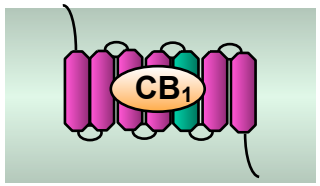
Cannabis and the cannabinoids



Iain S. McGregor

Professor of Psychopharmacology and ARC Professorial Fellow

Psychopharmacology Laboratory, School of Psychology, University of Sydney, Australia.

Psychopharmacology

http://www.psych.usyd.edu.au/staff/iain/

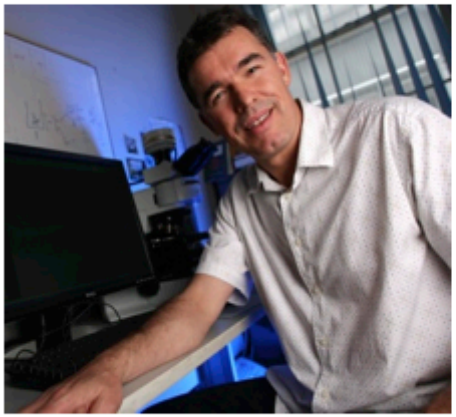
mcgregor_lab Workshops solar psychopharm ZooMobile LABVIEW FOREX new music 09 Wikipedia disability

Psychopharmacology Laboratory

Principal Investigator

Professor Iain S. McGregor *MA (Oxon) PhD (Sydney)*

Professor of Psychopharmacology, ARC Professorial Fellow



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Welcome to the Psychopharmacology Laboratory at the University of Sydney.

My role is director of the laboratory and I am also involved in teaching various courses. I completed my undergraduate degree in Experimental Psychology at the University of Oxford and gained my PhD in Psychology at the University of Sydney.

I have broad research interests in the areas of neuroscience and psychopharmacology. I am particularly interested in assessing the long term effects of addictive drugs and alcohol on behaviour and brain function. I am also interested in the development of animal models of anxiety disorders and depression and in the pharmacological treatment of these disorders.

When I am not busy being a neuroscientist and psychopharmacologist I enjoy playing music, bushwalking and mountain biking.

1. Overview of cannabis and cannabinoid action in the brain

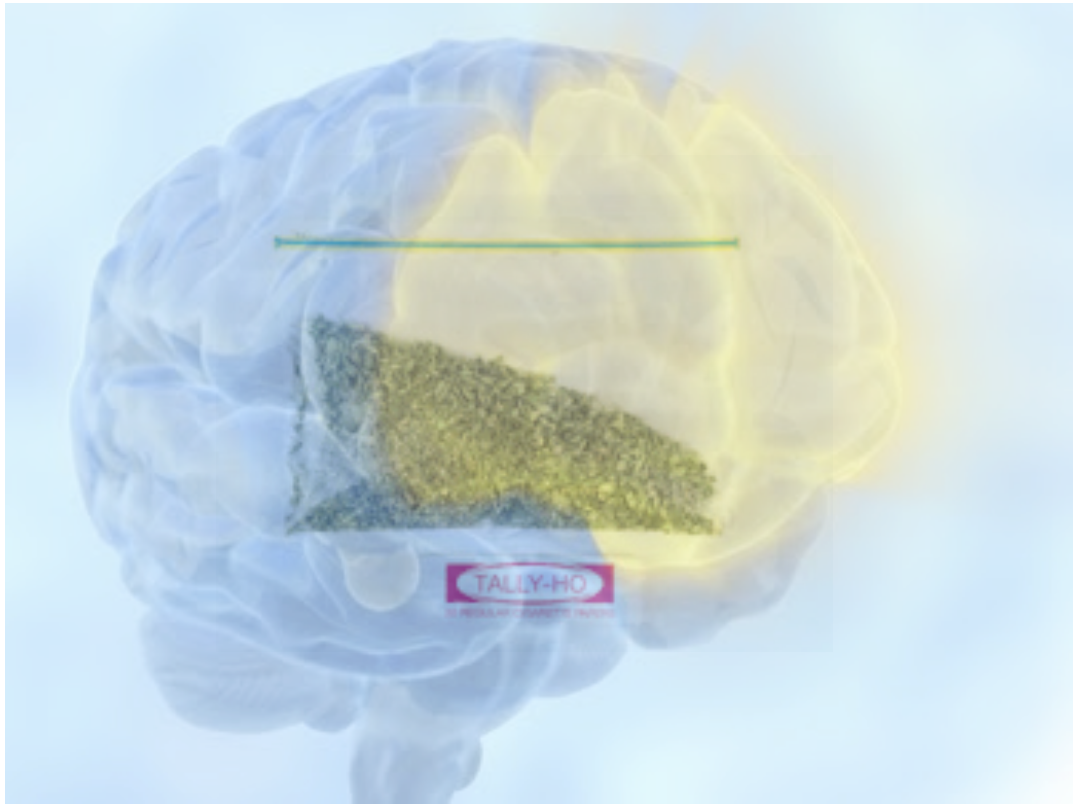
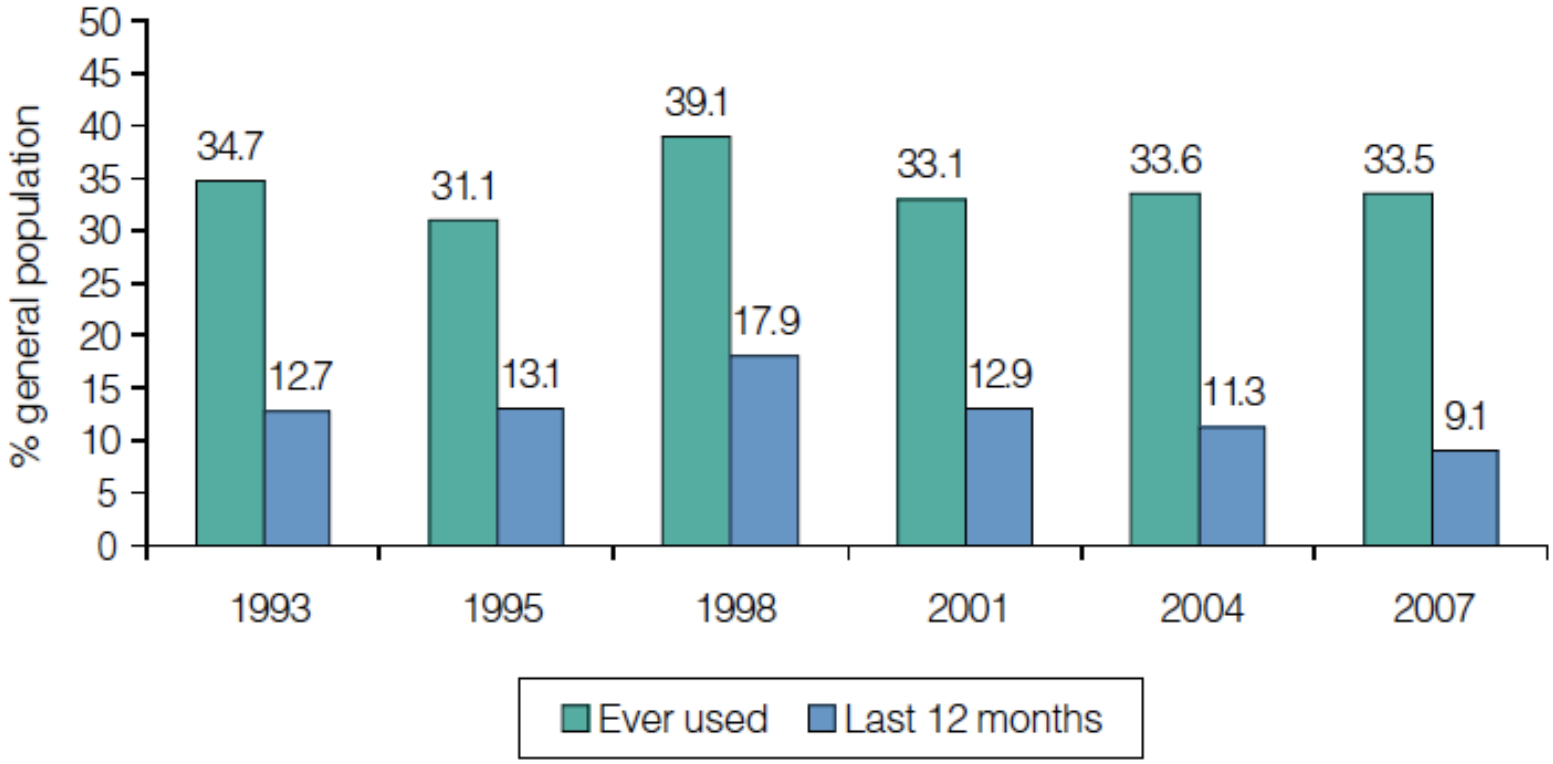


