



Neuropsychiatric Effects of Cannabis

Igor Grant, MD

University of California, San Diego

Center for Medicinal Cannabis Research



Cannabis and Neuropsychiatry: Overview

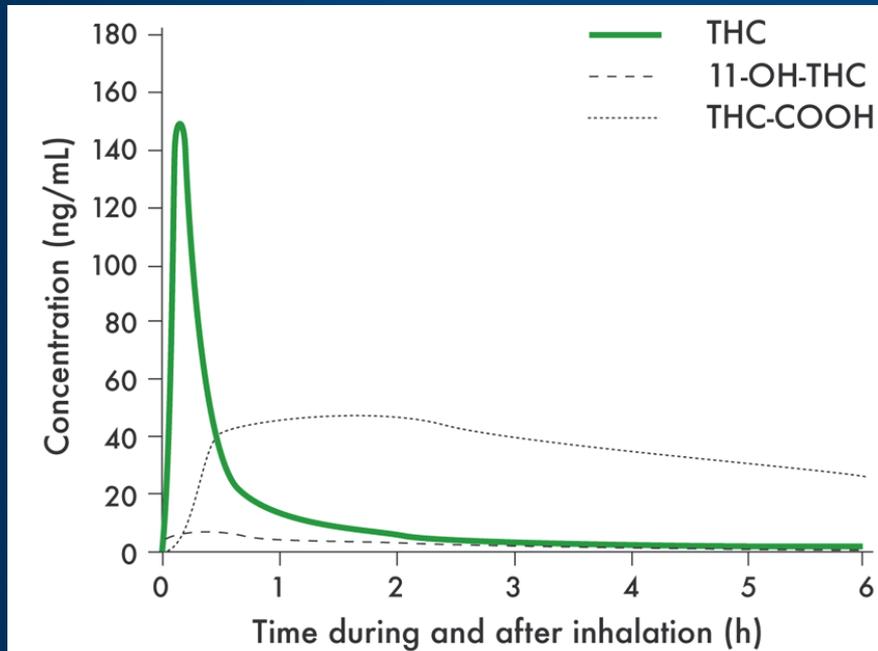
- **Purpose:** to review the effects of cannabis on the brain and behavior
- **Focus:** on those neuropsychiatric phenomena that may be particularly relevant in evaluating risk:benefit of medicinal cannabis
 - » Neurocognitive – attention, perceptual, verbal, memory, processing speed, executive functions, etc.
 - » Complex cognitive-behavioral – driving as an example
 - » Serious psychiatric – eg., vulnerability to schizophrenia and depression
- **The time course of these neuropsychiatric effects can be grouped as:**
 - » Acute – minutes to hours after dosing
 - » Intermediate (residual) – days to weeks after stopping regular use
 - » Long term (persistent) - months to years after stopping regular use

Acute Effects of Cannabis Use

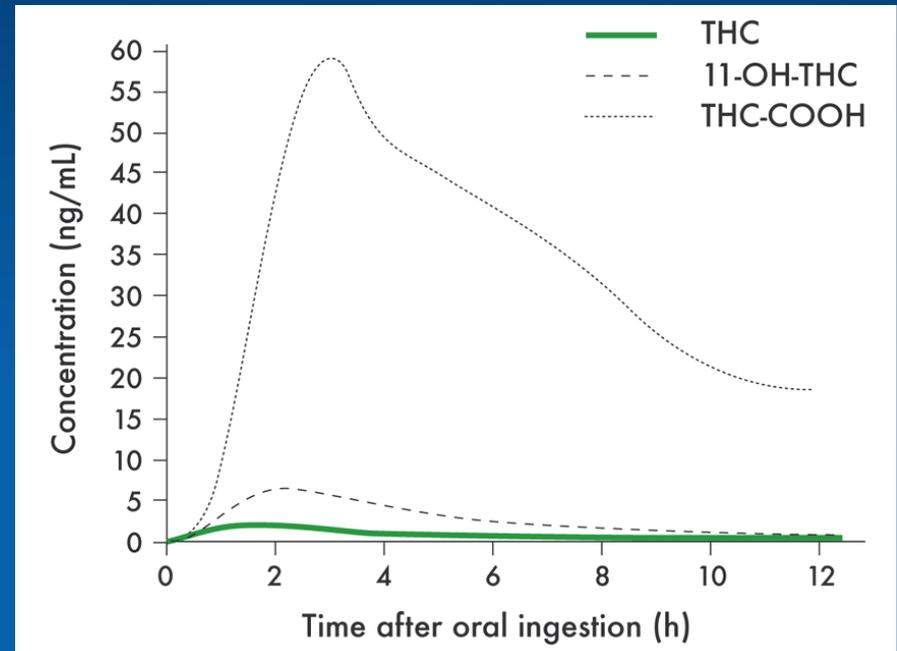
- **Cardiovascular:** ↑ HR; vasodilation; ↓ BP
- **Neurological:** psychomotor slowing; cerebellar signs; drowsy; fatigued;
- **Cognitive:** memory; time sense; executive
- **Emotional:** giddy; calm; anxious; depressed
- **Ideational:** unusual insights; paranoid
- **Perceptual:** dissociation; illusions; hallucinations; synesthesia (eg., “seeing music”)
- **Appetitive:** hunger

Plasma THC Levels – Smoked vs. Oral

inhaled cannabis ~34mg THC



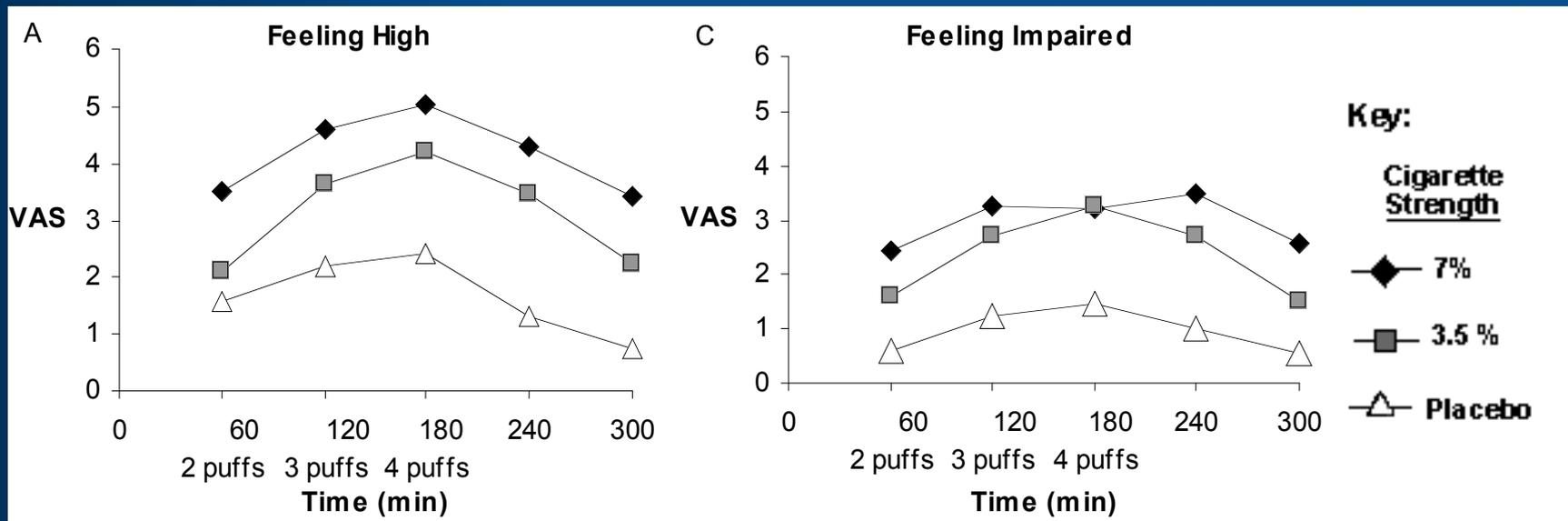
15mg oral THC (dronabinol)



Mean plasma concentrations of Δ^9 -tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THC-COOH) following administration smoked cannabis vs. oral dronabinol.

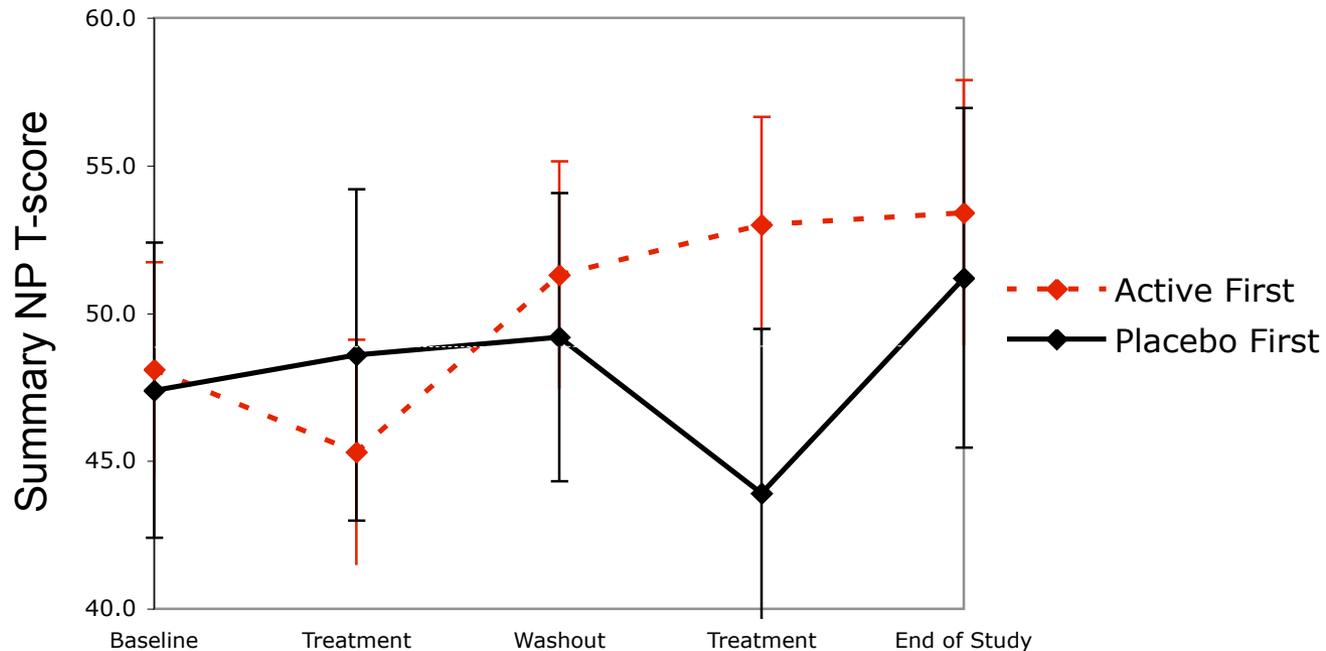
Source: Grotenhermen, et al. 2003. *Clin Pharmacokinet* 2003; 42 (4): 327-360.

