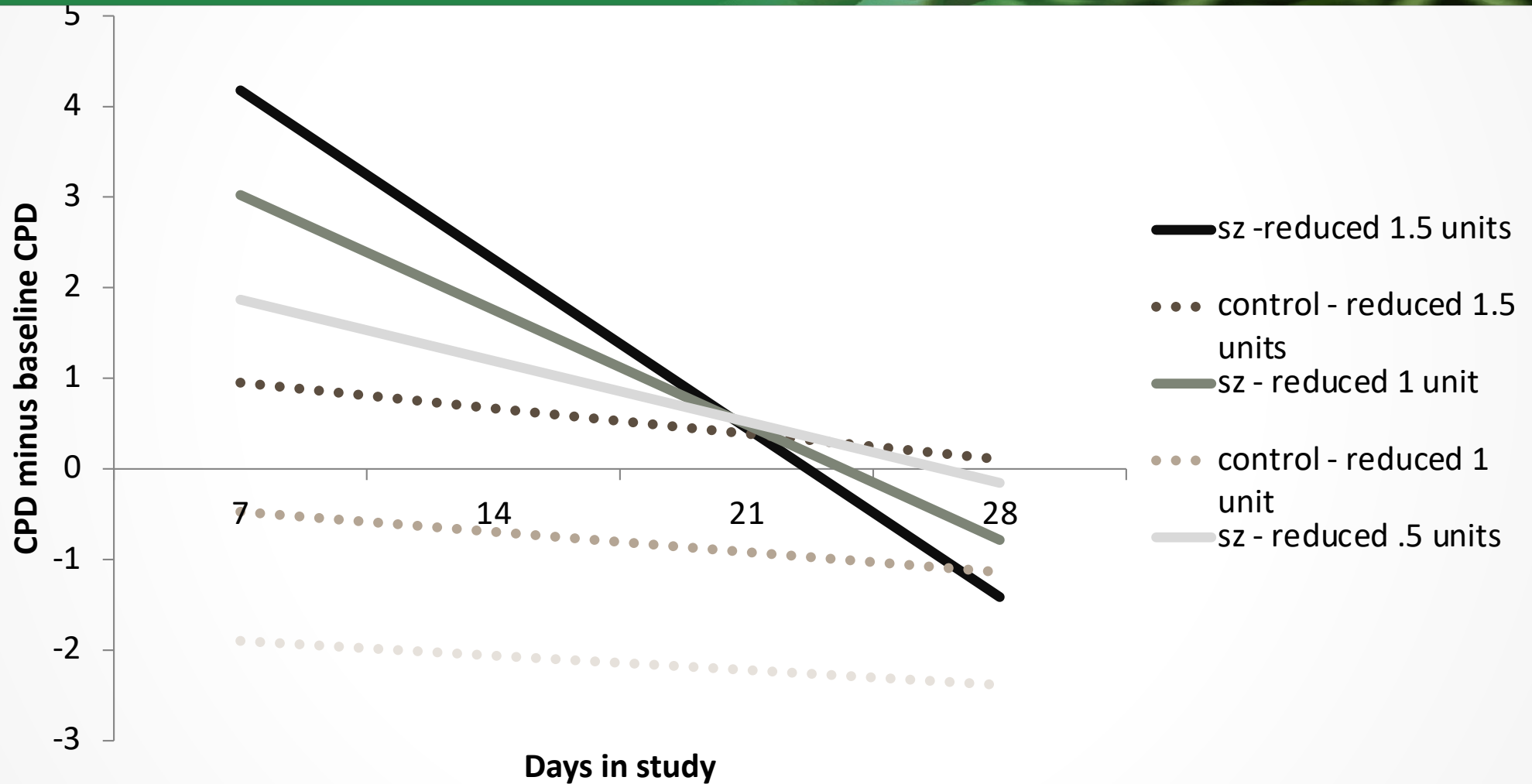
Time; [F(4, 72) = 2.172,  $p=0.080$ ];  
Time x group; [F(4, 72) = 0.420,  $p=0.793$ ]

\*One-way ANOVA in abstainers:  
[F(4, 40) = 3.944,  $p=0.009$ ]