Figure 1: Prevalence of cannabis use in Australia, 1993-2007



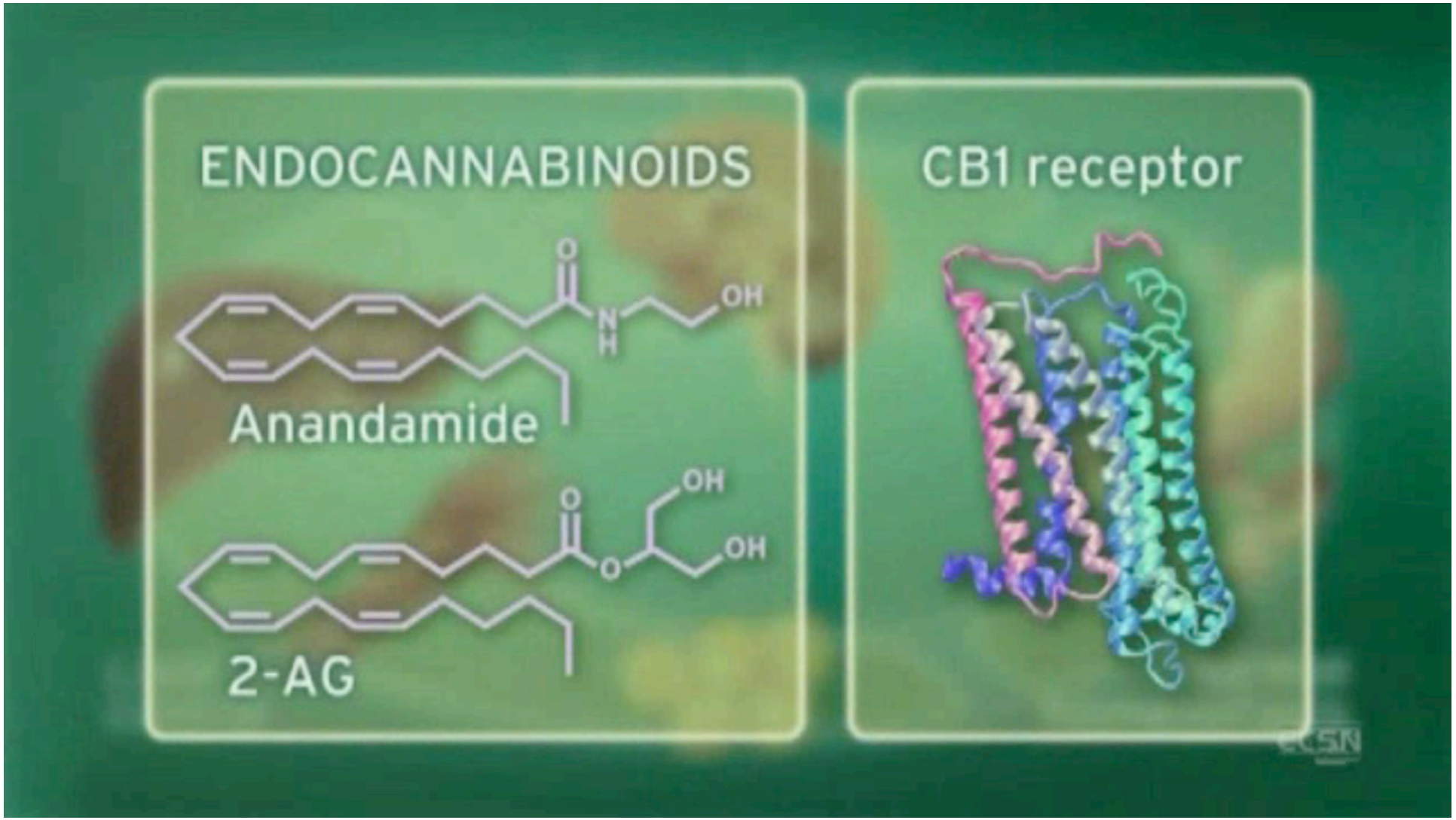
Source: National Drug Strategy Household Survey (1993-2007)

