

**Is there a relationship between cognition and residual blood levels of cannabis metabolites in non-intoxicated heavy cannabis consumers?**

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and the Agonist Replacement for Cannabis Dependence (ARCD) Study Group

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# Cannabis and Cognition

- Acute intoxication clearly impairs cognition
  - Even in regular consumers (Ramaekers; 2016)
- Safety, and in particular, driving are important considerations, especially in chronic dosing in treatment contexts
  - Most jurisdictions have legal thresholds for driving
- But, cannabis components accumulate on chronic consumption / dosing
  - Huestis, 2013
- So: what does blood level of cannabis metabolites tell us about cognitive impairment in non-intoxicated **chronic consumers**?



# Legal Cut-off Concentrations of THC and Metabolites

THC (in blood)		THC-COOH (in blood)	
<1ng/mL	Italy, Slovenia	<1ng/mL	Italy
1ng/mL	Belgium, Denmark, Ireland, Finland, France, Germany, Greece, Pennsylvania, Luxembourg,	5ng/mL	Finland, Ireland, Slovenia, Nevada
2ng/mL	UK, Nevada, Czech Republic	10ng/ml	UK
3ng/mL	Netherlands*	50ng/ml	Poland, Iowa, Ohio
<b>5ng/mL</b>	<b>Poland, ?Canada, Colorado, Montana, Washington</b>		

REVIEW Open Access

## Establishing legal limits for driving under the influence of marijuana

Kristin Wong<sup>1</sup>, Joanne E Brady<sup>1,2</sup> and Guohua Li<sup>1,2,3\*</sup> *Injury Epidemiology* 2014, **1**:26

ADDICTION

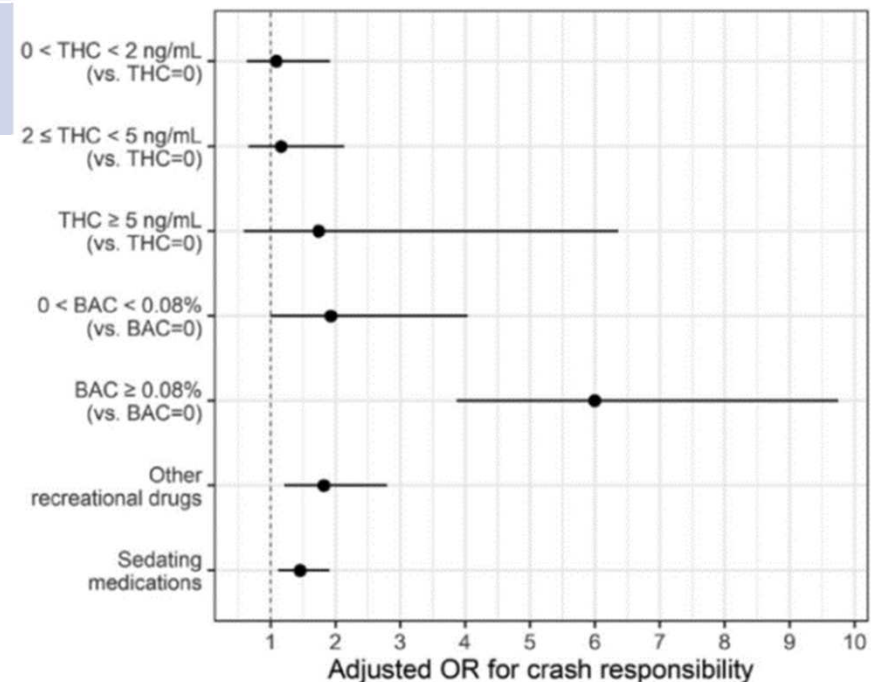
RESEARCH REPORT

SSA SOCIETY FOR THE STUDY OF ADDICTION

doi:10.1111/add.14663

### Cannabis use as a risk factor for causing motor vehicle crashes: a prospective study

Jeffrey R. Brubacher<sup>1</sup>, Herbert Chan<sup>2</sup>, Shannon Erdelyi<sup>2</sup>, Scott Macdonald<sup>3</sup>, Mark Asbridge<sup>4</sup>, Robert E. Mann<sup>5</sup>, Jeffrey Eppler<sup>6</sup>, Adam Lund<sup>7</sup>, Andrew MacPherson<sup>8</sup>, Walter Martz<sup>9</sup>, William E. Schreiber<sup>2</sup>, Rollin Brant<sup>2</sup> & Roy A. Purssell<sup>2</sup>



Characteristic	Total (N = 128)
Age, mean (SD), y	35.0 (10.9)
Female sex	30 (23.4)
Born in Australia	107 (83.6)
Aboriginal or Torres Strait Islander	10 (7.8)
Tertiary education	49 (38.3)
Employment as main source of income	71 (55.5)
In a relationship	45 (35.2)
Have ≥1 child	44 (34.4)
Current legal problems	8 (6.2)
Baseline cannabis use	
No. of days cannabis used in last 28, mean (SD)	25.7 (4.5)
Amount of cannabis used, mean (SD), g/d	2.3 (2.1)
Age at first cannabis use, mean (SD), y (range, 5-40 y)	15.5 (3.9)
Duration since first regular cannabis use, mean (SD), y	15.7 (9.8)
ICD-10 score, mean (SD) (maximum = 8)	7.1 (1.2)
Other variables	
Fagerström nicotine dependence score, mean (SD) (maximum = 10) <sup>a</sup>	2.7 (2.7)
AUDIT score, mean (SD) (maximum = 50)	4.5 (4.7)
BPRS-18 score, mean (SD) (maximum = 128)	23.8 (11.7)