Acute Psychoactive Effects of Cannabis: subjective ratings



Source: *Wilsey, et al. 2008, Pain, 9(6):506-521.*

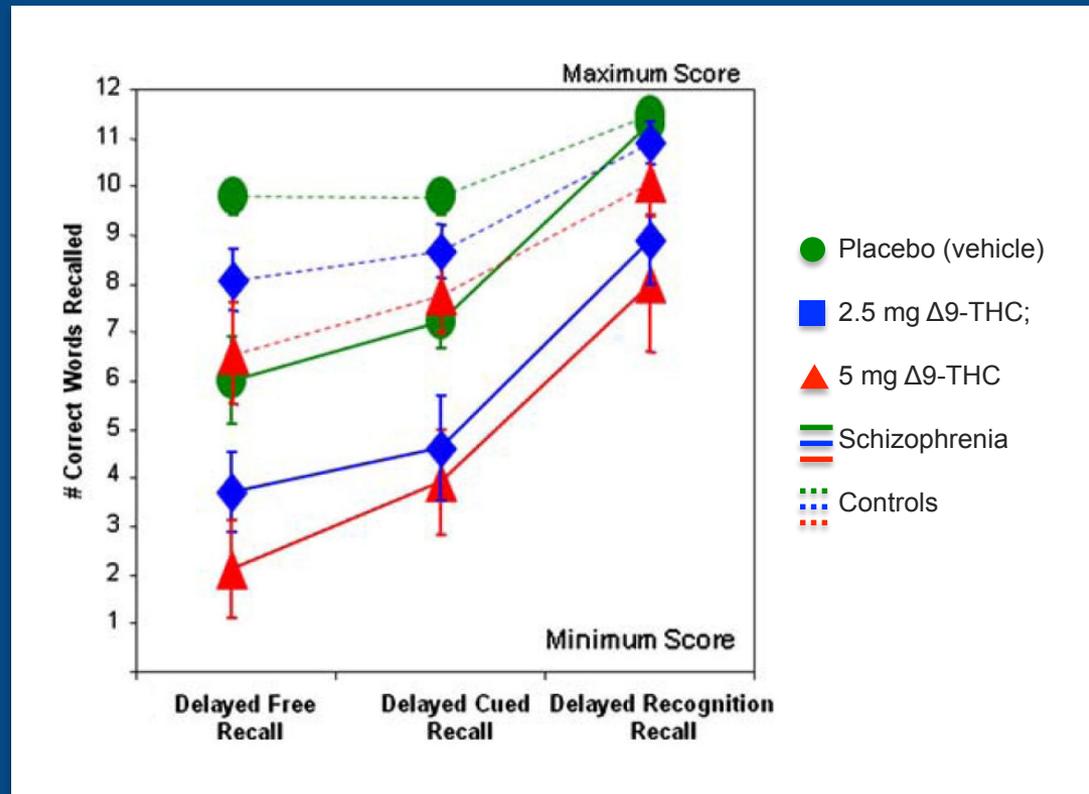
Neurocognitive Effects after 3 days of daily cannabis administration to neuropathy patients



Neuropsychological t-scores after active and placebo cannabis administration. Active cannabis reduced the NP T score by a median of 7.3 points (IQR = -10.6, - 2.6), $p < 0.001$. Treatment=third day; washout=2 wk after last treatment; Y axis= NP global T score

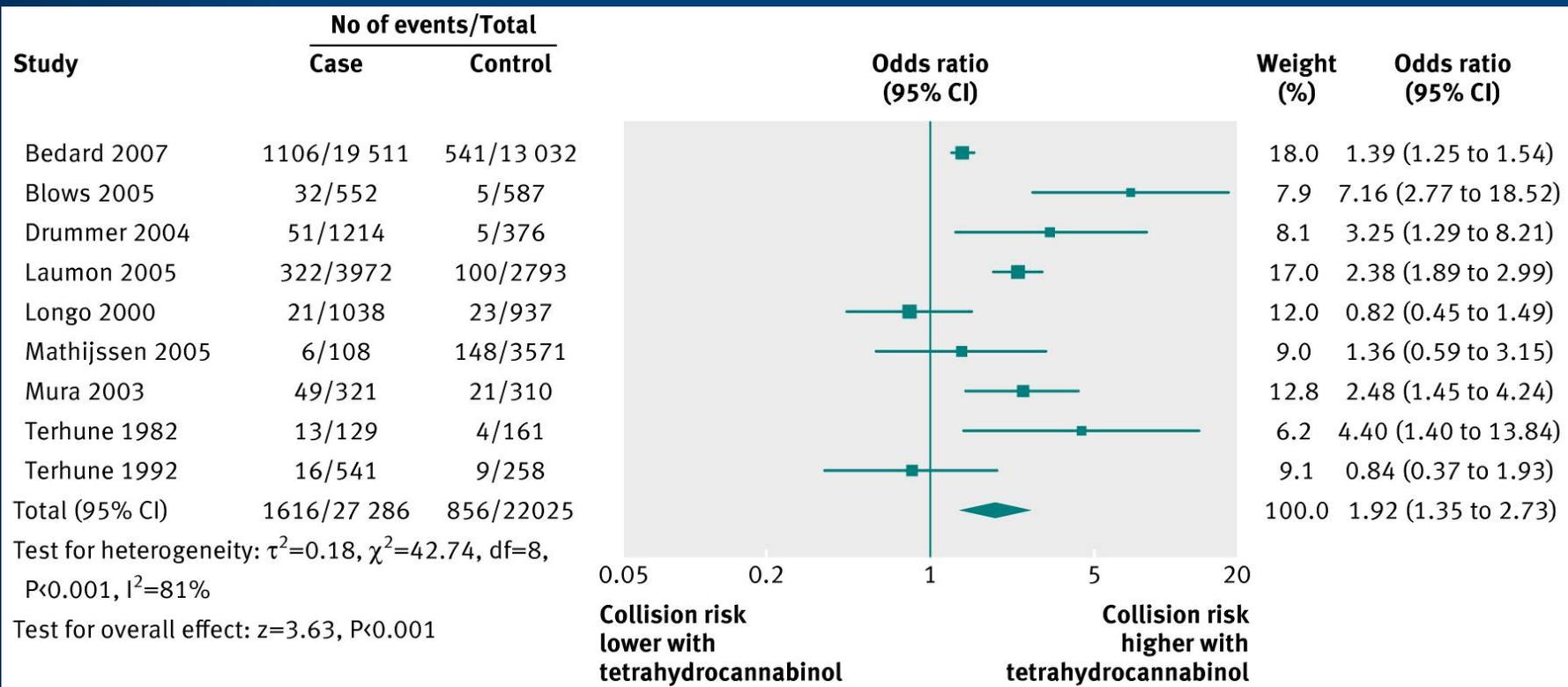
Source: *Ellis et al 2008 Neuropsychopharmacology, 34:672-80.*

Memory Impairments from Acute THC may have more clinical significance in those with subtle deficits: example of controls and schizophrenics



Adapted from: *D' Souza et al. Eur Arch Psychiatry Clin Neurosci. 2009; 259(7):413–431.*

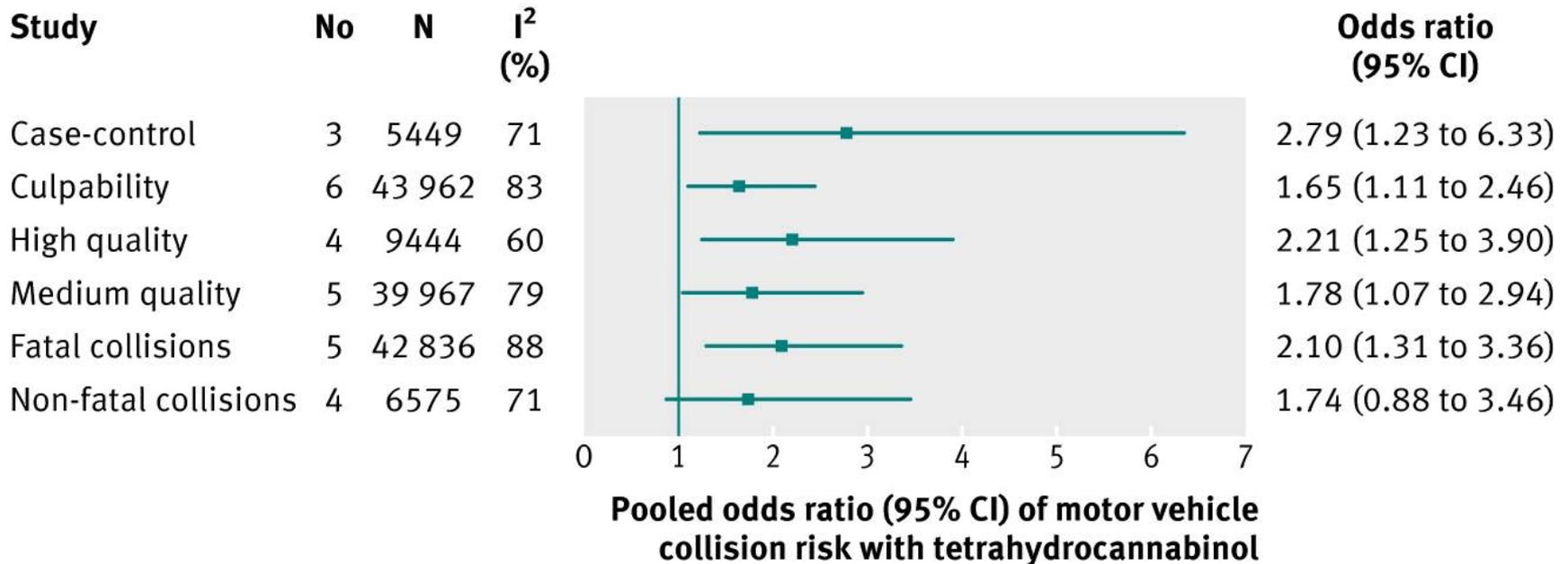
MJ intoxication slightly increases motor vehicle collision risk



Meta-analysis of observational studies investigating the association between acute cannabis consumption and motor vehicle crashes.