Suggested citation: Roxburgh, A. and Burns, L. (2008). Cannabis use among sentinel groups of drug users in Australia: Findings from the Illicit Drug Reporting System (IDRS) and the Ecstasy and Related Drugs Reporting System (EDRS). Drug Trends Bulletin, June 2008. Sydney: National Drug and Alcohol Research Centre, University of New South Wales.

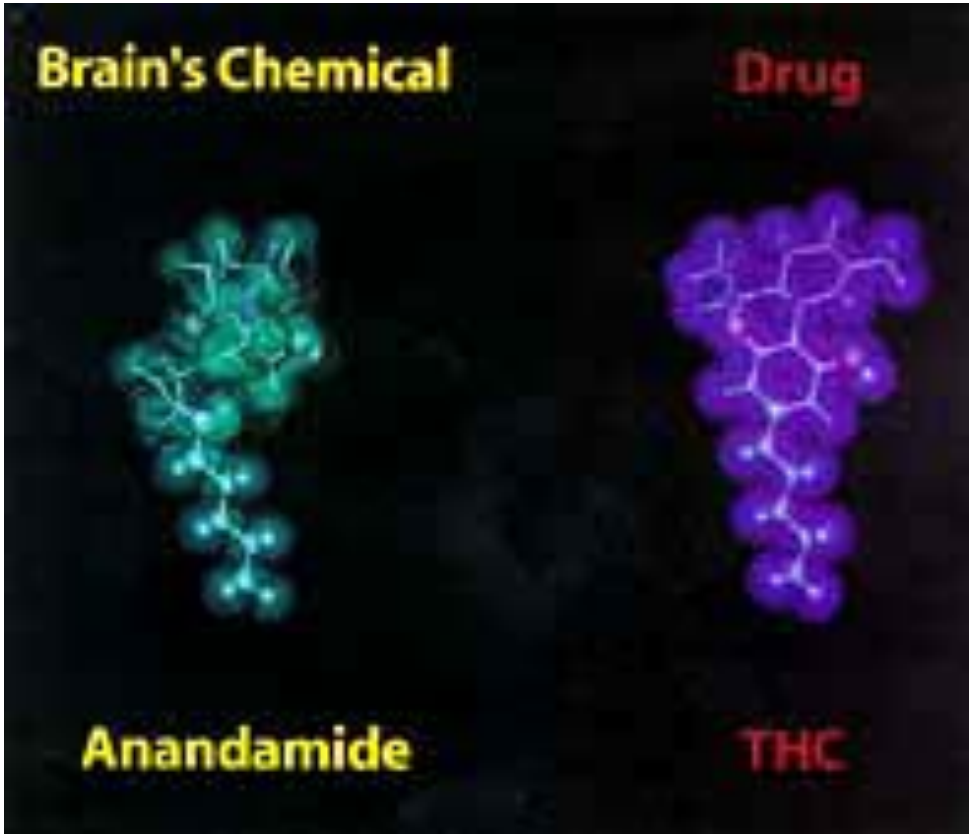

NICE PEOPLE TAKE DRUGS
Release
www.release.org.uk

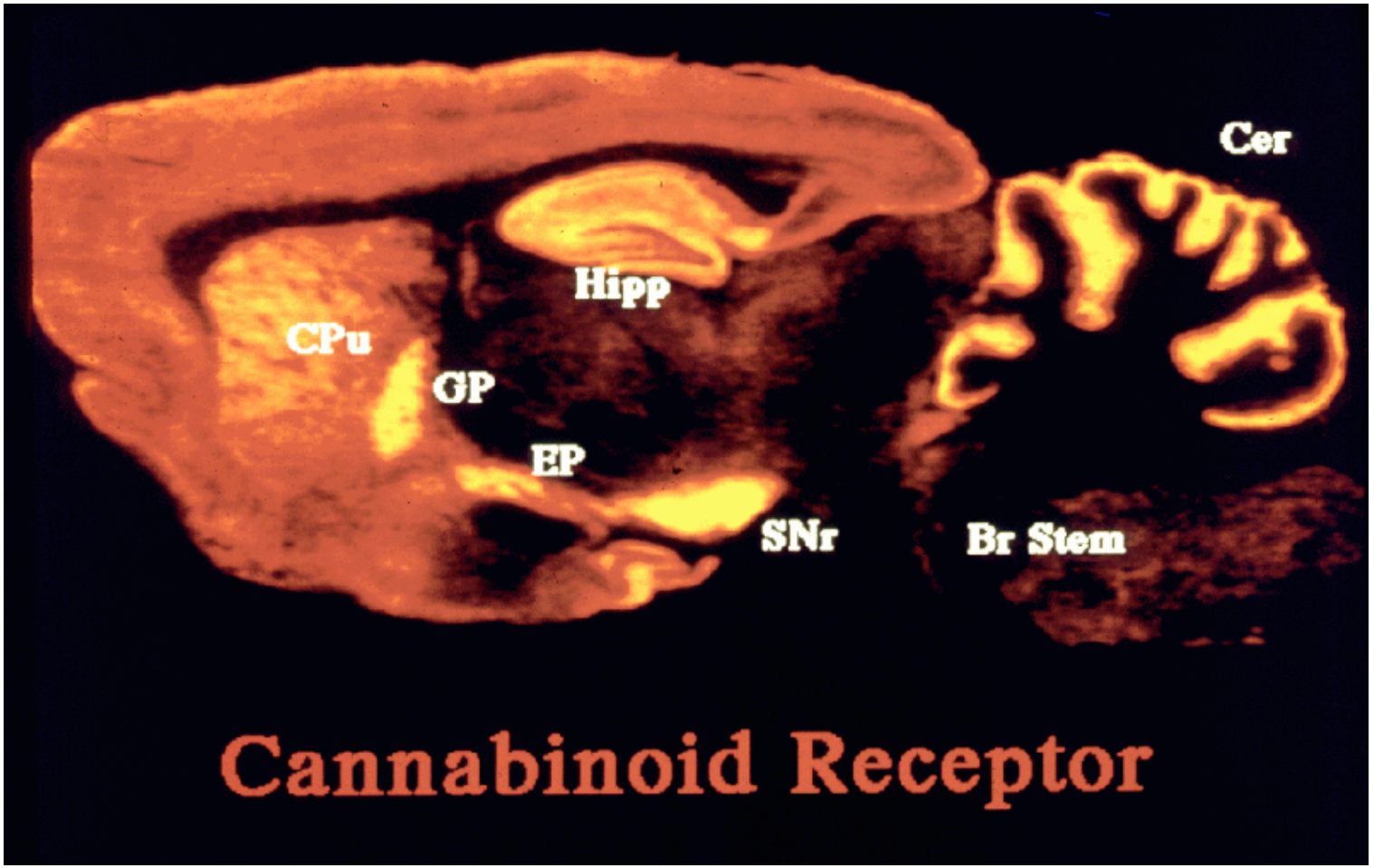
We all have cannabis in our brains:

the *endocannabinoids*



http://www.endocannabinoid.net/

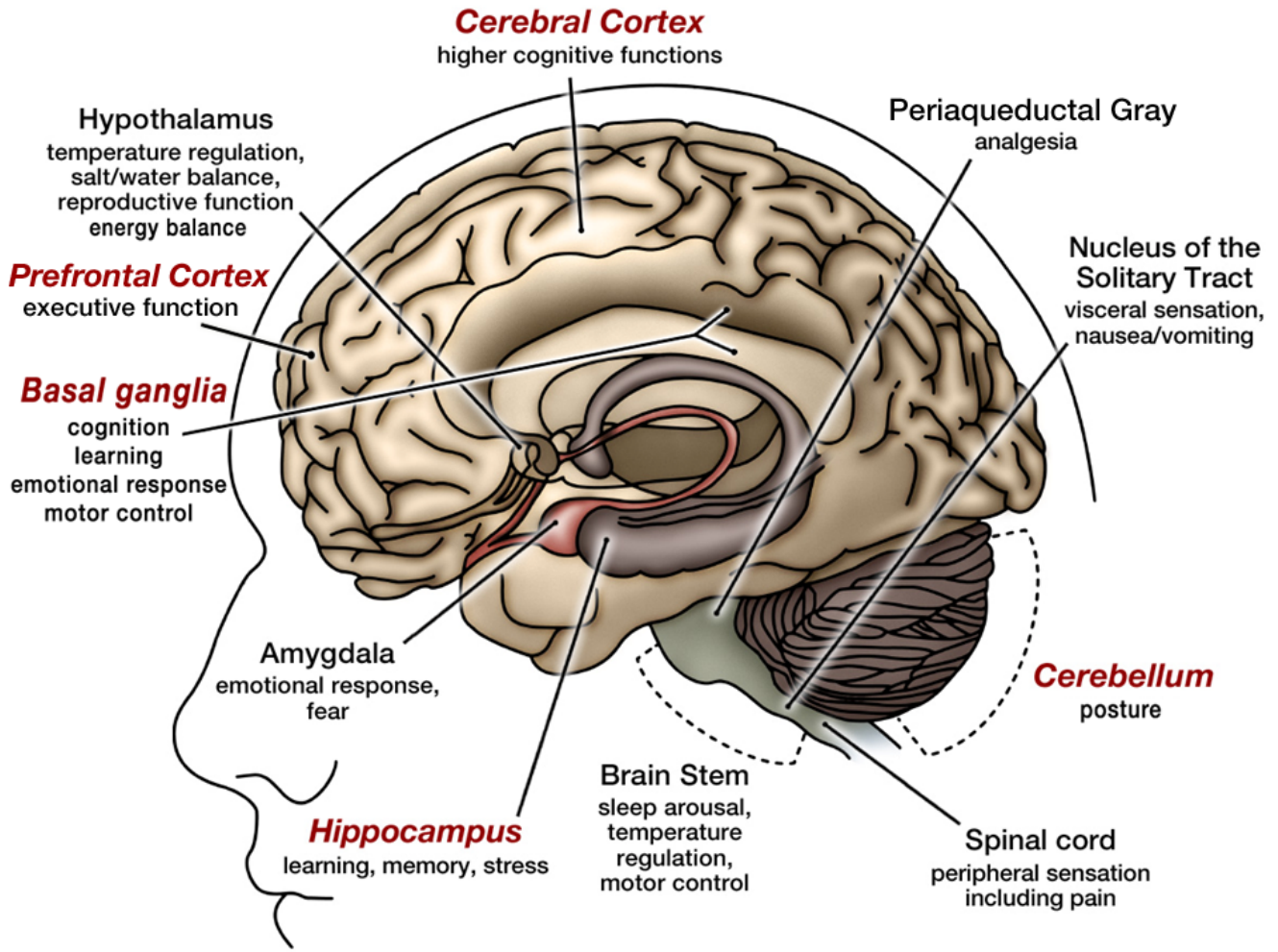

Brain's Chemical
Drug
Anandamide
THC



Courtesy of Dr Miles Herkenham

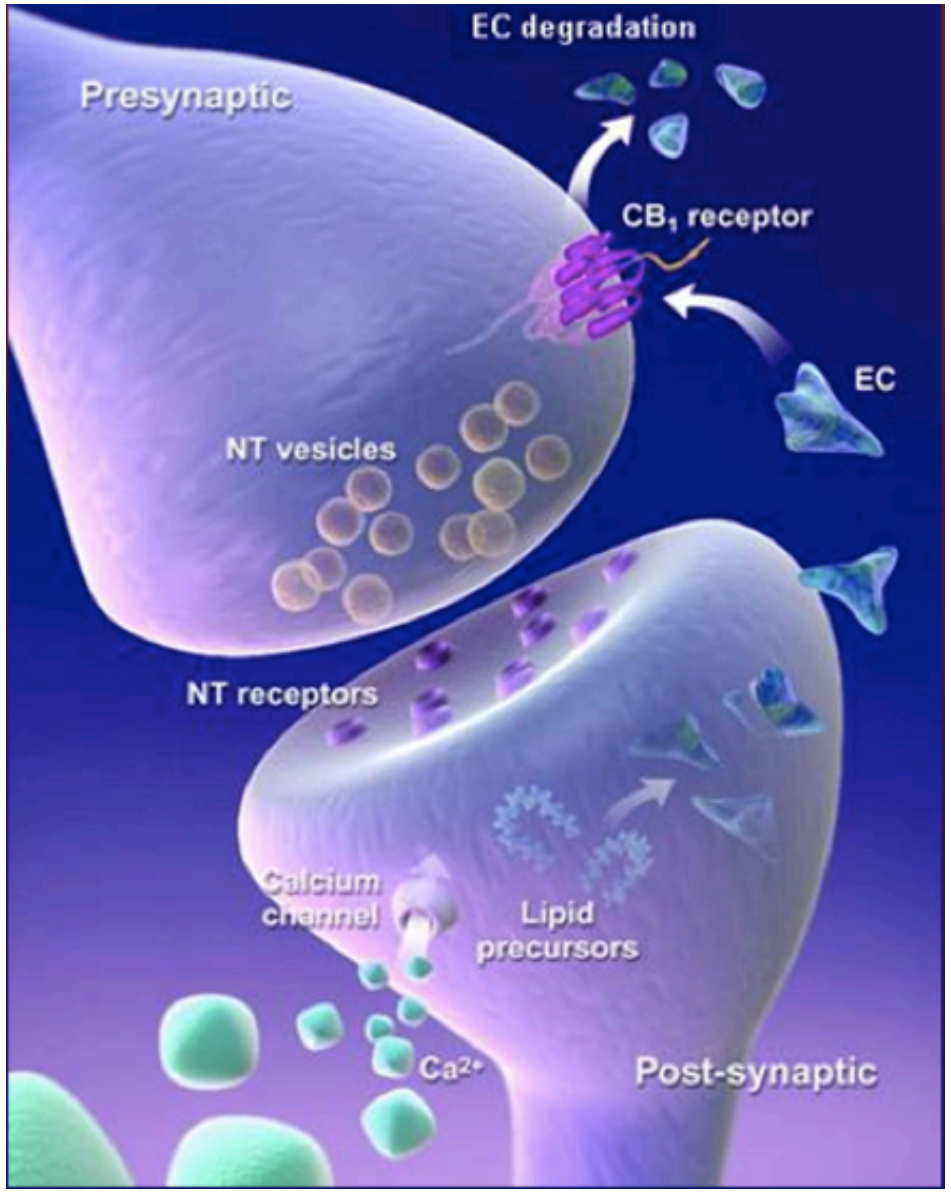
Brain Regions That Express the CB_1 Receptor

Red = abundant CB_1 receptor expression **Black = moderately abundant CB_1 receptor expression**