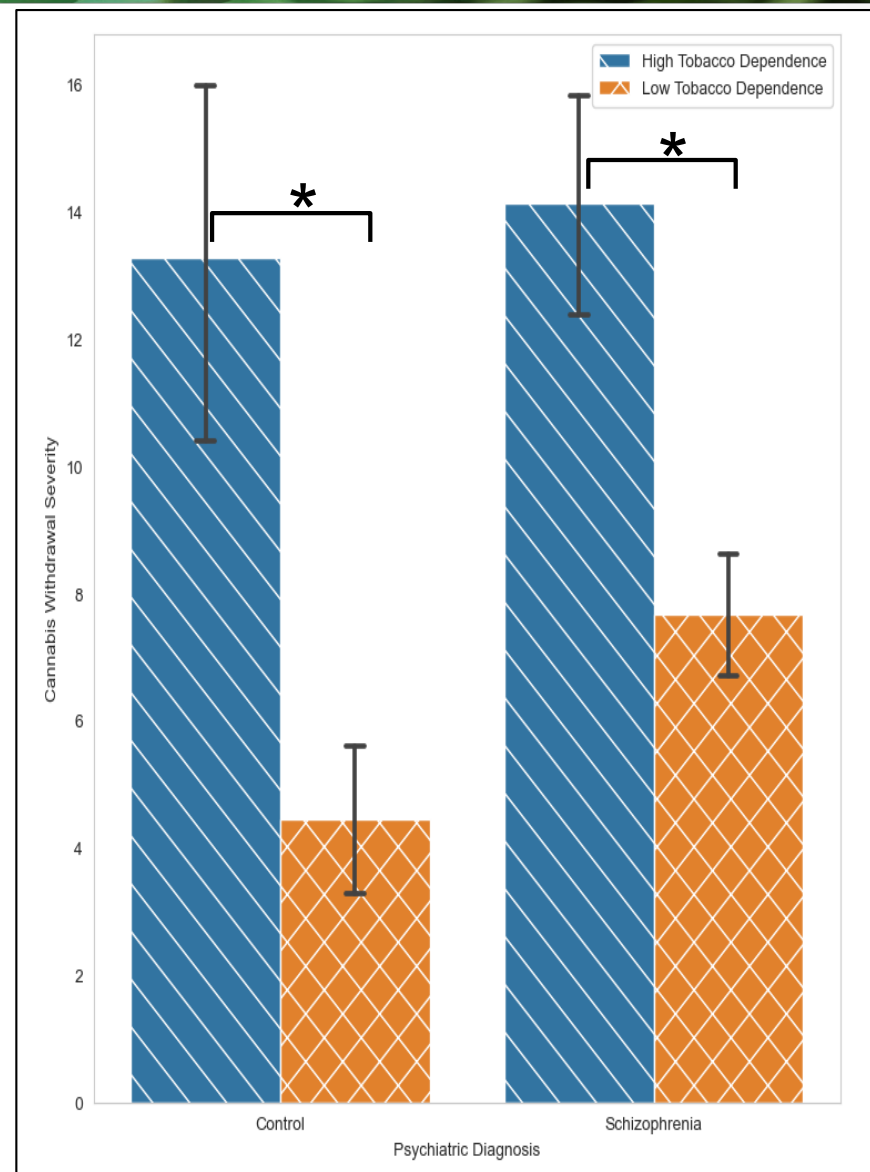
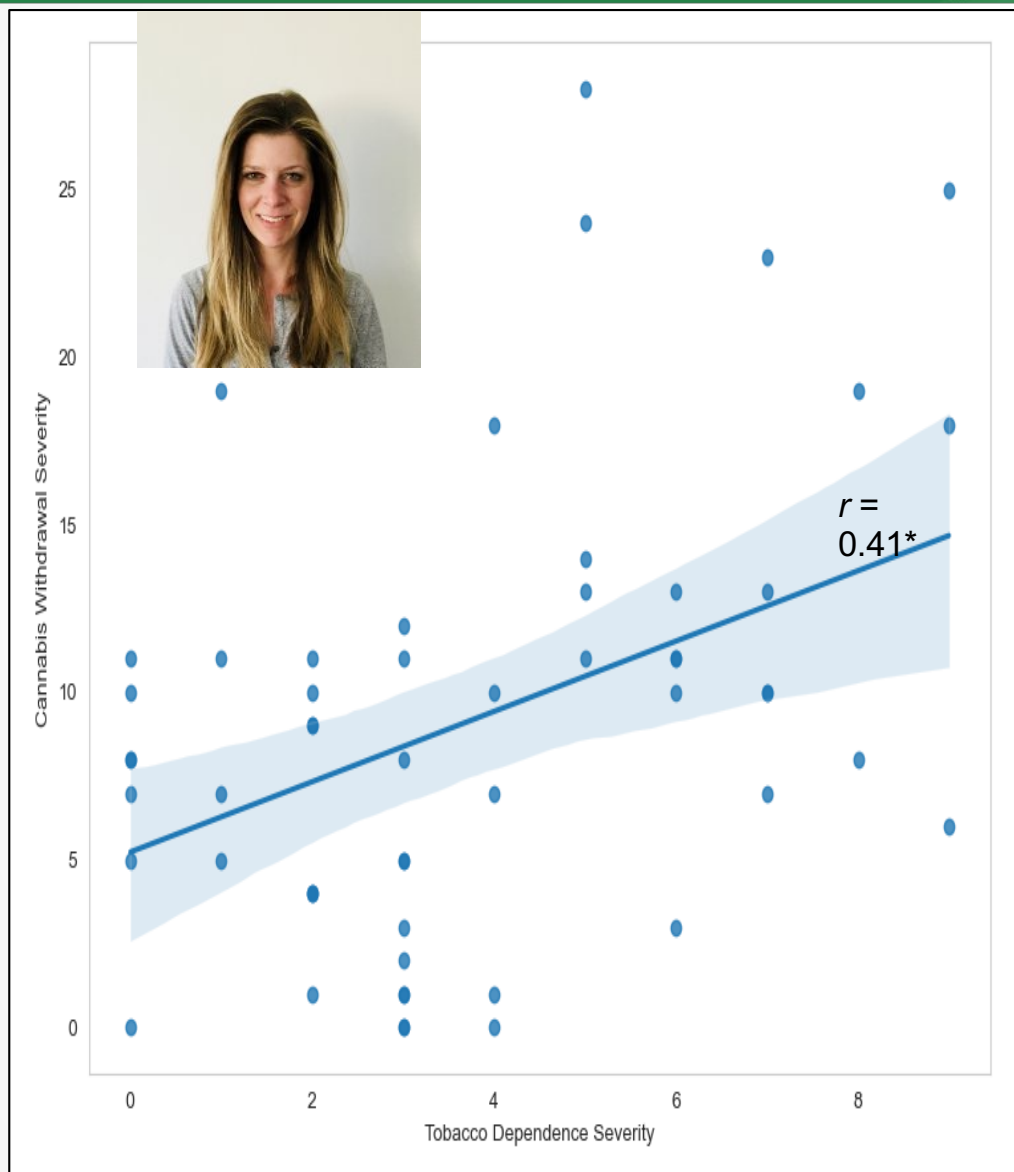
# Effects of Cannabis Reduction on Changes in Cigarette Use over Time