Source: Asbridge, et al., *BMJ*. 2012; 344:e536

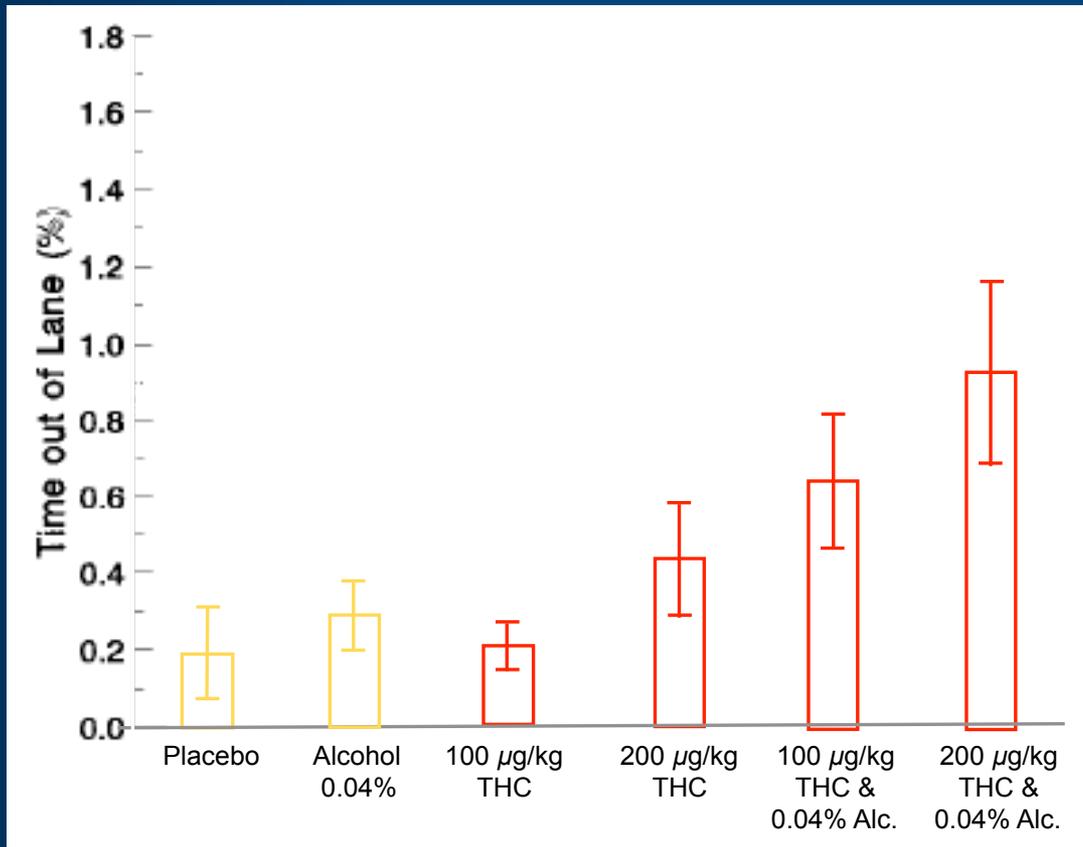
Odds Ratios for MJ intoxication on driving sorted by type of study



Pooled odds ratio (95% CI) of motor vehicle collision risk with tetrahydrocannabinol for subgroups of studies.

Source: *Asbridge, et al., BMJ. 2012; 344:e536*

Driving and Cannabis: Effects of Alcohol

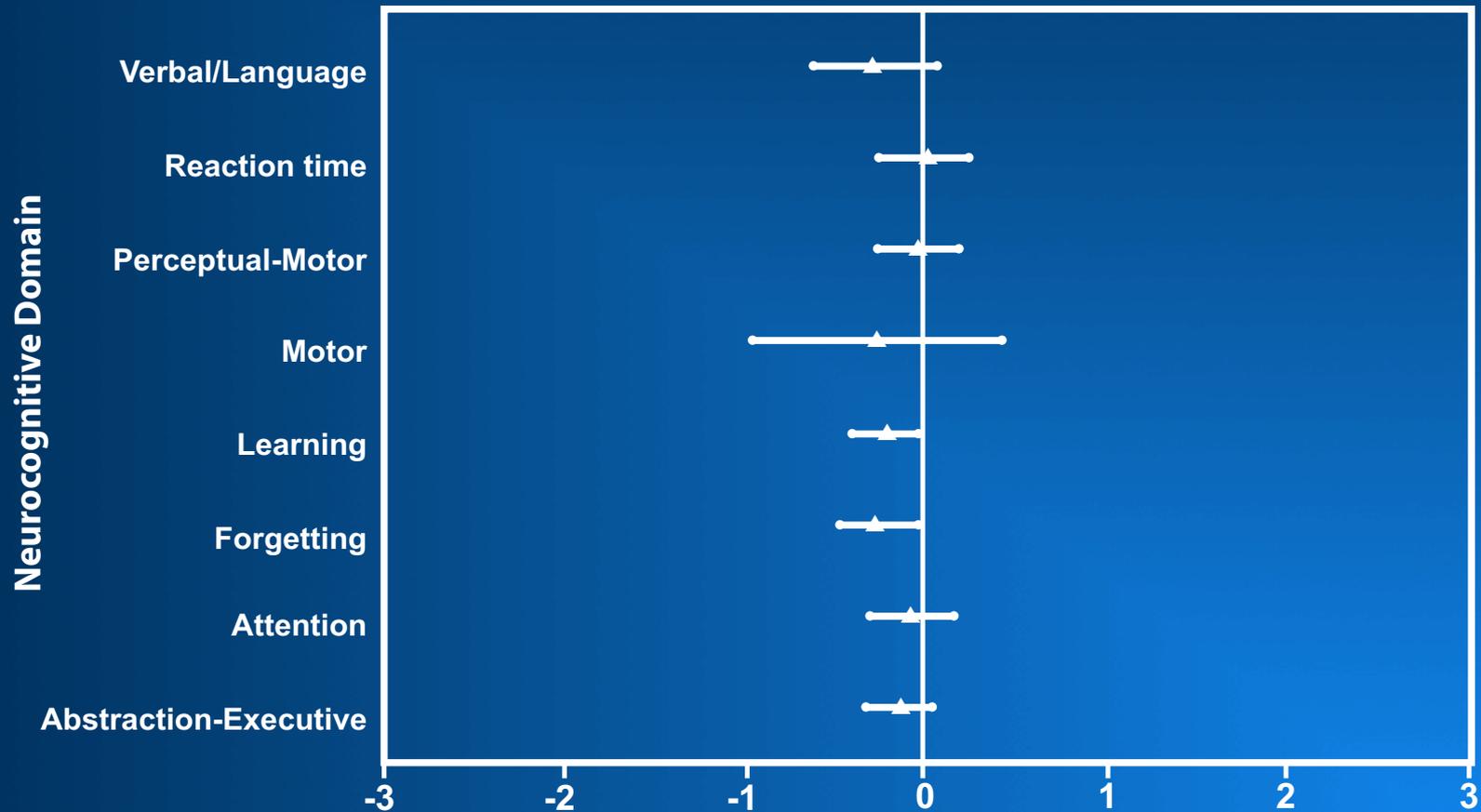


Geometric mean (+SE) of time out of lane (TOL, per cent) in first and second repetitions of the Road Tracking Test in every condition. Target blood alcohol level (BAC) was 0.04 g/dl.

Source: Adapted from Ramaekers, et al. Marijuana, Alcohol and Actual Driving Performance. Human Psychopharmacol. Clin. Exp. 15, 551-558 (2000).

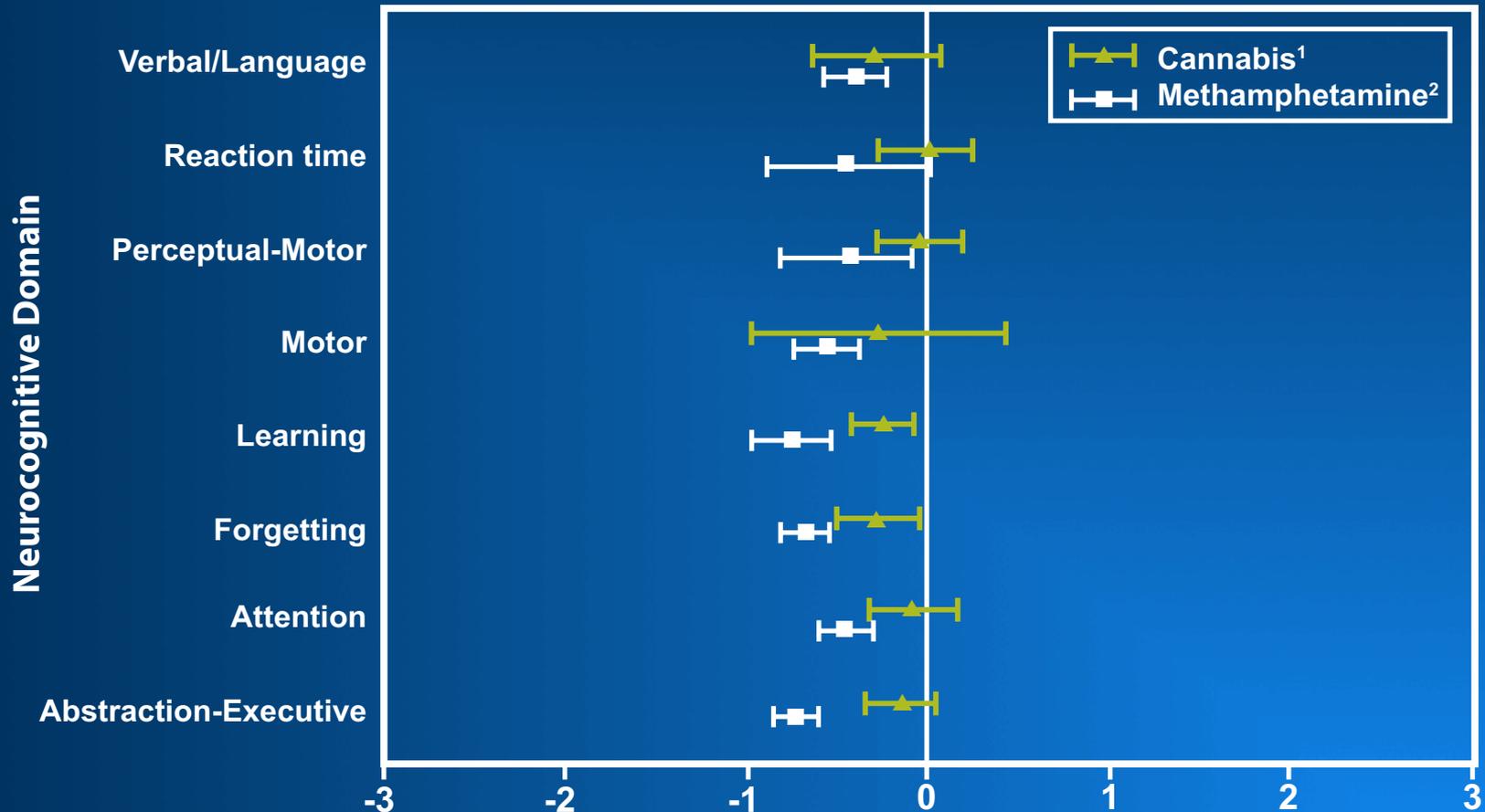
Long Term Neurocognitive Effects of Marijuana