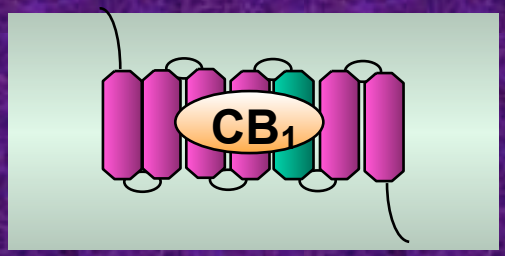
http://www.endocannabinoid.net/

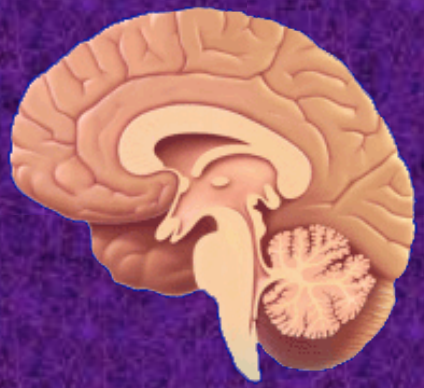
Endocannabinoids act as retrograde messengers regulating the release of glutamate and GABA



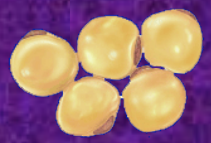
Courtesy of Vincenzo Di Marzo

CB_1 Receptors: not just in the brain!