# Methods

Baseline assessments of trial to cease cannabis use in dependent smokers (n=128 [116 with bloods])

JAMA Internal Medicine | [Original Investigation](#)

## Nabiximols for the Treatment of Cannabis Dependence A Randomized Clinical Trial

Nicholas Lintzeris, MBBS, PhD; Anjali Bhardwaj, PhD; Llewellyn Mills, PhD; Adrian Dunlop, MBBS, PhD; Jan Copeland, PhD; Iain McGregor, PhD; Raimondo Bruno, PhD; Jessica Gugusheff, PhD; Nghi Phung, MBBS, PhD; Mark Montebello, PhD; Therese Chan, BPharm; Adrienne Kirby, BSc(Hons); Michelle Hall, GradCertHlthSc; Meryem Jefferies, PhD; Jennifer Luksza, PhD; Marian Shanahan, PhD; Richard Kevin, PhD; David Allsop, PhD; for the Agonist Replacement for Cannabis Dependence (ARCD) study group

*JAMA Intern Med.* 2019;179(9):1242-1253. doi:10.1001/jamainternmed.2019.1993

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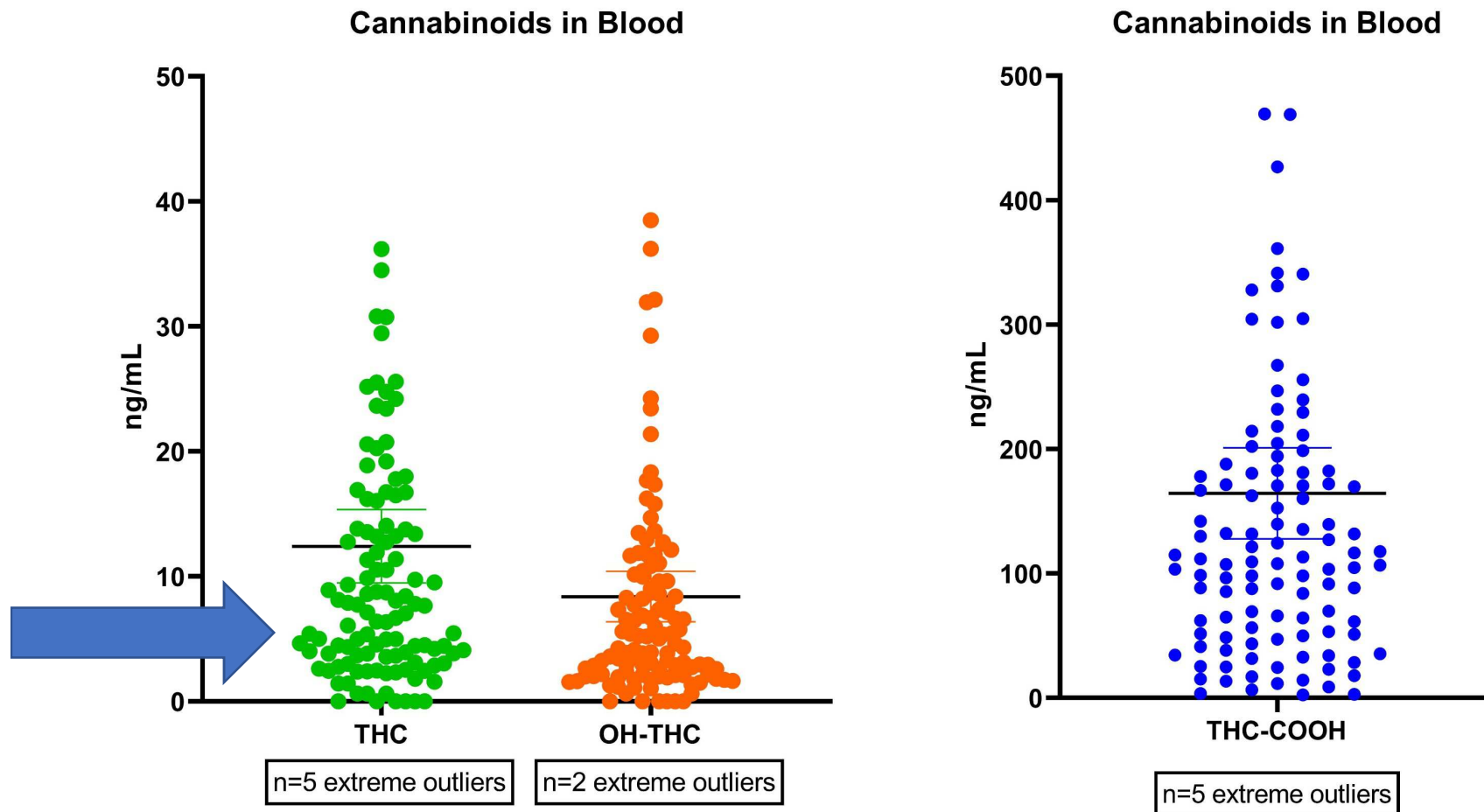
# Assessments