Results of Meta-analysis of 15 NP studies



Source: Data from Grant et al. (2003) JINS. 9;679-689

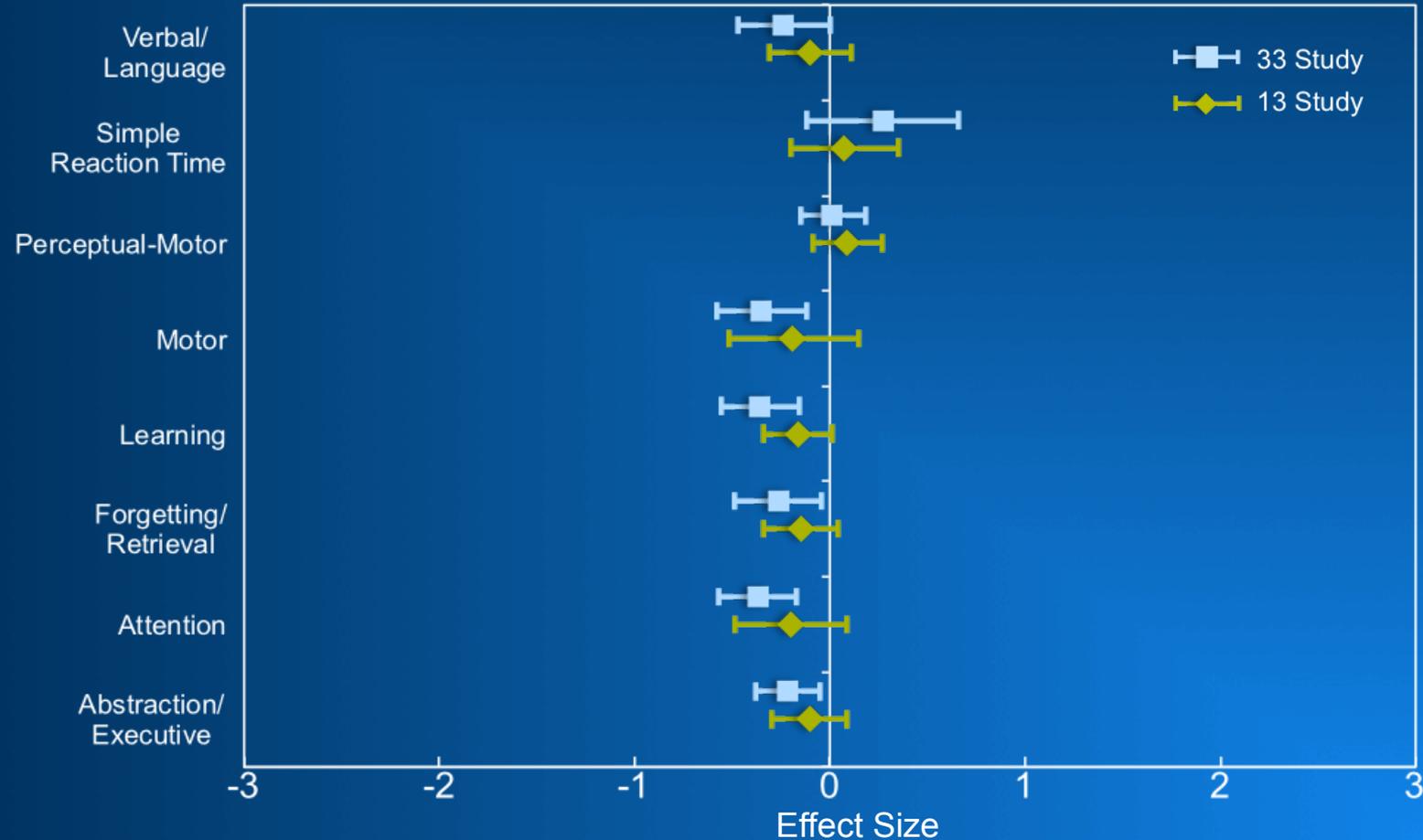
Long Term Neurocognitive Effects Methamphetamine vs. Cannabis



¹Data from Grant et al. (2003) JINS. 9;679-689.

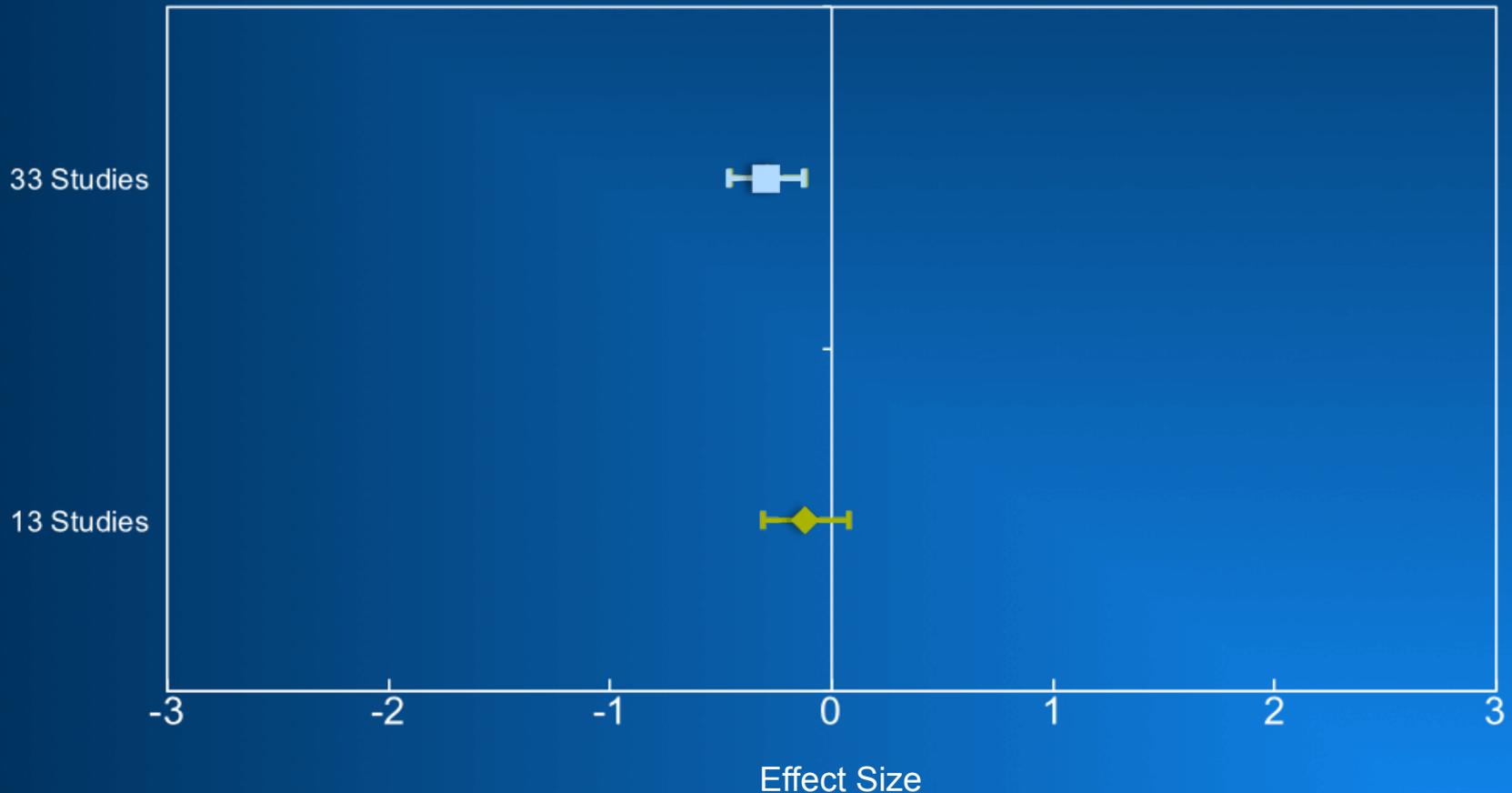
²Data from Scott et al. (2007) Neuropsychol Rev. 17;275-297.

Persisting neurocognitive deficits? Meta-analyses based on 33 Studies of nonintoxicated MJ users and subset of 13 studies with minimum 25 days abstinent