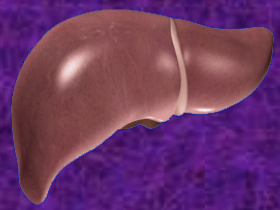


Brain

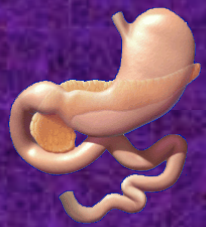


Adipose Tissue

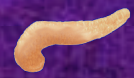
Muscle



Liver



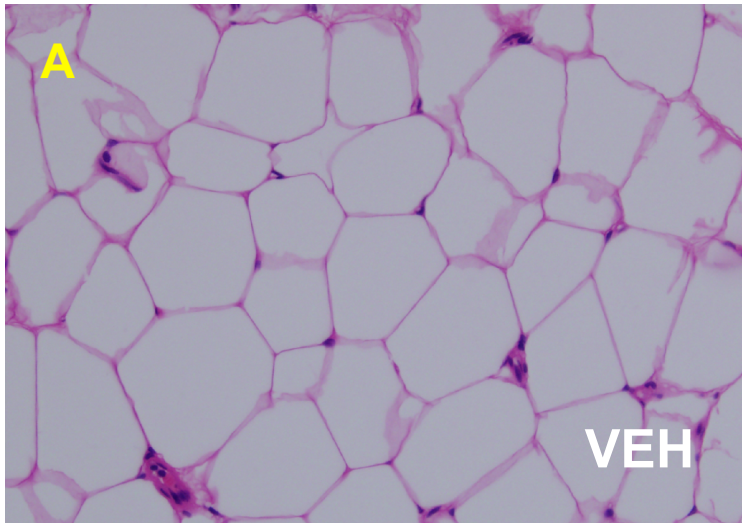
GI Tract

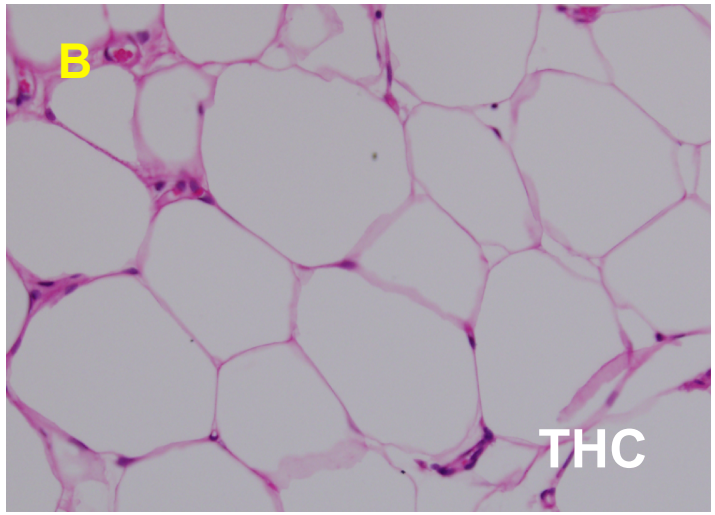


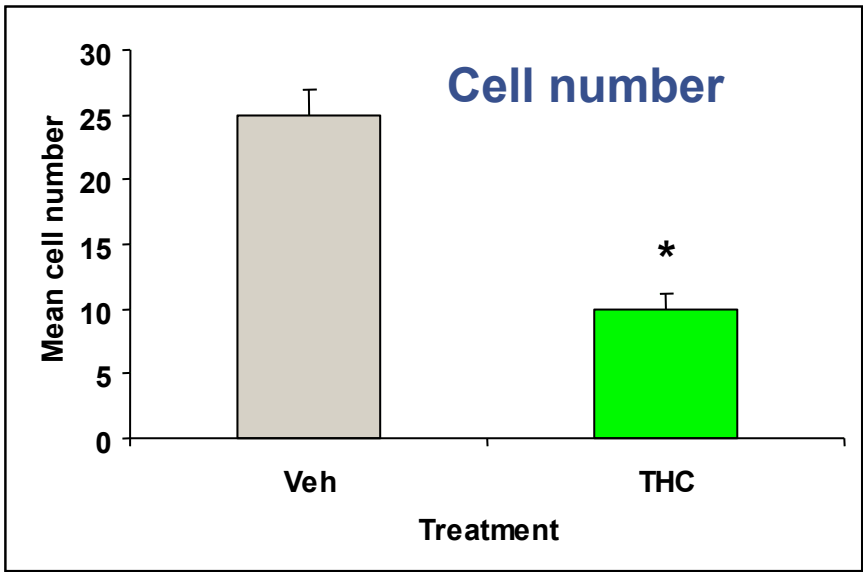
Pancreas

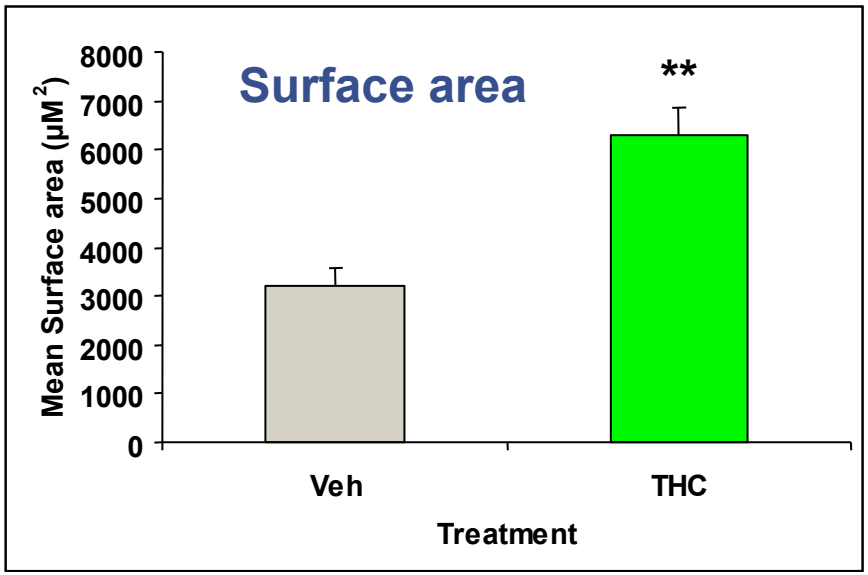
http://www.endocannabinoid.net/

THC exposure *in vivo* increases the size of adipocytes (fat cells) while decreasing their number