Penscreen software (V6) for Android Tablets



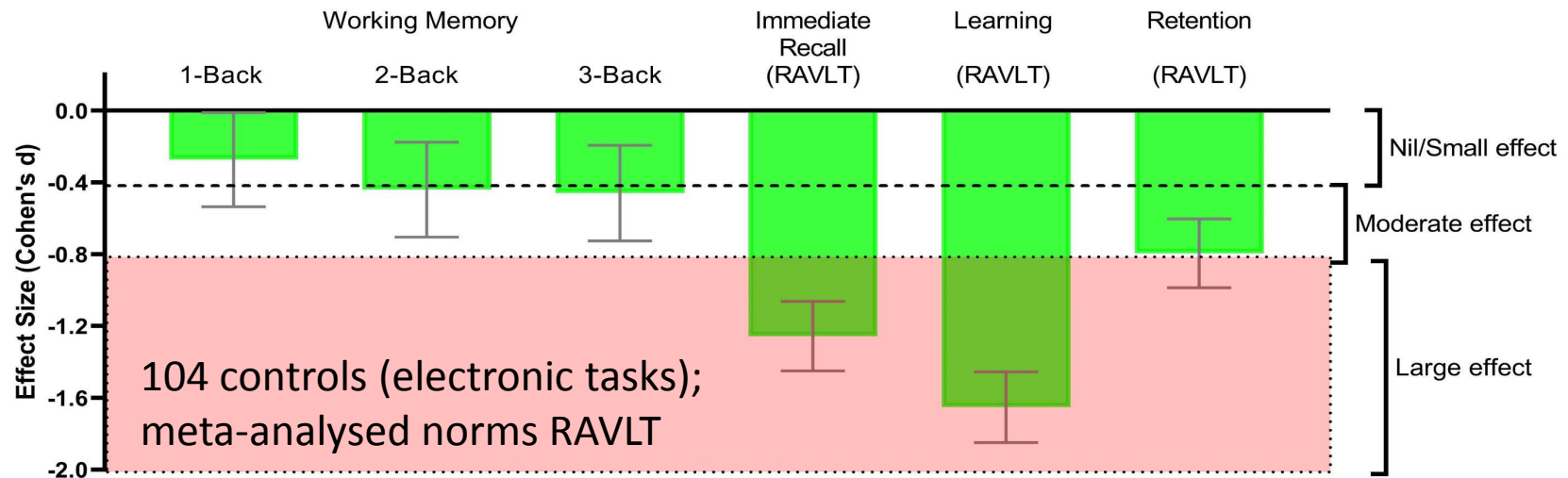
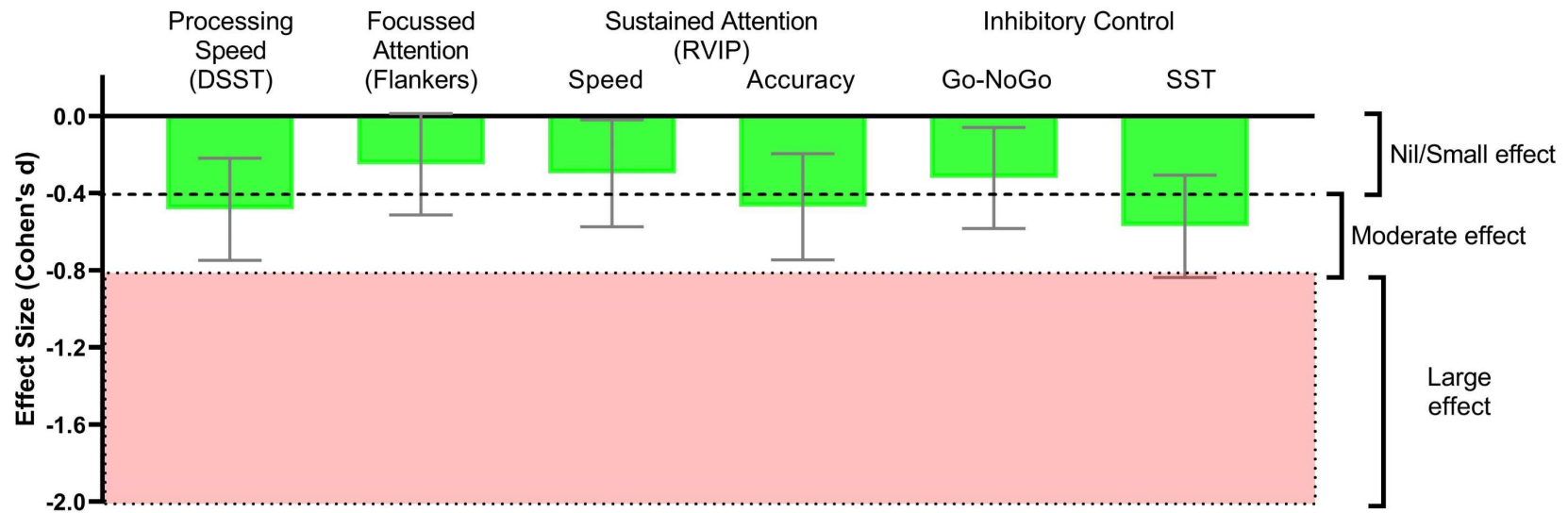
Domain	Task	Format
General cognitive function	Wechsler Test of Adult Reading	P&P
Processing speed	Digit Symbol Substitution Test	Electronic
Focussed Attention	Arrow Flankers (impairment)	Electronic
Sustained attention	Rapid Visual Information Processing	Electronic
Inhibitory Control	Go- No-Go ; Stop Signal Task	Electronic
Working Memory	1-, 2-, 3-back Task	Electronic
Immediate Recall	Ray Auditory Verbal Learning Task	P&P
Verbal Learning & Retention	Ray Auditory Verbal Learning Task	P&P