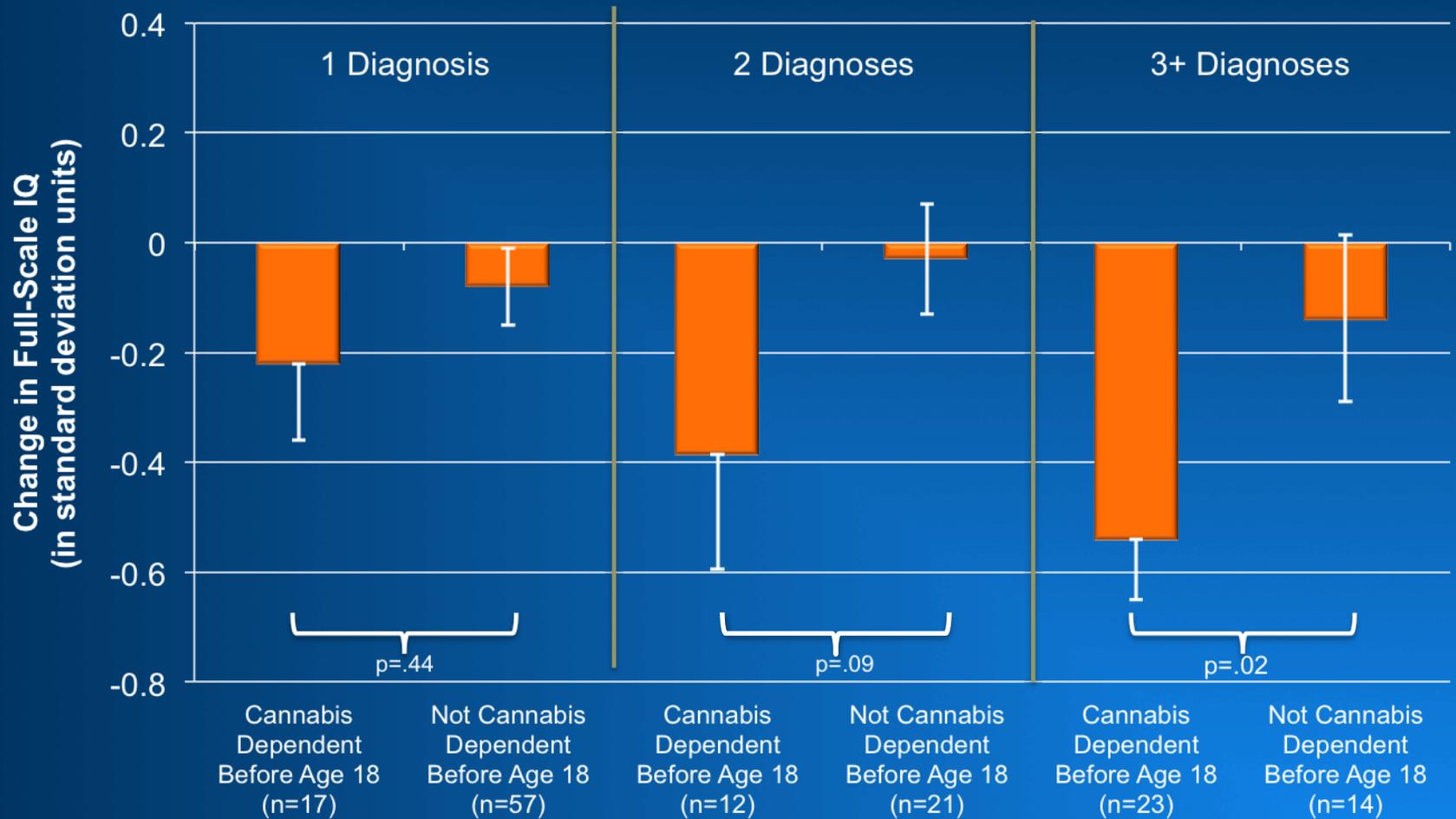
Schreiner & Dunn, Experimental and Clinical Psychopharmacology, 2012, 20(5):420-429.

Persisting neurocognitive deficits? Meta-analyses based on 33 Studies of nonintoxicated MJ users and subset of 13 studies with minimum 25 days abstinent



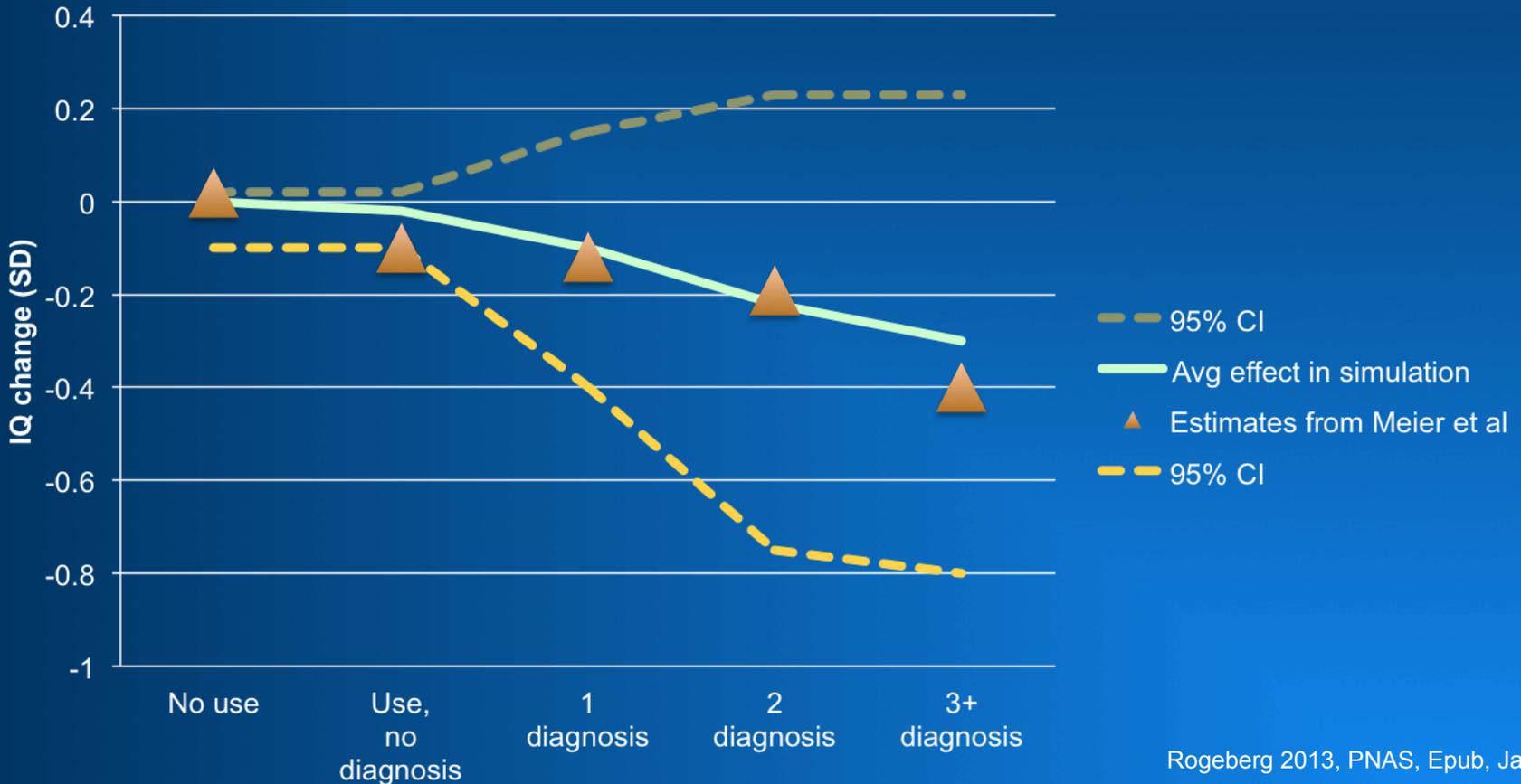
Schreiner & Dunn, *Experimental and Clinical Psychopharmacology*, 2012, 20(5):420-429.

Does Cannabis dependence before age 18 lower IQ 20 yrs later?



Meier M H et al. PNAS 2012;109:E2657-E2664

Alternative causal model predicting worse IQ in early onset, repetitive MJ users: predicted follow-up IQ from SES model (blue line) vs actual Dunedin data (orange triangles)



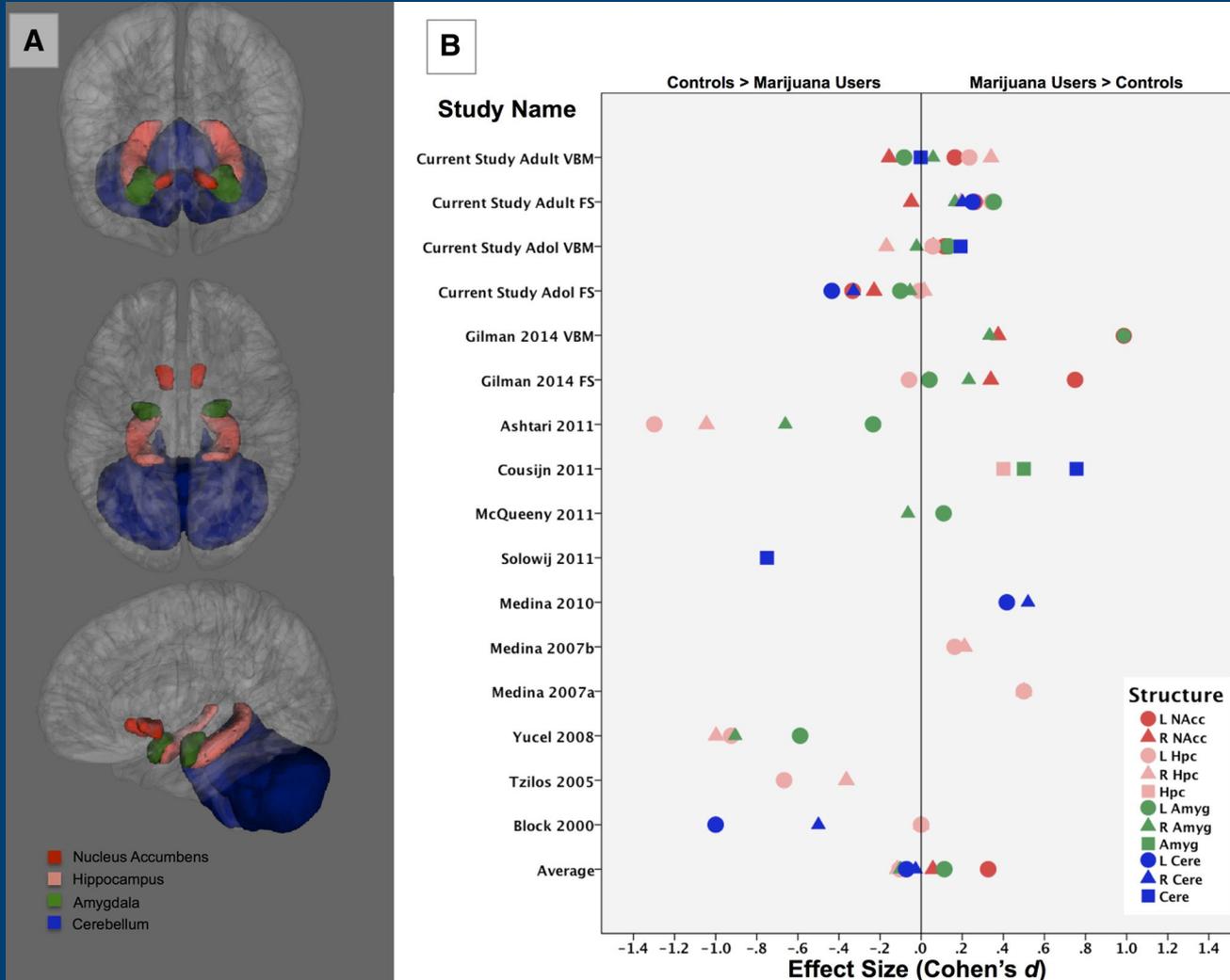
Rogeberg 2013, PNAS, Epub, Jan 14

Brain Structure Marijuana Users vs. Non Users

Study	Method	Result
Co, 1977	CT	NS
Keuhnle, 1977	CT	NS
Hannerz, 1983	CT	NS
Wiesbeck, 1991	CT	NS
Aasly, 1993	vMRI	Cerebral & Cerebellar Atrophy
Wilson, 2000	vMRI	Reduced Whole Brain / Grey Volume
Block, 2000	vMRI	NS
Tzilos, 2005	vMRI	NS
Matochik, 2005	vMRI	Regional Volume Loss of Parahippocampal
Jager, 2007	vMRI	NS
Yucel, 2008	vMRI	Reduced hippocampal, amygdala volumes
Gruber, 2005	MRI DTI	NS
DeLisi, 2006	MRI DTI	NS
Arnone, 2008	MRI DTI	NS
Zalesky, 2012	MRI DTI	NS
Medina ^a , 2007	MRI	NS
Medina ^b , 2007	MRI	NS
Mata, 2010	MRI	NS
McQueeney, 2011	MRI	NS
Lopez-Larson, 2011	MRI	NS
Cousijn, 2011	MRI	NS
Ashtari, 2011	MRI	Reduced hippocampal volume, increased whole brain volume
Schacht, 2012	MRI	Reduced hippocampal volume
Batalla, 2013	MRI (VBM)	NS

Sources: Quickfall & Crockford (2006). J Neuropsychiatry Clin Neurosci. 18(3):318-32. Martin-Santos, et al. (2010). Psychological Medicine. 40:383-398. Rochetti, et al. (2013). Psychiatry Clin Neurosci. 2013 Nov;67(7):483-92.