(Using Maximum Likelihood Estimation Analyses)

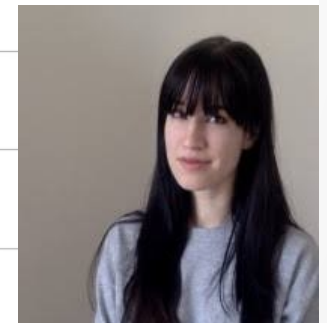
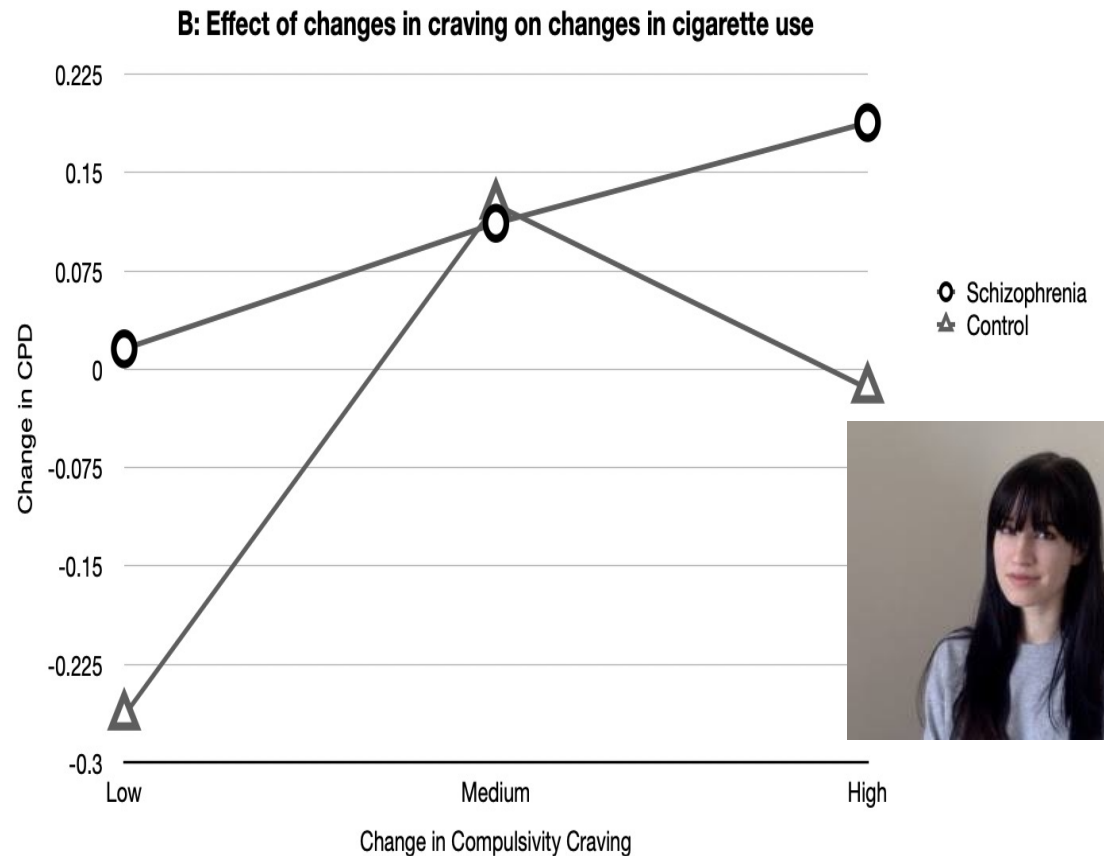
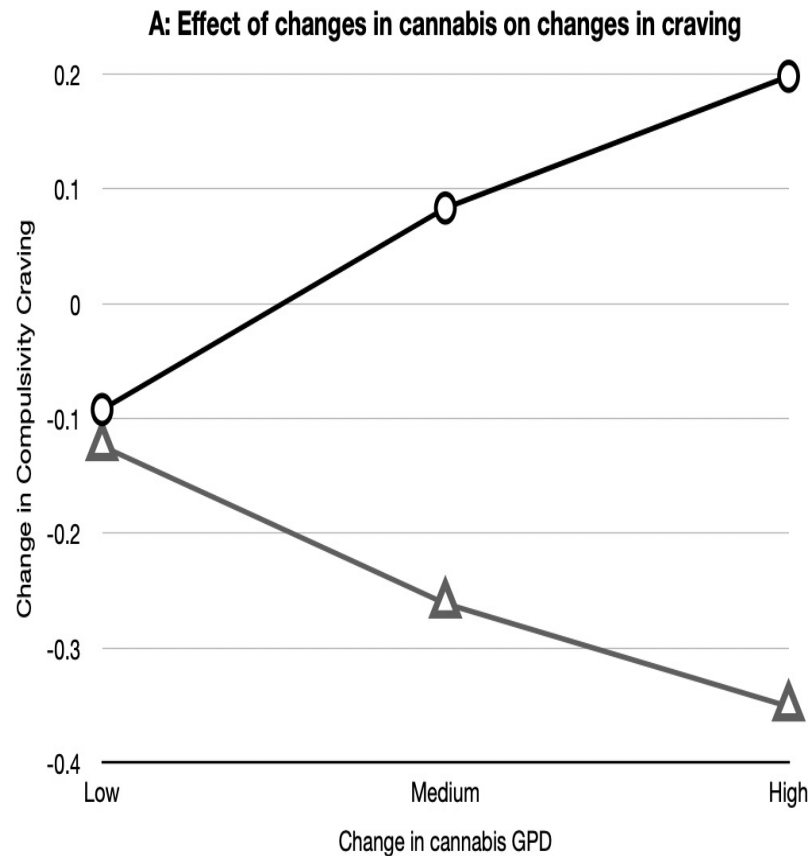