# Did they have identifiable levels of cannabis in blood (in the afternoon)?

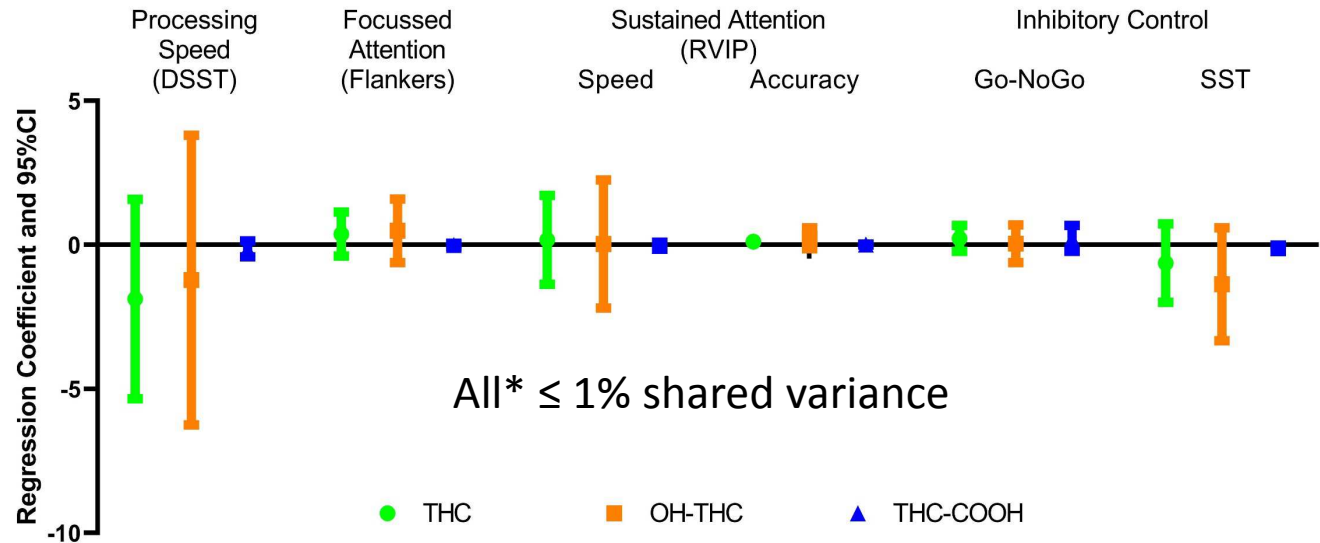


92% >1ng/mL; 60% >5ng/mL THC

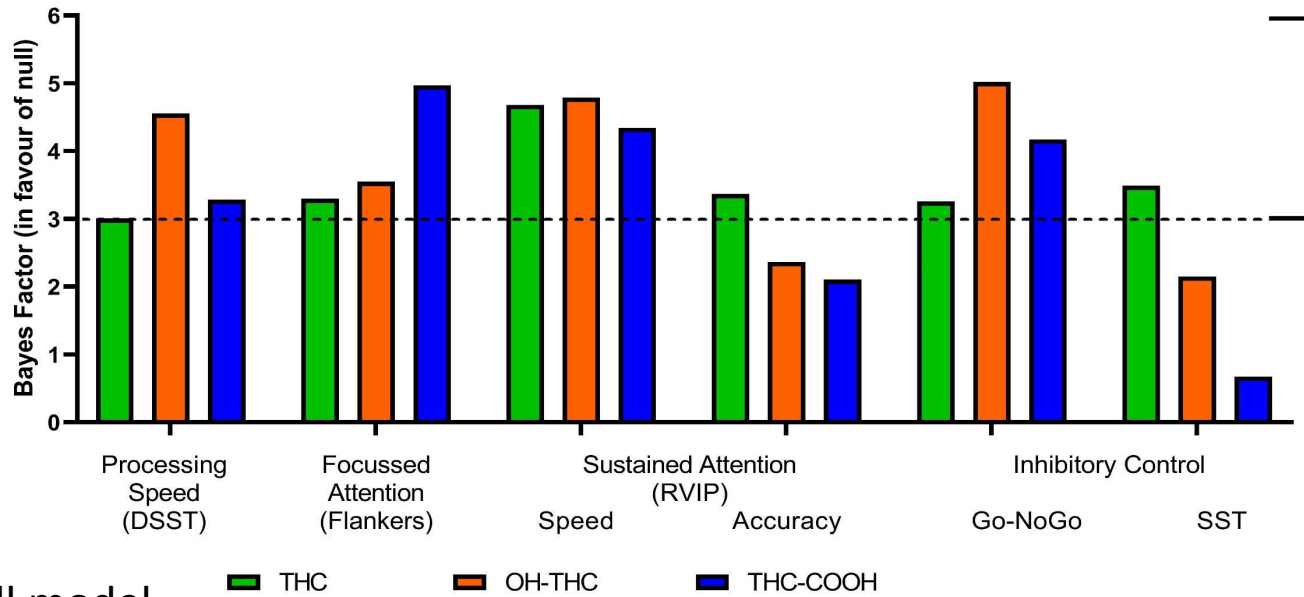
# Did they demonstrate any impairment? (compared to controls)