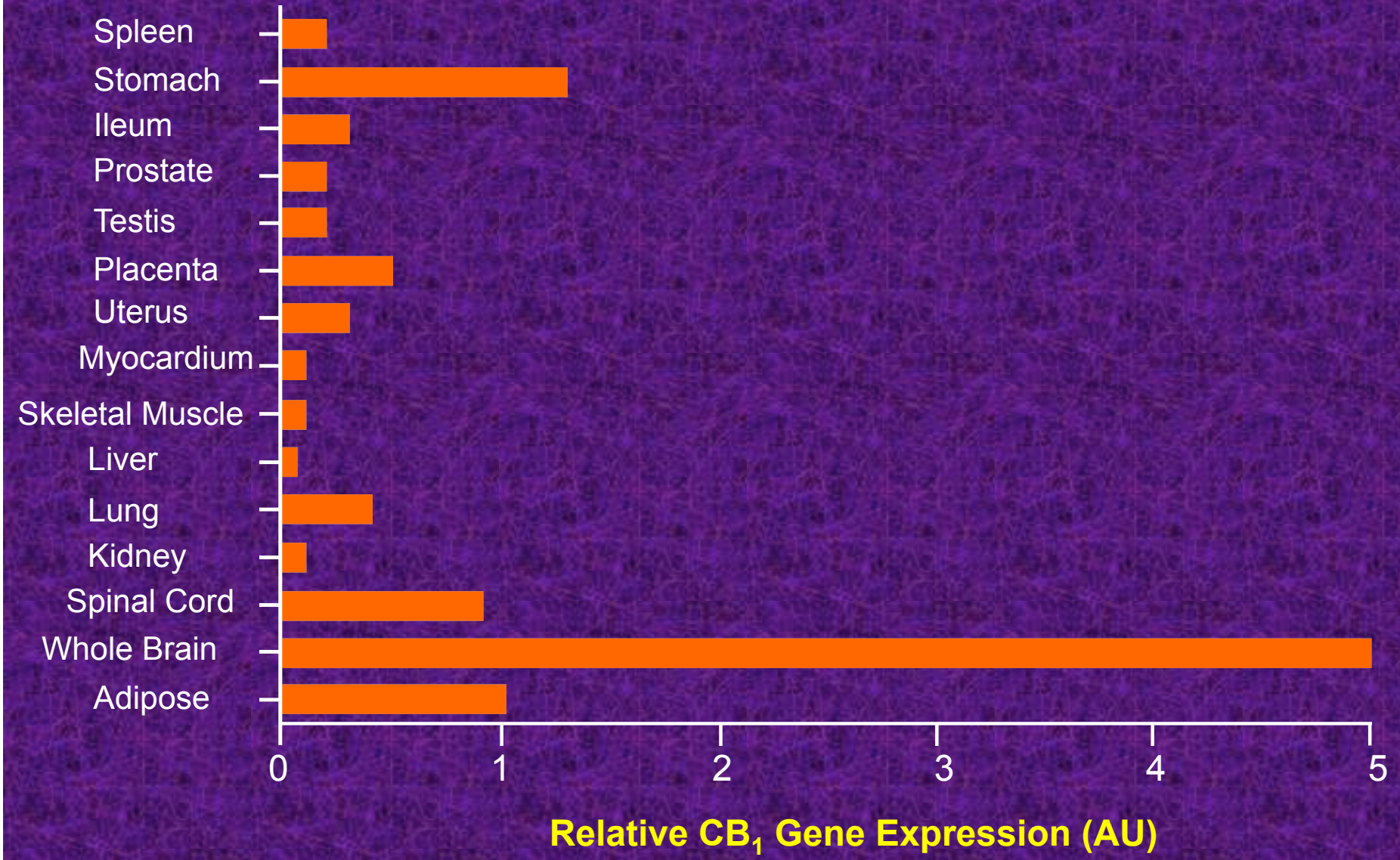






Gunasekaran, Arnold, Denyer, McGregor, under review

Expression of the CB_1 Receptor Gene in Human Tissue



Engeli S et al. *Diabetes.* 2005;54:2838-2843.

Effects of blocking the endocannabinoids with the CB1 antagonist rimonabant (*Accomplia*)

- Reduced appetite, body weight and adiposity
- Beneficial effect in type 2 diabetes
- Inhibition of alcohol, tobacco and opiate self-administration
- Cognition enhancement
- Depression and dysphoria
- Anxiety
- Nausea

Relax, eat, rest, forget and protect

Di Marzo et al, 1998

2. Acute THC-related effects: new findings from animal models

Schizophrenia Research 113 (2009) 123–128

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Assessing the impact of cannabis use on trends in diagnosed schizophrenia in the United Kingdom from 1996 to 2005

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ABSTRACT

A recent systematic review concluded that cannabis use increases risk of psychotic outcomes independently of confounding and transient intoxication effects. Furthermore, a model of the association between cannabis use and schizophrenia indicated that the incidence and prevalence of schizophrenia would increase from 1990 onwards. The model is based on three factors: a) increased relative risk of psychotic outcomes for frequent cannabis users compared to those who have never used cannabis between 1.8 and 3.1, b) a substantial rise in UK cannabis use from the mid-1970s and c) elevated risk of 20 years from first use of cannabis. This paper investigates whether this has occurred in the UK by examining trends in the annual prevalence and incidence of schizophrenia and psychoses, as measured by diagnosed cases from 1996 to 2005. Retrospective analysis of the General Practice Research Database (GPRD) was conducted for 183 practices in England, Wales, Scotland and Northern Ireland. The study cohort comprised almost 600,000 patients each year, representing approximately 2.3% of the UK population aged 16 to 44. Between 1996 and 2005 the incidence and prevalence of schizophrenia and psychoses were either stable or declining. Explanations other than a genuine stability or decline were considered, but appeared less plausible. In conclusion, this study did not find any evidence of increasing schizophrenia or psychoses in the general population from 1996 to 2005.

Psychological Medicine, Page 1 of 16. © Cambridge University Press 2009
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REVIEW ARTICLE

Neuroimaging in cannabis use: a systematic review of the literature

R. Martín-Santos[1,2,3]*, A. B. Fagundo[2,4], J. A. Crippa[1,3,5], Z. Atakan[1,3], S. Bhattacharyya[1], P. Allen[1], P. Fusar-Poli[1], S. Borgwardt[1,6], M. Seal[1,7], G. F. Busatto[8] and P. McGuire[1,3]

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[2] *Neuropsychopharmacology Group, IMIM-Hospital del Mar and Department of Psychiatry; Institute of Neurosciences, Hospital Clinic, IDIBAPS, CIBERSAM, Barcelona, Spain*
[3] *INCT Translational Medicine, Brazil*
[4] *Universidad Autónoma de Barcelona, Barcelona, Spain*
[5] *Department of Neurosciences and Behaviour, School of Medicine of Riberão Preto, São Paulo University, Brazil*
[6] *Psychiatric Out-patient Department (SJB), University Hospital Basel, Basel, Switzerland*
[7] *Melbourne Neuropsychiatry Centre, The University of Melbourne, Australia*
[8] *Department of Psychiatry, School of Medicine, Sao Paulo University, Brazil*

Background. We conducted a systematic review to assess the evidence for specific effects of cannabis on brain structure and function. The review focuses on the cognitive changes associated with acute and chronic use of the drug.