Rabin, Dermody and George (2018). Drug Alcohol Depend. 185: 181-188.

# Relationship Between Cannabis Withdrawal Severity and Tobacco Dependence Level in Schizophrenia versus Controls



# Changes in Tobacco Craving as a Function of Cannabis Use in Schizophrenia and Controls



Johnstone, S. et al. (2023). Am. J. Drug Alcohol Abuse, under revision.

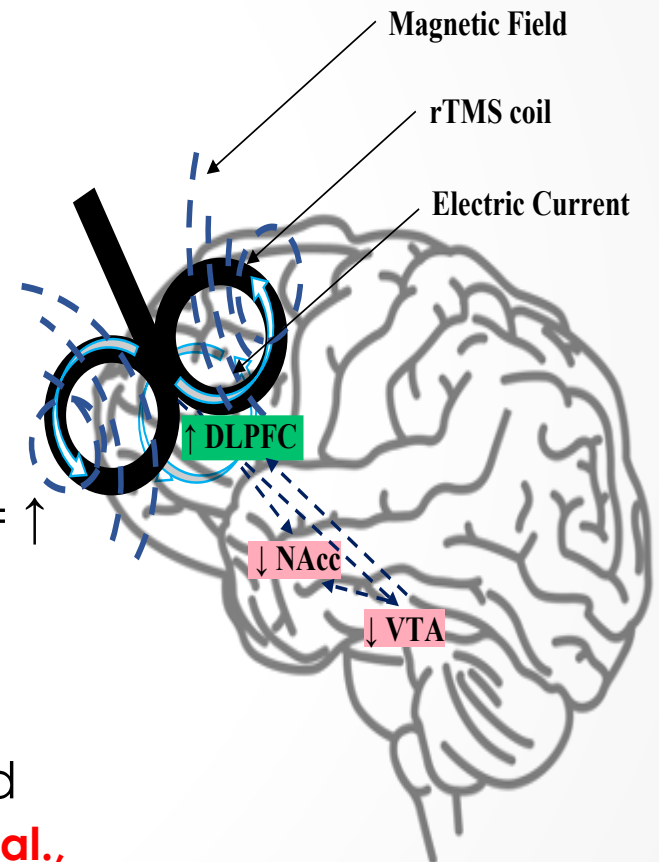
# Conclusions – Cannabis Abstinence and Tobacco Studies

- In cross-sectional studies, there was evidence that being a former or never cannabis user was associated with higher levels of tobacco smoking (*Rabin et al., 2014. Am. J. Addict. 24: 170-175*).
- In prospective studies of the effects of 28 days of cannabis abstinence in cigarette smoking ( $\geq 5$  CPD) cannabis users with and without schizophrenia, *increases in cannabis withdrawal and craving were associated with increases in tobacco smoking in schizophrenia, but NOT non-psychiatric controls* (*Rabin et al., 2018. Drug Alcohol Depend. 185: 181-188*).