# Does this impairment relate to plasma levels of cannabis metabolites?



*Error bars crossing zero = no significant relationship*

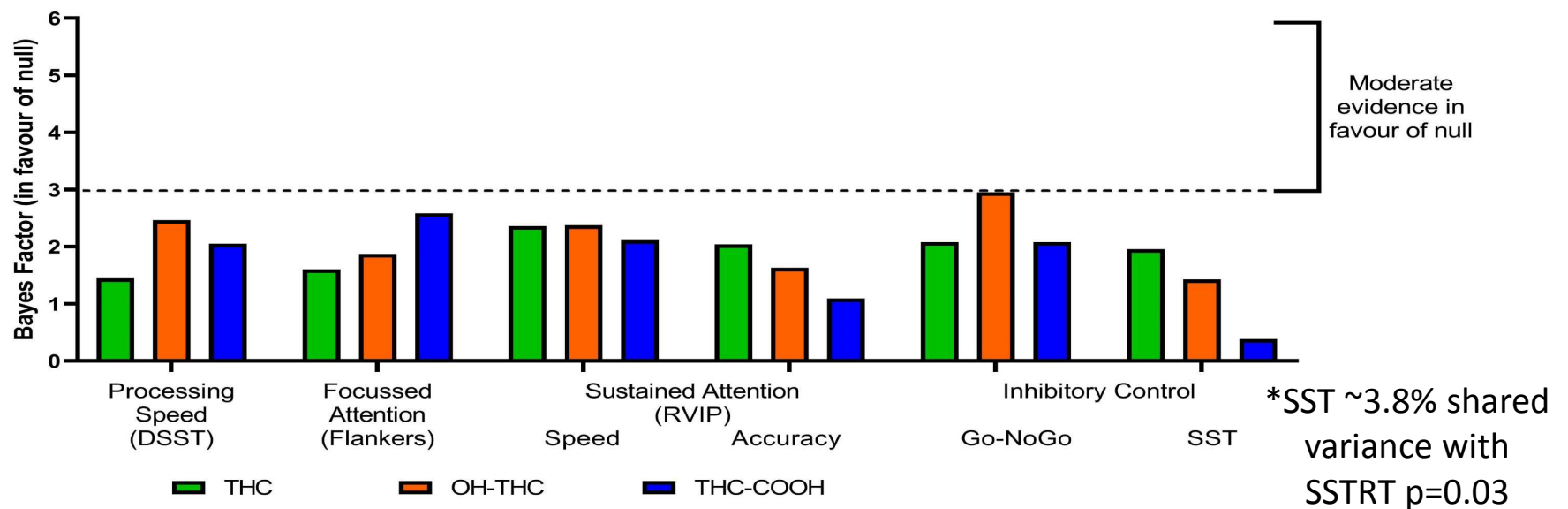
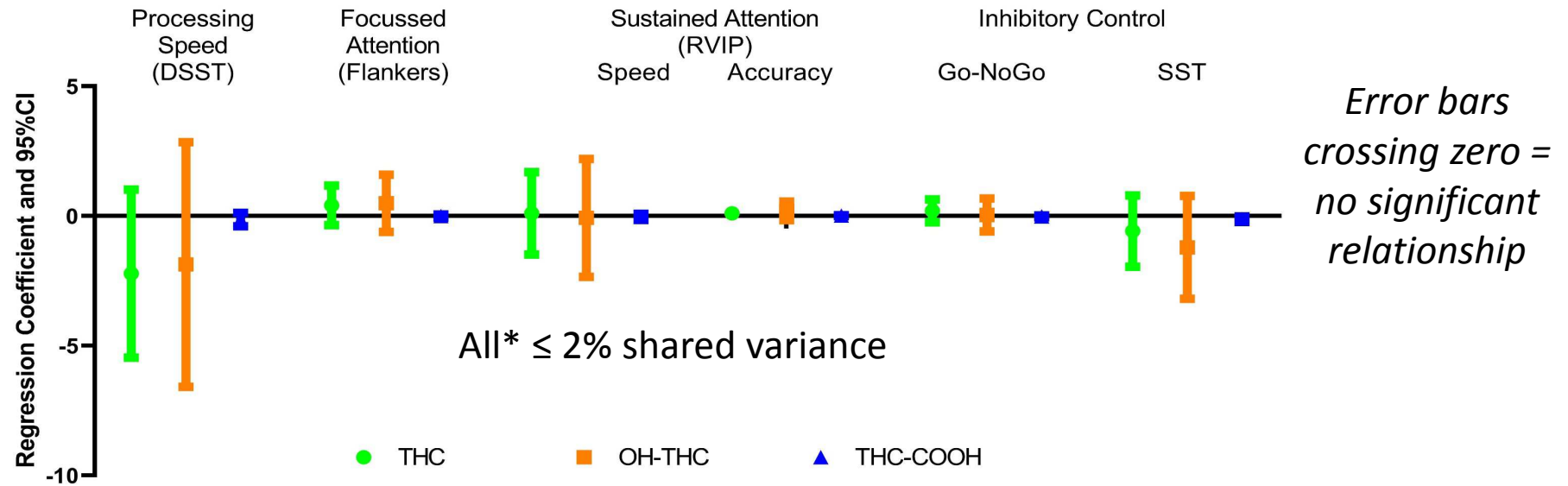