Daily marijuana use not associated with brain morphometric measures in 2015 study that matched MJ and non MJ users on cofactors that may be linked to brain changes, eg., alcohol use



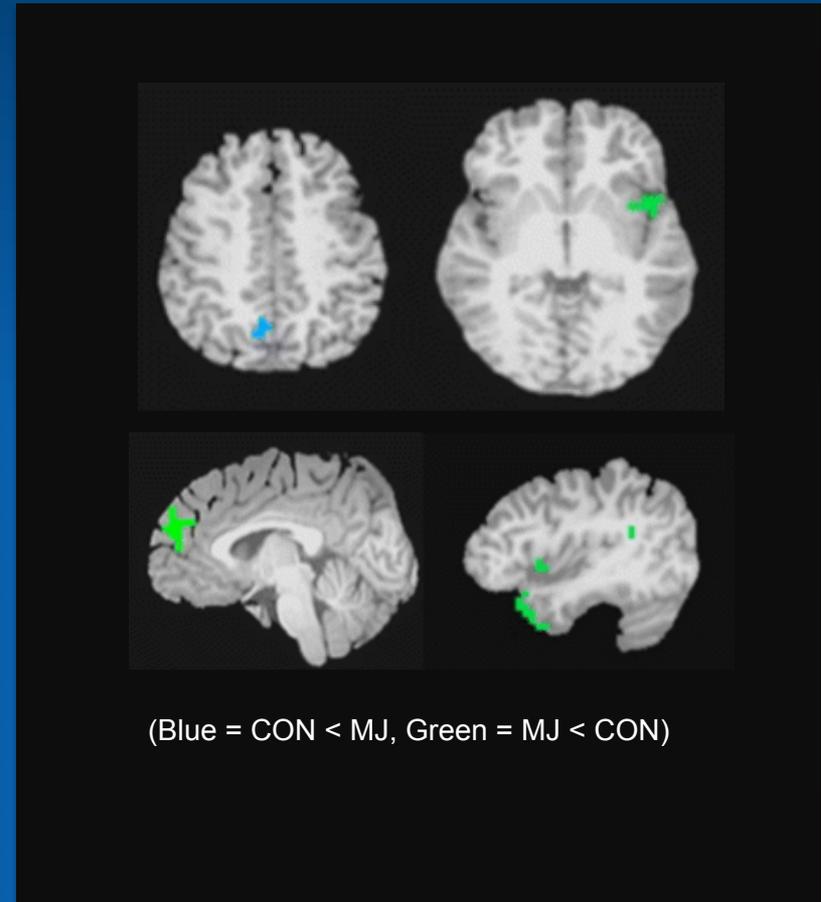
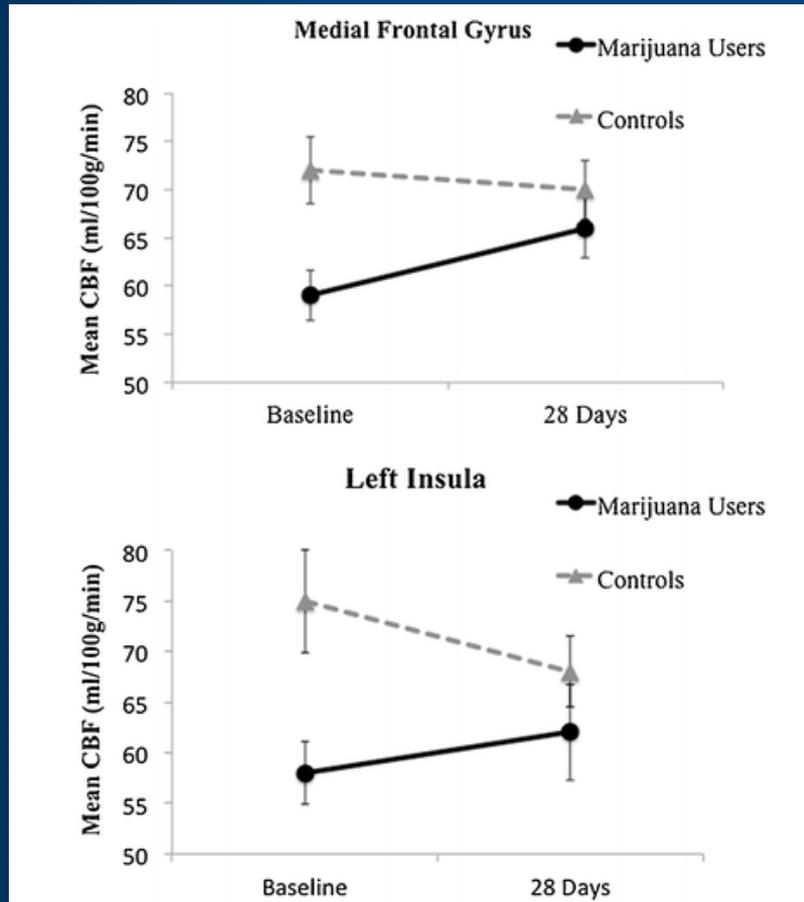
Weiland, et al. J Neurosci. 2015 Jan 28;35(4):1505-12.

Functional Brain Imaging Studies

- **In acutely cannabis intoxicated:**
 - » ↑ cerebral blood flow
 - » ↑ activation (anterior cingulate, frontal lobe, cerebellum)
 - » No consistent change in cerebral metabolic rate
- **In abstinent longer term cannabis users:**
 - » ↓ cerebral blood flow
 - » ↓ activation on fMRI
 - » No consistent change in cerebral metabolic rate
 - » **Note: effects of co-occurring tobacco use not always accounted**

Source: Quickfall & Crockford (2006) J Neuropsychiatry Clin Neurosci. 18(3):318-32.

Cerebral blood flow differences between adolescent MJ users and nonusers disappear after 28 days abstinence

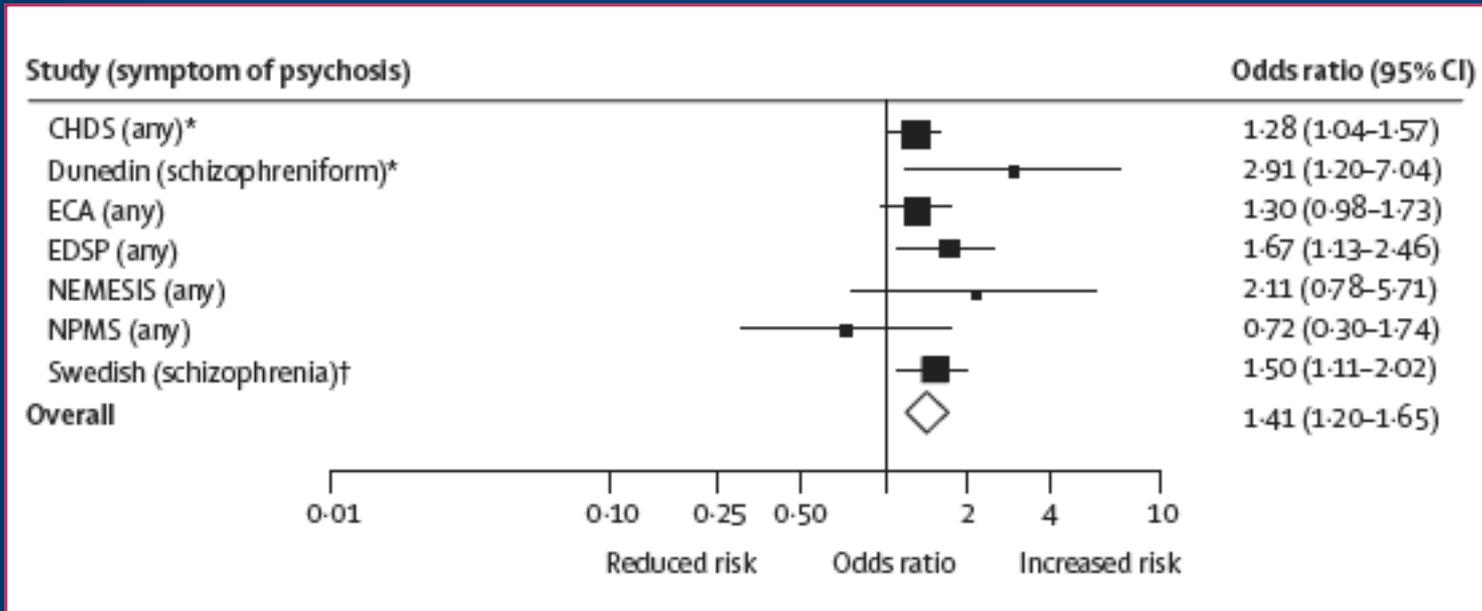


Jacobus et al, 2012. Psychopharmacology, Aug;222(4):675-84.

Cannabis and Schizophrenia

- Does cannabis cause schizophrenia?