# Repetitive Transcranial Magnetic Stimulation (rTMS) for Addiction Treatment in Schizophrenia

- rTMS uses weak magnetic pulses to alter neuronal firing of inhibitory/excitatory pathways in the brain.
- Both low and high frequency rTMS procedures directed to DLPFC have shown therapeutic promise/tolerability in preliminary studies:
  - **Schizophrenia**
    - rTMS enhances hypoactive DLPFC function = ↑ cognitive control (**Barr et al., 2013**)
  - **Substance Use Disorders (e.g., CUD)**
    - rTMS to DLPFC normalizes hyperactive subcortical regions (NAcc, VTA) = normalized reward processing (**Coles et al., 2018; Mehta et al., 2023**)



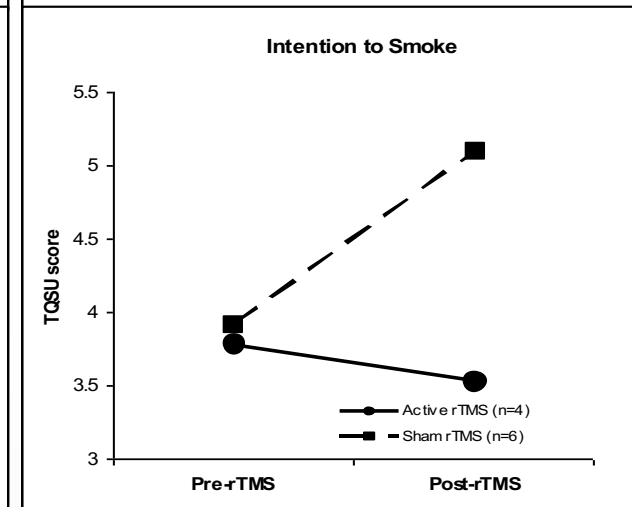
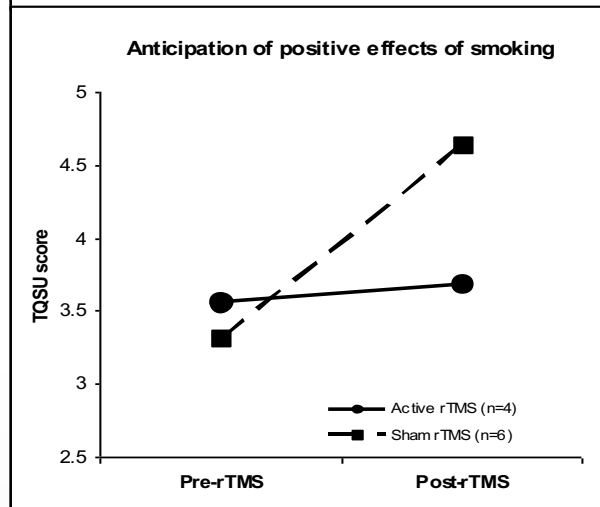
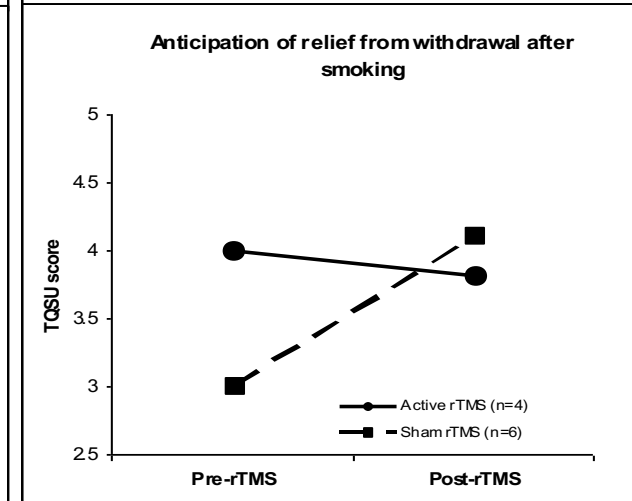
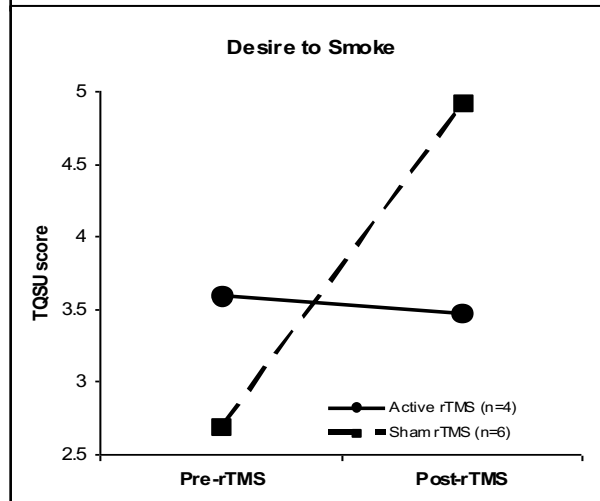
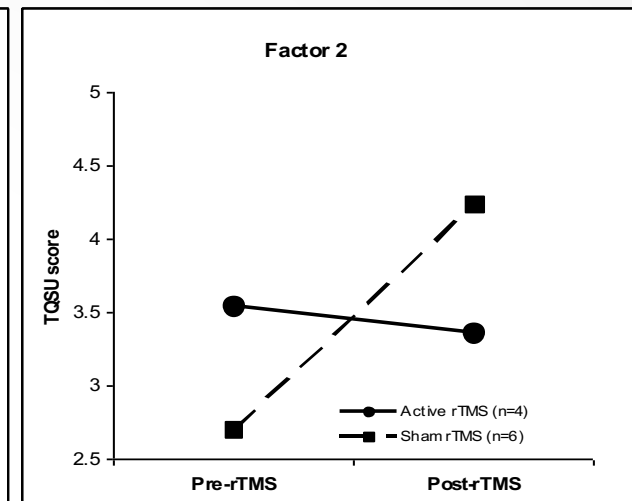
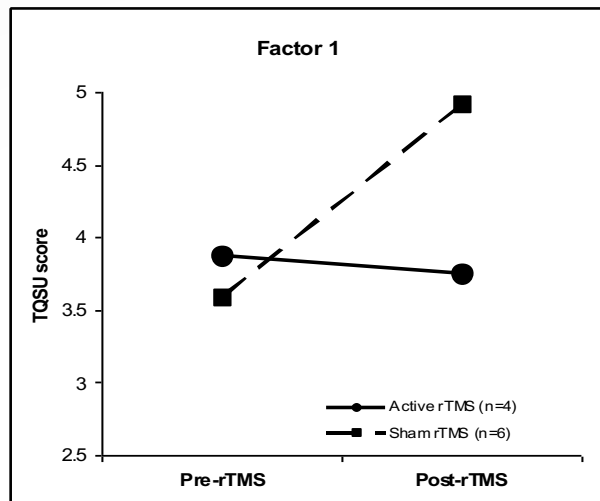
# DLPFC rTMS reduces tobacco cravings in patients with schizophrenia