\*SST  $\sim 3.8\%$  shared variance with SSTRT  $p=0.03$

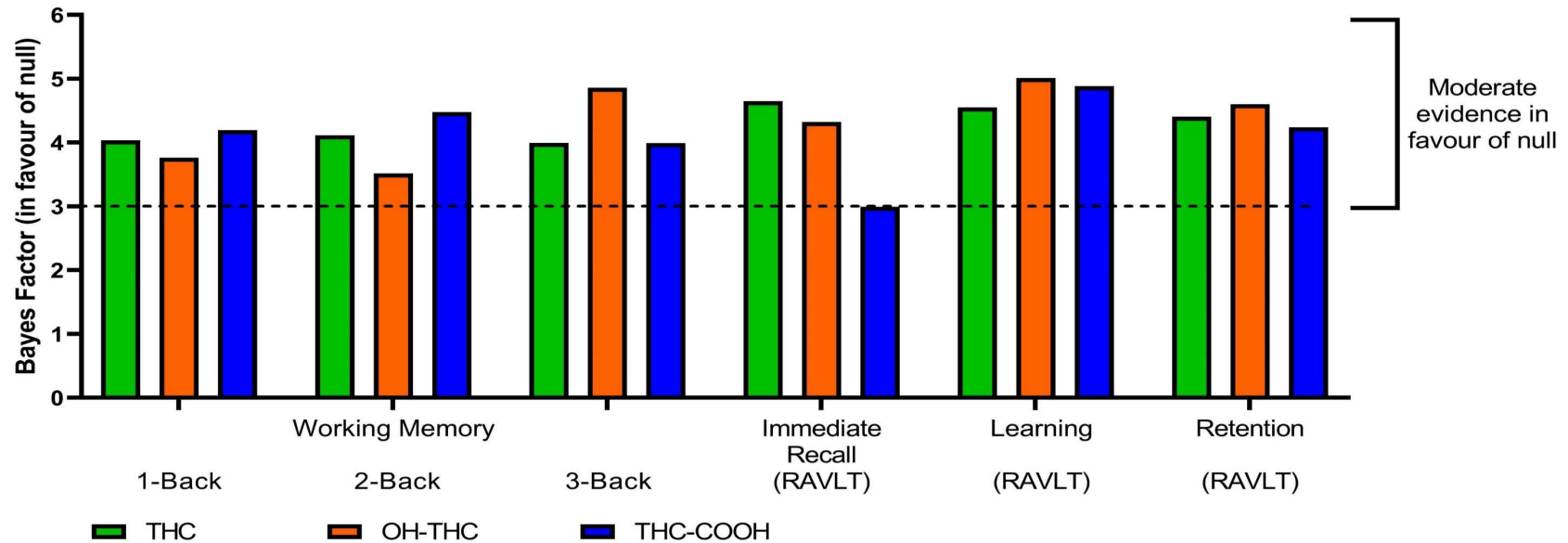
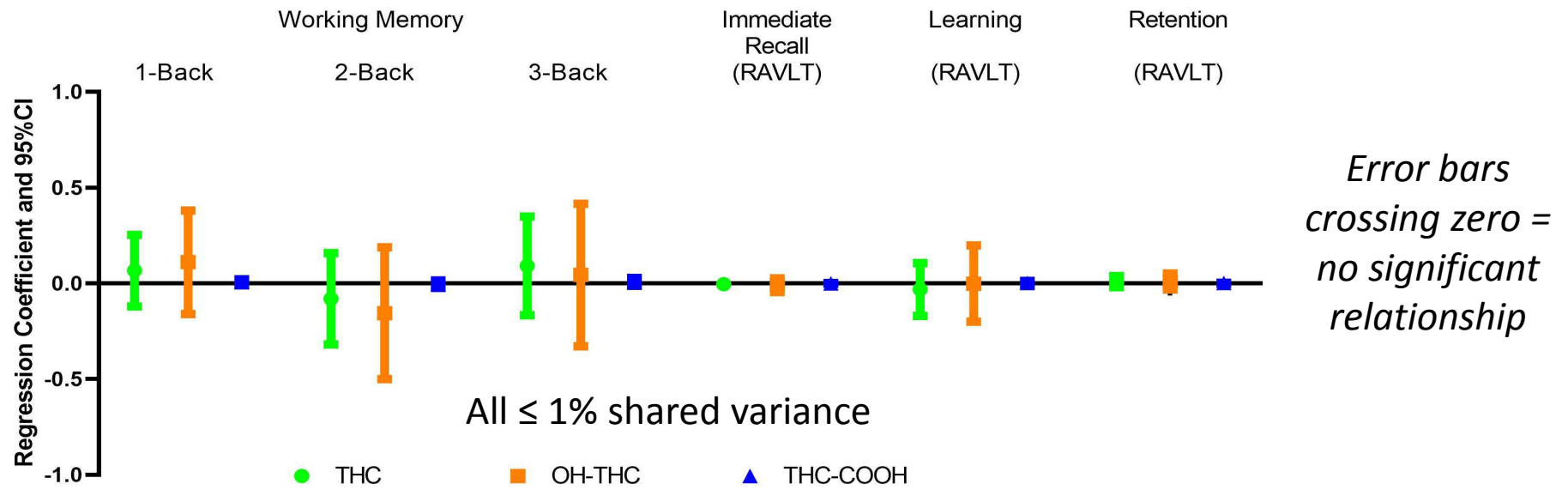
BF vs null model