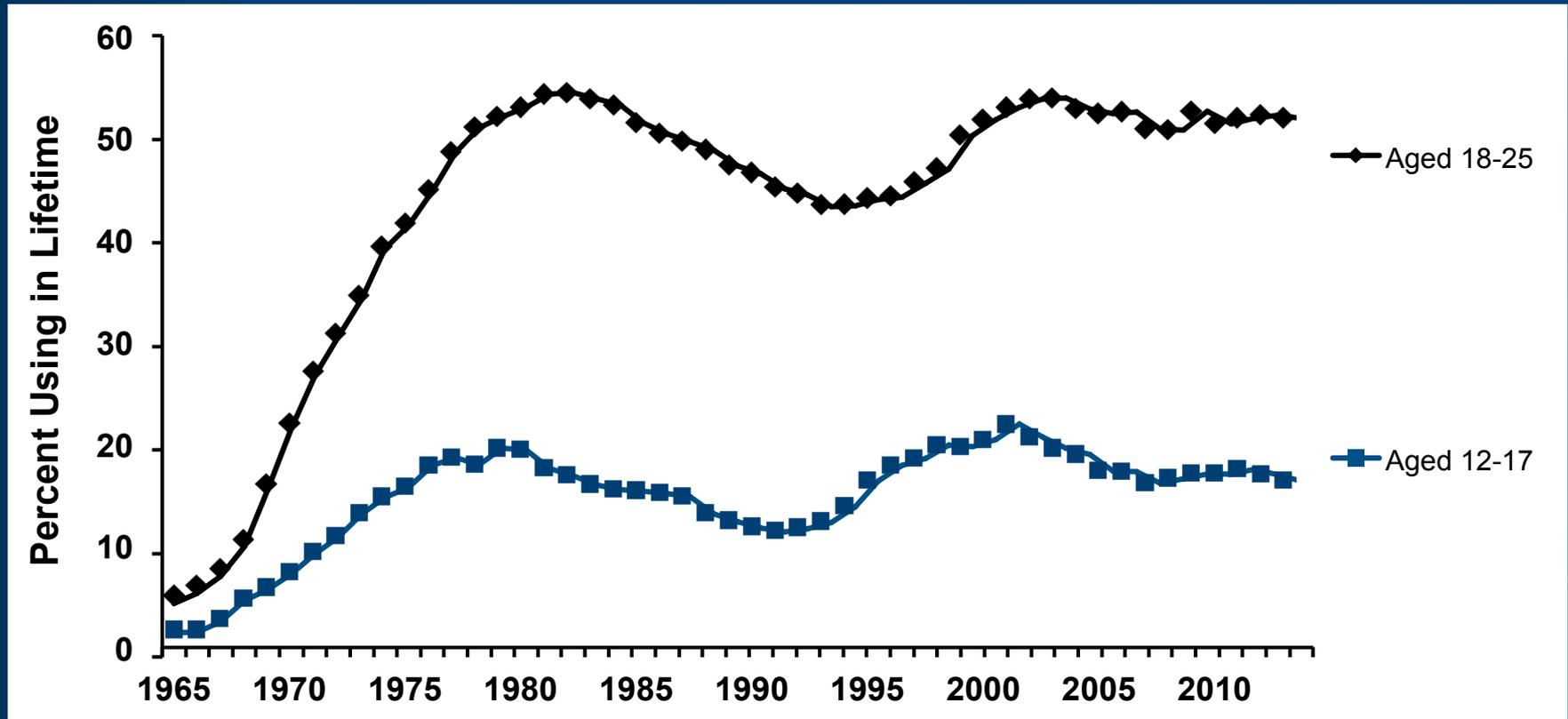
Cannabis and Schizophrenia



- Forest plot showing adjusted odds ratios and 95% CI for any psychosis outcome according to ever use of cannabis in individual studies. Pooled adjusted odds ratio **1.41**, 95% CI **1.20 - 1.65**.

Source: Moore, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 2007; 370: 319–28

Prevalence of Cannabis Use in the U.S.

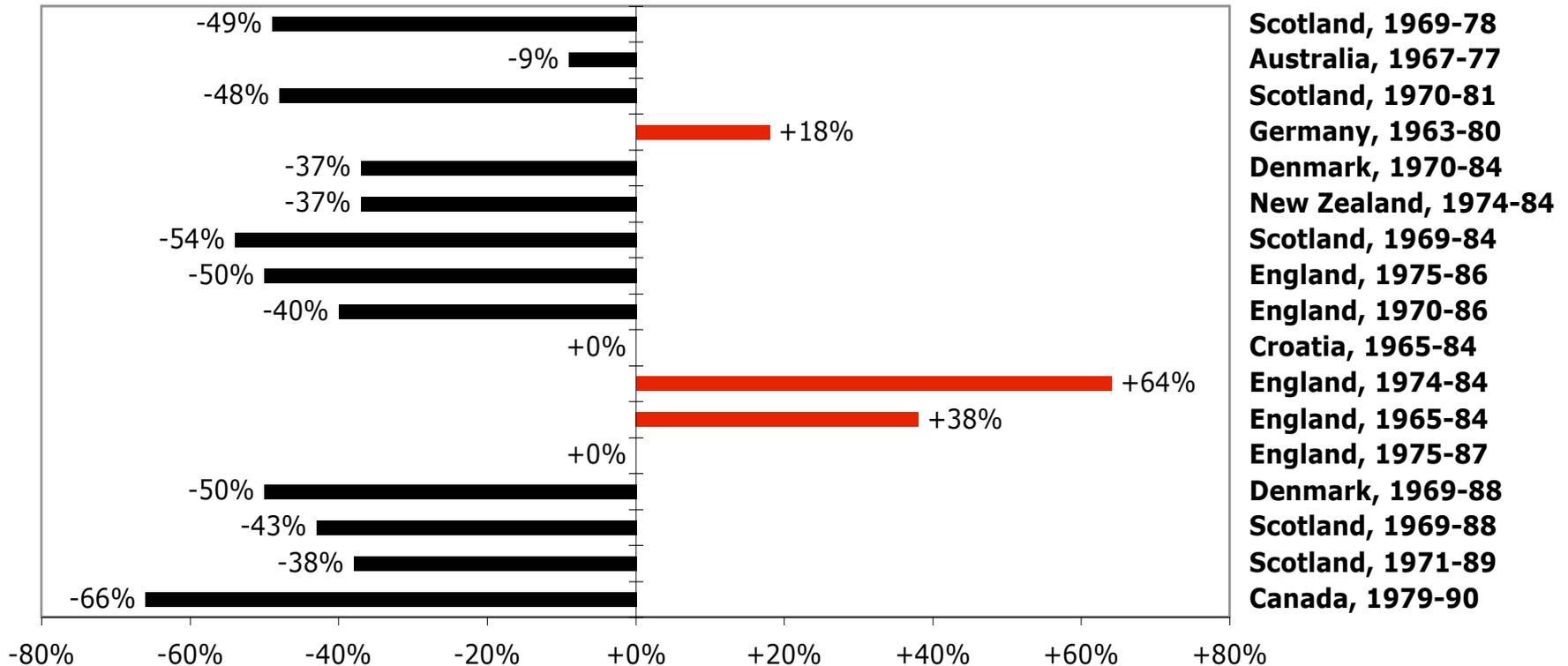


Percentages are calculated using a weighted ratio estimate. Lifetime drug use status and age group, for each specified year, were determined using the age, date of first use, and interview date for each respondent.

Source: Data from National Survey on Drug Use and Health. 2002-2013.

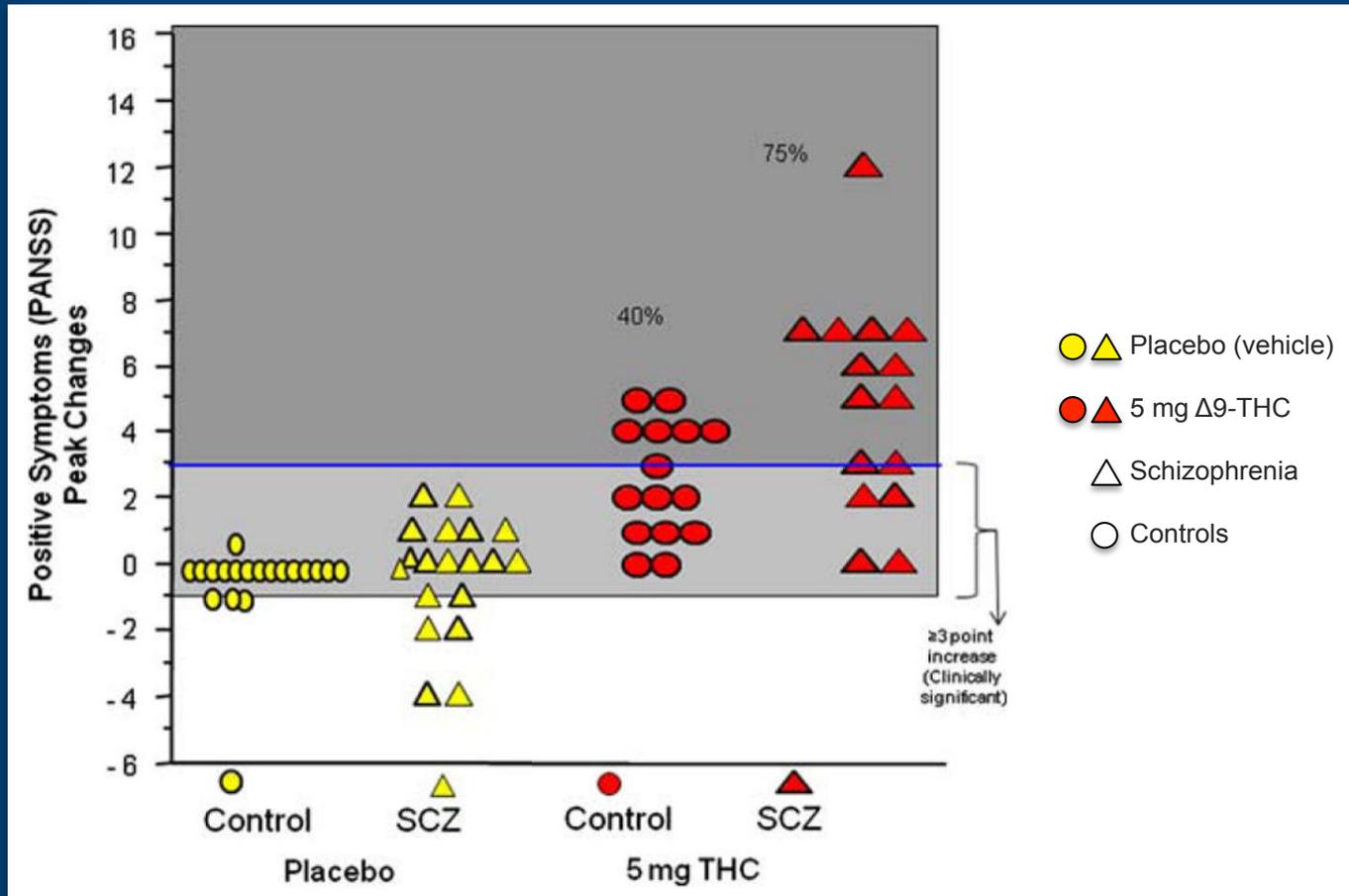
Schizophrenia Over Time

Change in Incidence of Schizophrenia by Study Location, 1965-1990



Source: Data from Warner R. Time Trends in Schizophrenia: Changes in Obstetric Risk Factors With Industrialization. Schizophrenia Bulletin. 1995. 21. 3;483-500.