Wing, V.C. et al. (2012).  
*Schizophrenia Res.* 139: 264-266.

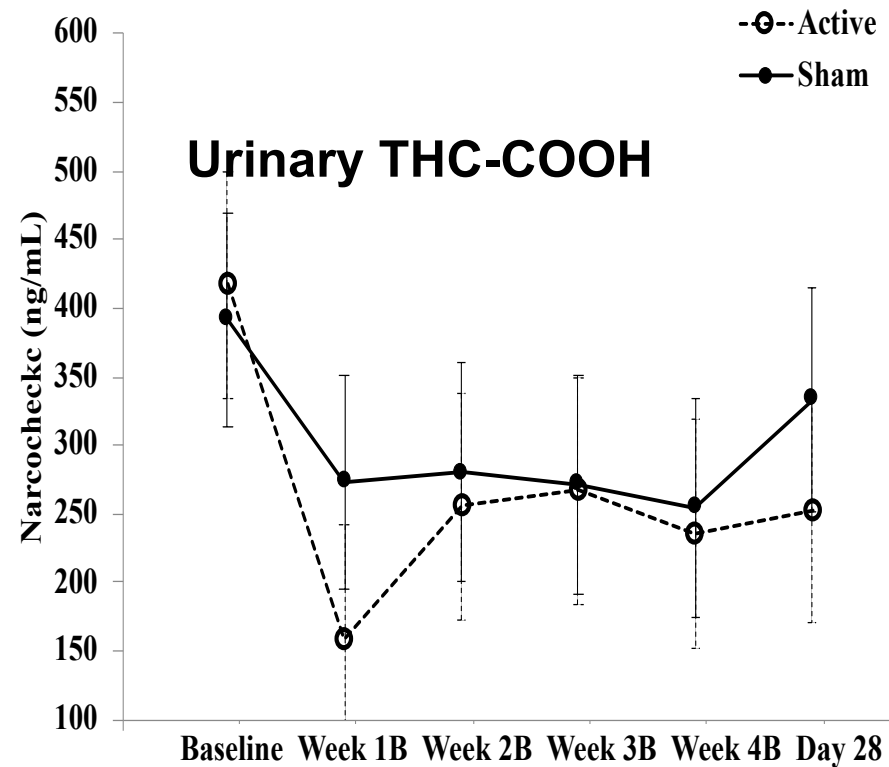
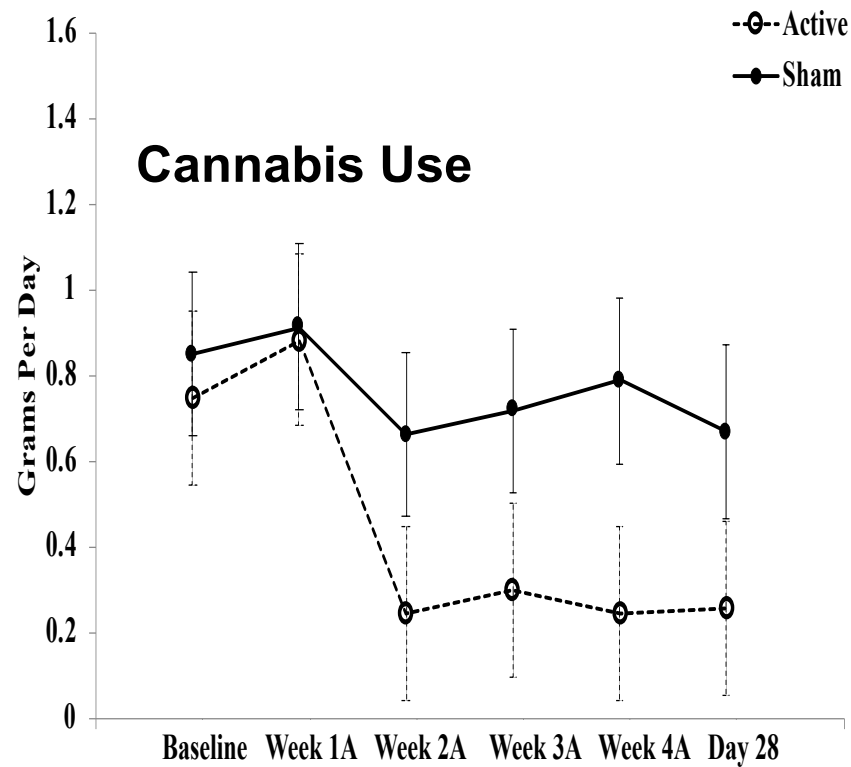