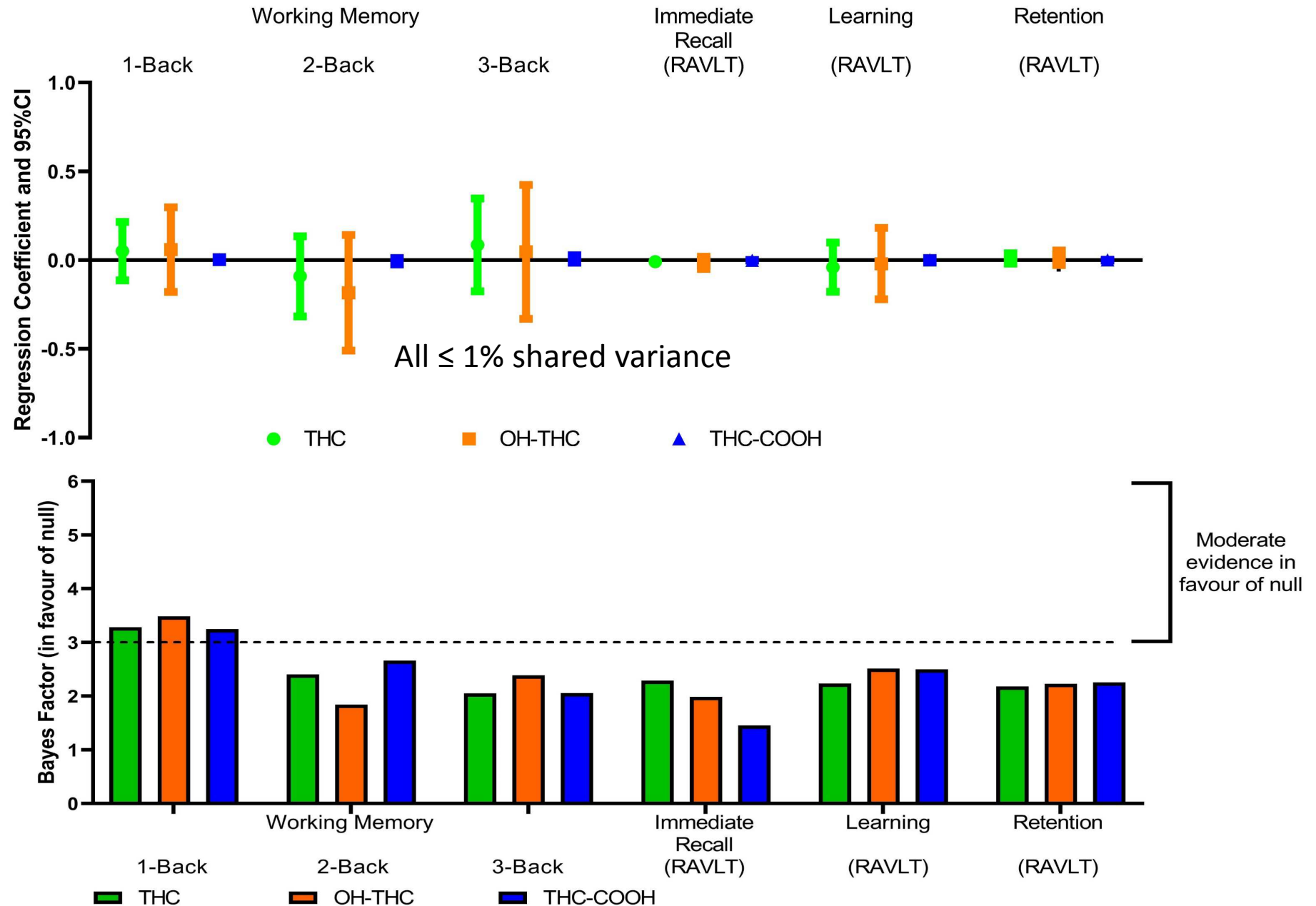
# Does this impairment relate to plasma levels of cannabis metabolites? (when we control for age, IQ and cannabis withdrawal)