Effects of acute THC on “positive psychotic” symptoms in controls vs schizophrenics



Adapted from: D' Souza et al. *Eur Arch Psychiatry Clin Neurosci.* 2009; 259(7):413–431.

Meta-analysis finds persons with Diagnosis of Schizophrenia who have histories of cannabis use tend to perform better on neurocognitive testing

Cognitive domain	Mean d	SD	# of studies used in ES	Overlap %	Nfs
1. General cognitive ability and intelligence	0.48	0.51	4	64	15
2. Selective, sustained and divided attention	0.35	0.23	6	75	15
3. Executive abilities	0.14	0.49	7	88	3
4. Working memory and learning	0.07	0.40	5	94	1
5. Retrieval and recognition	0.12	0.50	6	90	1
6. Receptive and expressive language abilities	0.06	0.30	4	95	1
7. Visuo-spatial and constructional abilities	0.33	0.27	3	76	7

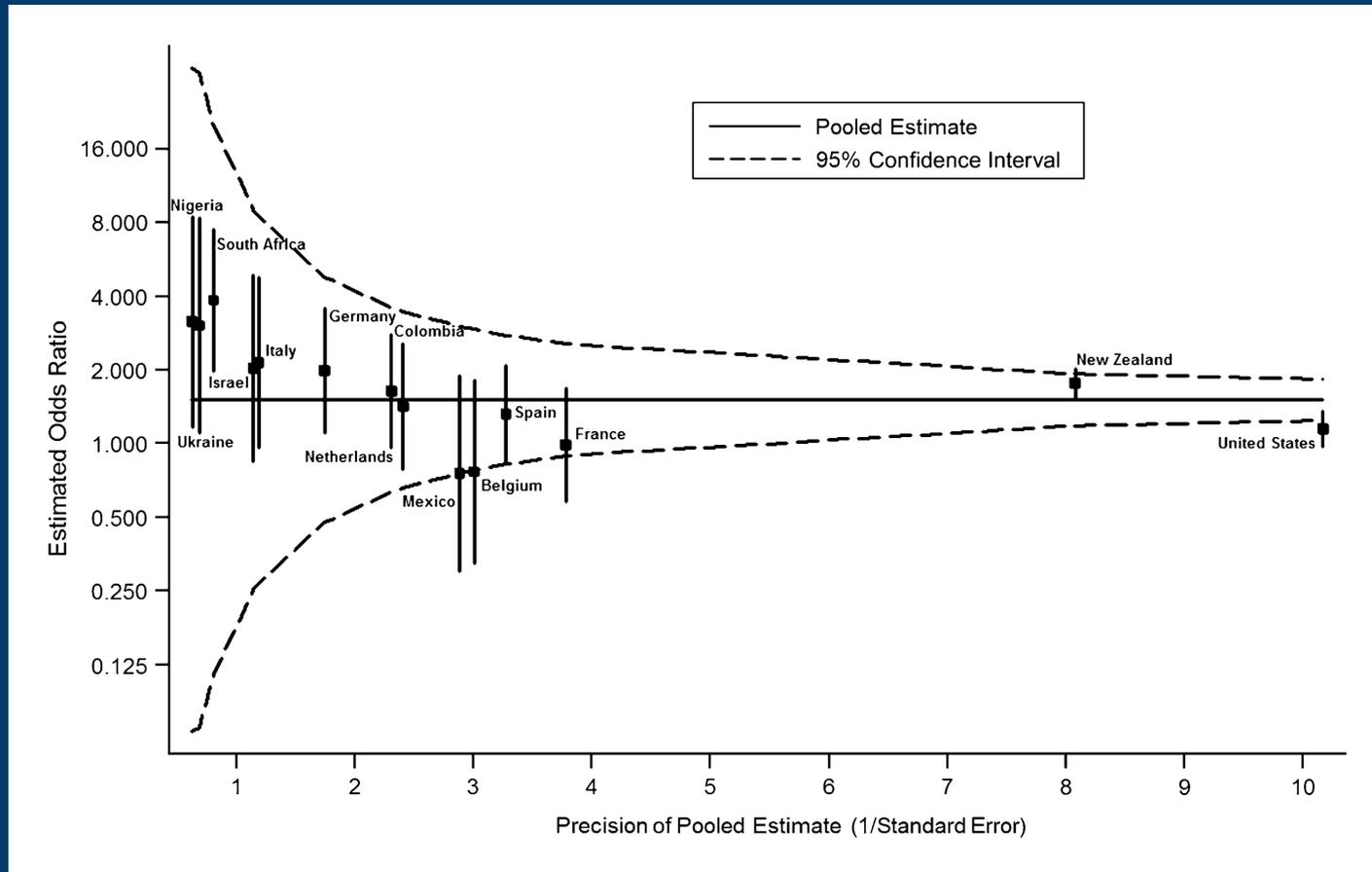
ES, effect size; Nfs, Orwin's fail safe N formula.

Rabin, et al. (2011) The effects of cannabis use on neurocognition in schizophrenia: A meta-analysis. Schizophrenia Research 128: 111-116

Cannabis and Depression

- Does cannabis cause depression?

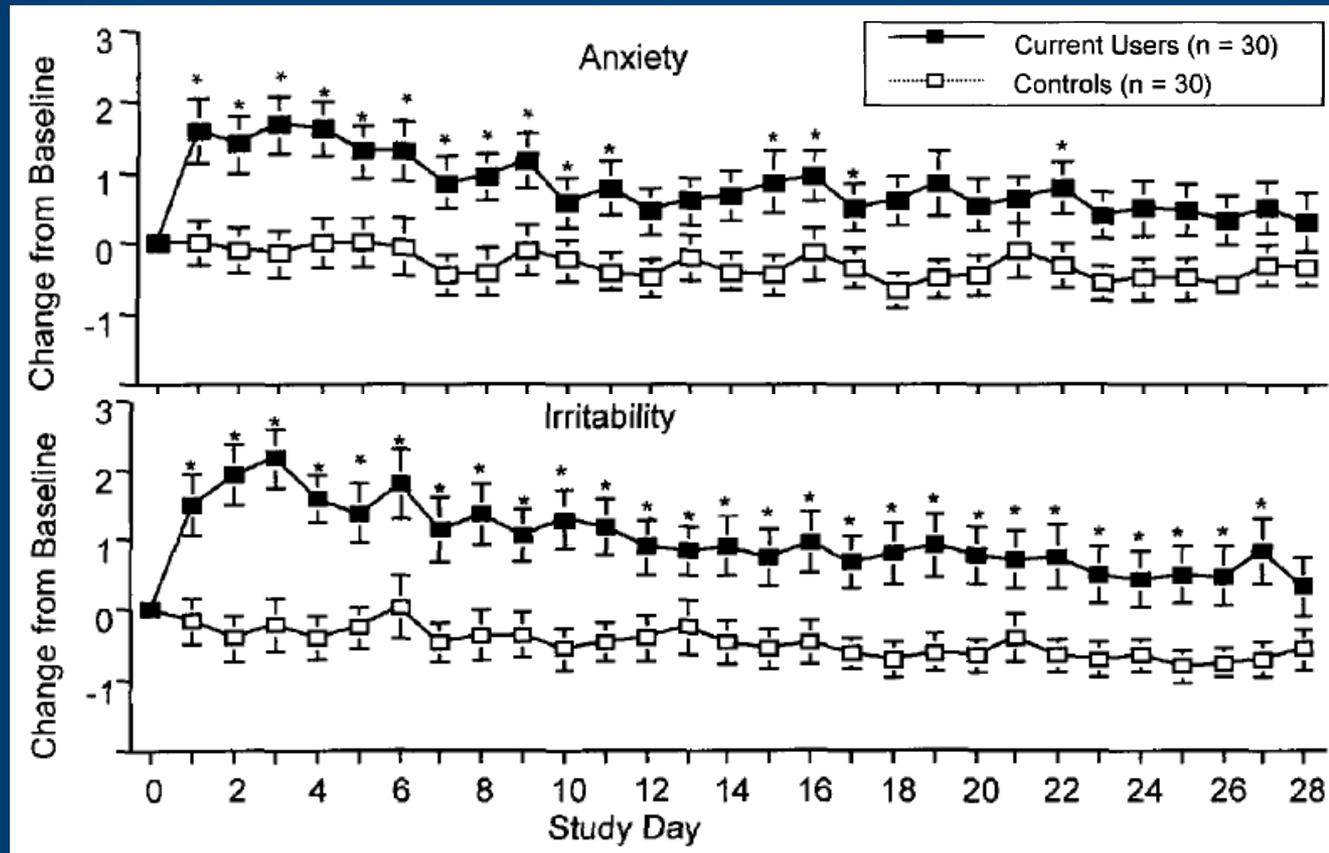
Relationship of starting MJ under age 17 and later depression



Estimated odds ratios for the association between early onset (age < 17 years) cannabis use and later onset (age ≥ 17 years) of a depression spell in different countries, World Health Organization World Mental Health Survey Initiative, 2001– 2005.

Source: De Graaf et al. *Am J Epidemiol.* 2010; 172:149-159

Is There a Cannabis Withdrawal Syndrome in Humans?



Source: Kouri & Pope. Abstinence symptoms during withdrawal from chronic marijuana use. *Exp Clin Psychopharmacol.* 2000. 8(4);483-92.

Cannabis and Neuropsychiatry

Summary

- Dose related acute effects of MJ on attention, memory, perception clearly established
- MJ intoxication may increase MVA risk slightly, much less than alcohol, but MJ + alcohol heighten impairment
- Upon cessation of chronic heavy use neurocognitive effects may persist for days to weeks, and may be accompanied by a mild abstinence syndrome
- Long term brain effects of chronic MJ use in adults not demonstrated in those beyond residual MJ effect period. If present, they are subtle and of unclear clinical significance.
- Effects on developing brain [eg., heavy use by teenagers] unclear; requires more and better designed studies that address alternative causation, eg., worse IQ trajectories in those at risk for MJ abuse
- There are associations between MJ use and schizophrenia/ psychosis, but the effect sizes are modest, and the direction of causality is unproven. Psychotic symptoms may be enhanced in schizophrenics during acute intoxication



Neuropsychiatric Effects of Cannabis

Thanks for your attention!

Igor Grant, MD

University of California, San Diego

Center for Medicinal Cannabis Research