## T-QSU Measures:

- Desire to smoke
- Anticipation of relief from withdrawal after smoking
- Anticipation of positive effects of smoking
- Intention to smoke



# Change in Cannabis Use in Active versus Sham rTMS Groups

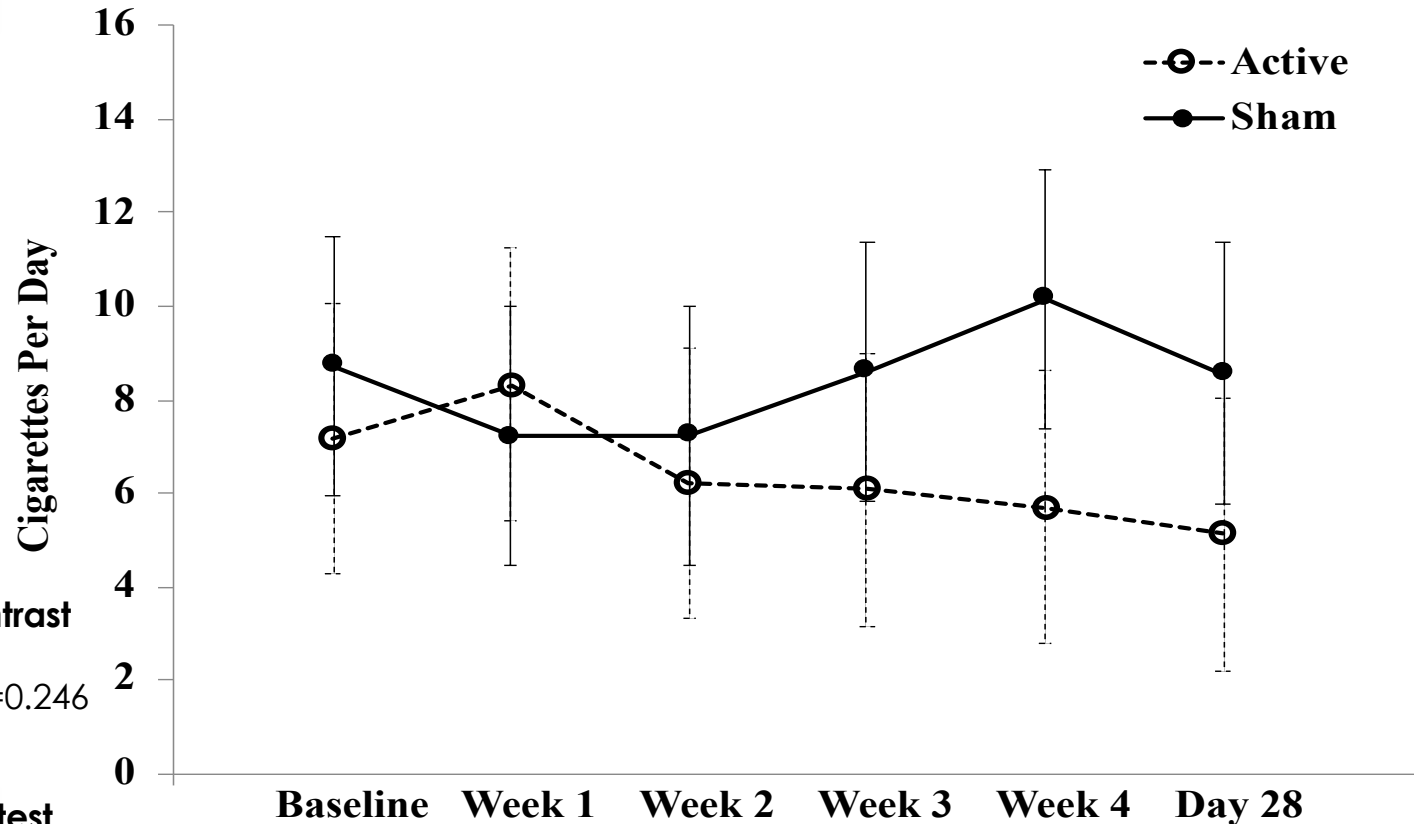


**Key Takeaway:** ↓ in cannabis use observed over time, with greater reductions in active vs. sham rTMS group.



*Kozak-Bidzinski, K. et al. (2022). NPJ Schizophrenia. 8:2.*

# Change in Tobacco Use Over Time in Active vs. Sham rTMS Groups



**Primary analysis: linear contrast test**

Estimate=1.85, df(82.04), p=0.246

**Secondary analysis: treatment\*time interaction test**

F=3.15, df(82.02), **p=0.012\***

Treatment: F=0.26, df(17),  
p=0.616

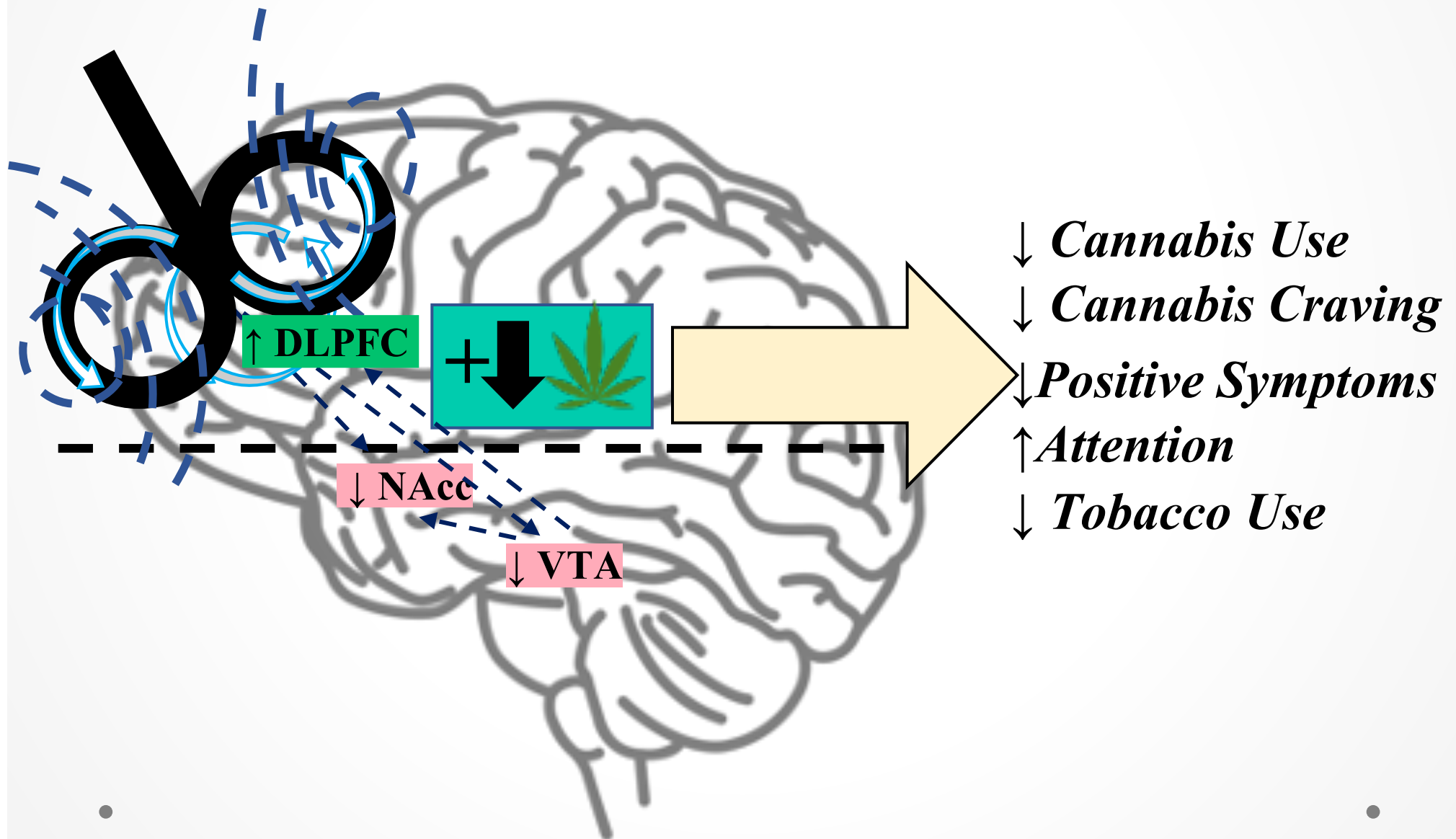
Time: F=0.97, df(82.02), p=0.441

- **Key Takeaway: Active rTMS may prevent compensatory tobacco use increases with cannabis reductions.**

***Kozak-Bidzinski, K. et al. (2022). NPJ Schizophrenia. 8:2.***



# Conclusions – rTMS Studies



# Discussion of Possible Mechanisms



- The increase in tobacco use with cannabis abstinence in SZ versus CTL subjects could represent compensation “addiction substitution” *(Rabin et al., 2018; Johnstone et al., 2023).*
- Patients with schizophrenia (versus controls) may be neurobiologically more sensitive to the effects of cannabis, as there are selective improvements in neurocognition (e.g. verbal learning and memory) in SZ versus CTL subjects with cannabis abstinence *(Rabin et al., 2017. Neuropsychopharmacology. 32: 2259-2271).*
- Further controlled studies of this cannabis and tobacco co-morbidity are warranted *(Rabin and George, 2015. Am. J. Addict. and McClure et al, 2020. Curr. Addict. Reports)*
- ***Suggests that cannabis and tobacco co-treatment in people with schizophrenia should be addressed sequentially versus concurrently.***



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National Institute  
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Advancing Addiction Science