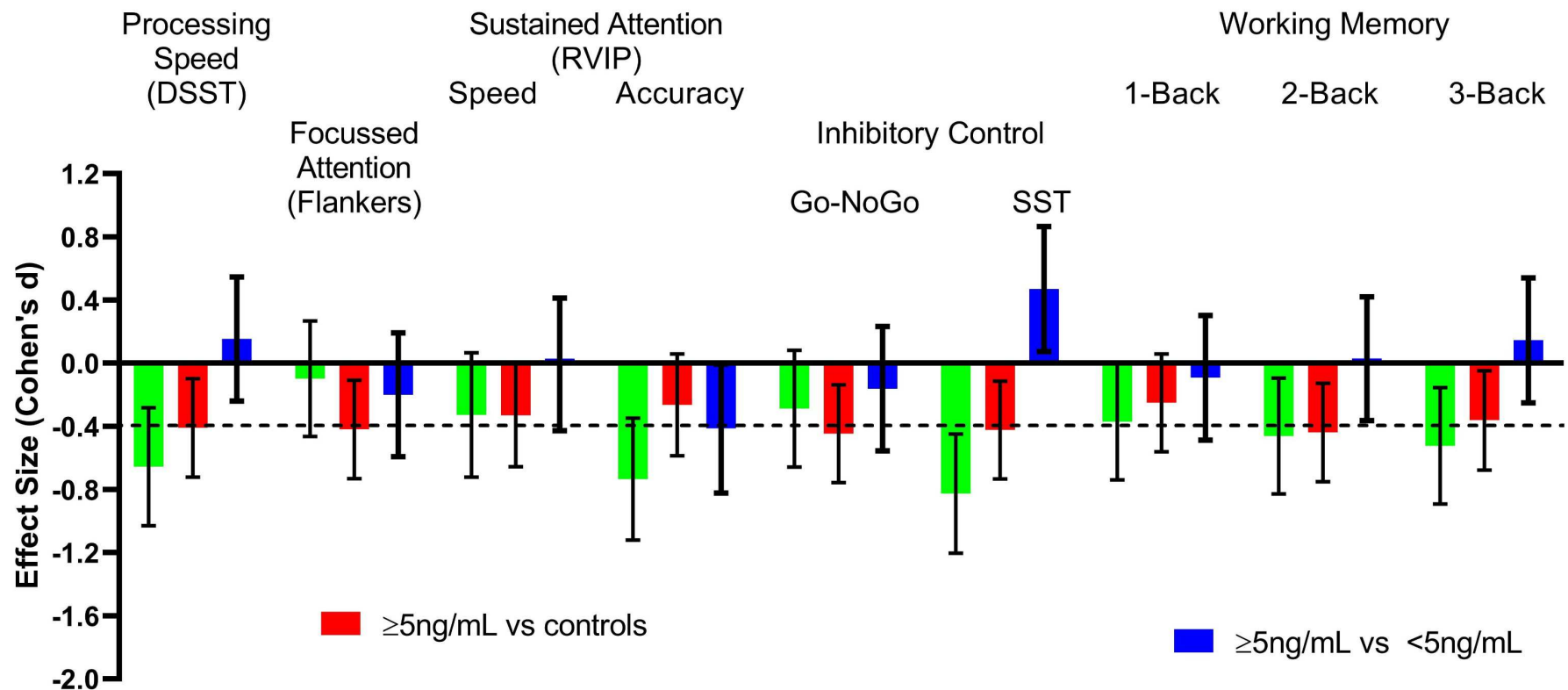
# Does this impairment relate to plasma levels of cannabis metabolites?



# Does this impairment relate to plasma levels of cannabis metabolites? (when we control for age, IQ and cannabis withdrawal)



# If we torture the data enough, will it confess? [examining a 5ng/mL cutoff]



**Green:** amount of impairment between low THC blood level group and controls (<5ng/mL)  
**Red:** amount of impairment between high THC blood level group and controls (≥5ng/mL)  
**Blue:** difference in impairment between high and low THC groups; *positive values mean low THC had more impairment than high THC groups*

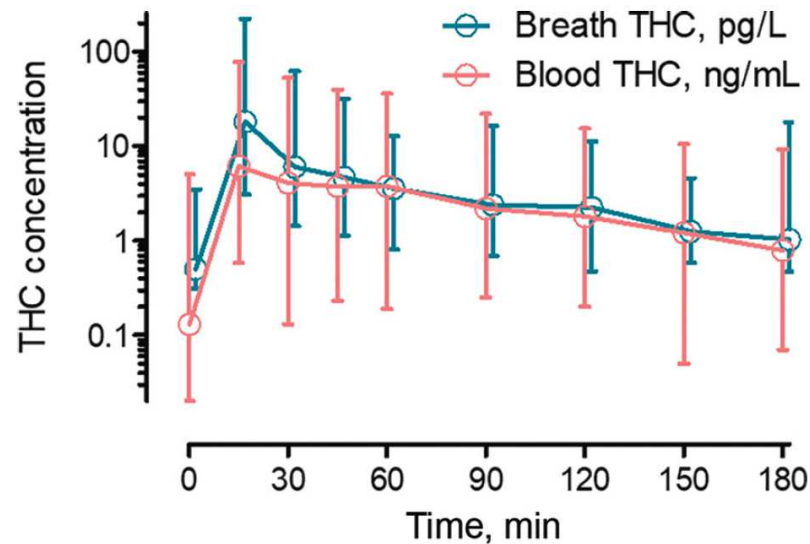
# Conclusions

- Recent studies (Ramaekers, 2016) demonstrate absence of tolerance to *acute* intoxication
  - We (unpublished) note tolerance at clinical dosing levels
- Here, in non-intoxicated near-daily consumers, small-moderate magnitude impairment present and ‘illegal’ blood levels
  - But these levels are *not* related to impairment
- Legal cutoffs are unrelated to impairment/safety risk
  - Need to move away from bloods and urines to impairment measures (more globally useful) or other modes -



# Big \$; new developments; pipe dreams?

## Acute-focussed Testing: Breath?



Clinical Chemistry 65:9  
1171-1179 (2019)

Drug Monitoring and Toxicology

Correlation of Breath and Blood  
 $\Delta^9$ -Tetrahydrocannabinol Concentrations and  
Release Kinetics Following Controlled  
Administration of Smoked Cannabis

Kara L. Lynch,<sup>1\*</sup> Y. Ruben Luo,<sup>1</sup> Shirin Hooshfar,<sup>1</sup> and Cassandra Yun<sup>1</sup>

## Impairment Testing

See Poster: “Don’t Touch that Drink!”