Method. We reviewed literature reporting neuroimaging studies of chronic or acute cannabis use published up until January 2009. The search was conducted using Medline, EMBASE, LILACS and PsycLIT indexing services using the following key words: cannabis, marijuana, delta-9-tetrahydrocannabinol, THC, cannabidiol, CBD, neuroimaging, brain imaging, computerized tomography, CT, magnetic resonance, MRI, single photon emission tomography, SPECT, functional magnetic resonance, fMRI, positron emission tomography, PET, diffusion tensor MRI, DTI-MRI, MRS and spectroscopy.

Results. Sixty-six studies were identified, of which 41 met the inclusion criteria. Thirty-three were functional (SPECT/PET/fMRI) and eight structural (volumetric/DTI) imaging studies. The high degree of heterogeneity across studies precluded a meta-analysis. The functional studies suggest that resting global and prefrontal blood flow are lower in cannabis users than in controls. The results from the activation studies using a cognitive task are inconsistent because of the heterogeneity of the methods used. Studies of acute administration of THC or marijuana report increased resting activity and activation of the frontal and anterior cingulate cortex during cognitive tasks. Only three of the structural imaging studies found differences between users and controls.

Conclusions. Functional neuroimaging studies suggest a modulation of global and prefrontal metabolism both during the resting state and after the administration of THC/marijuana cigarettes. Minimal evidence of major effects of cannabis on brain structure has been reported.

Estimated drug related harms (Nutt *et al* 2007)

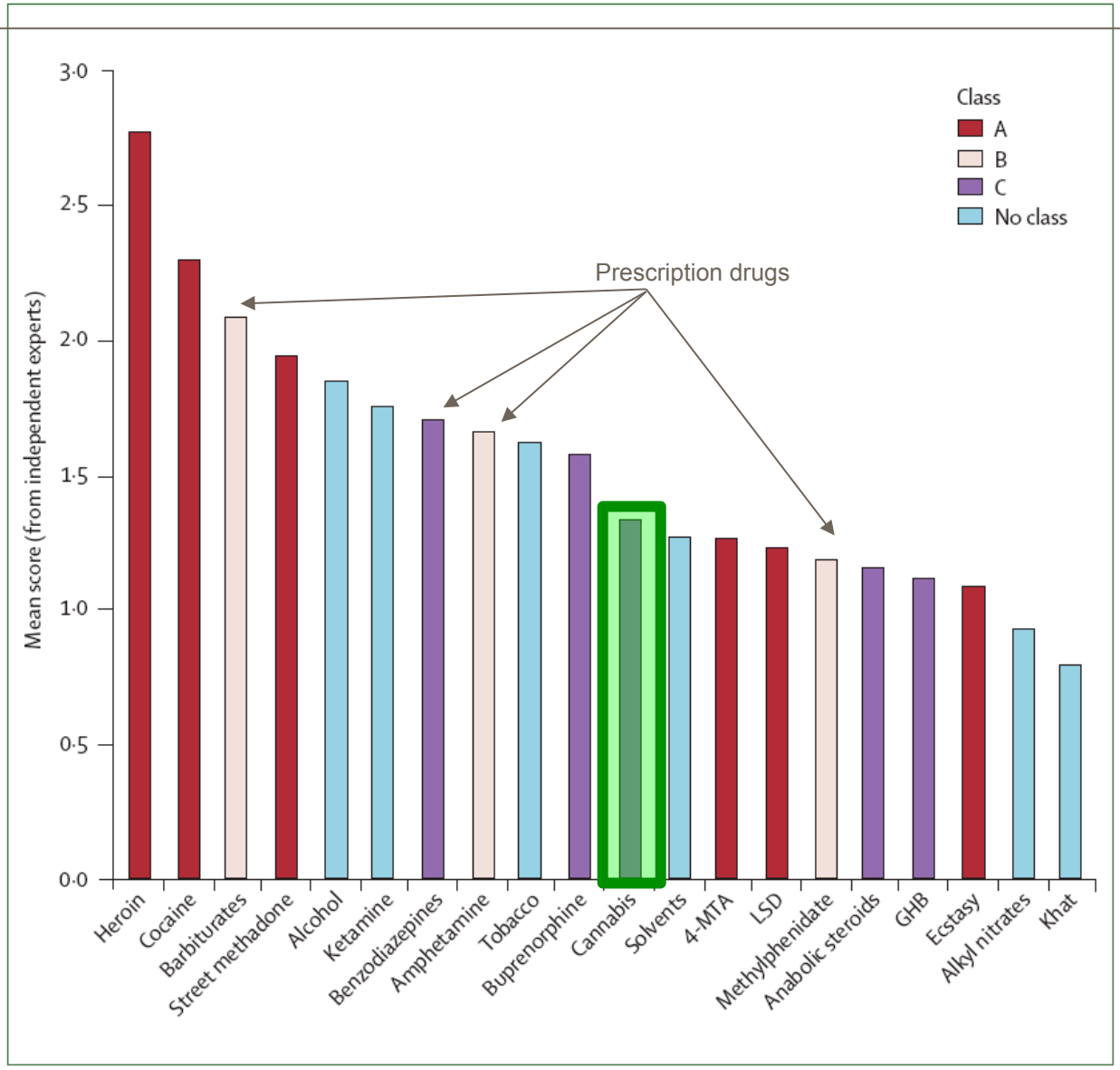
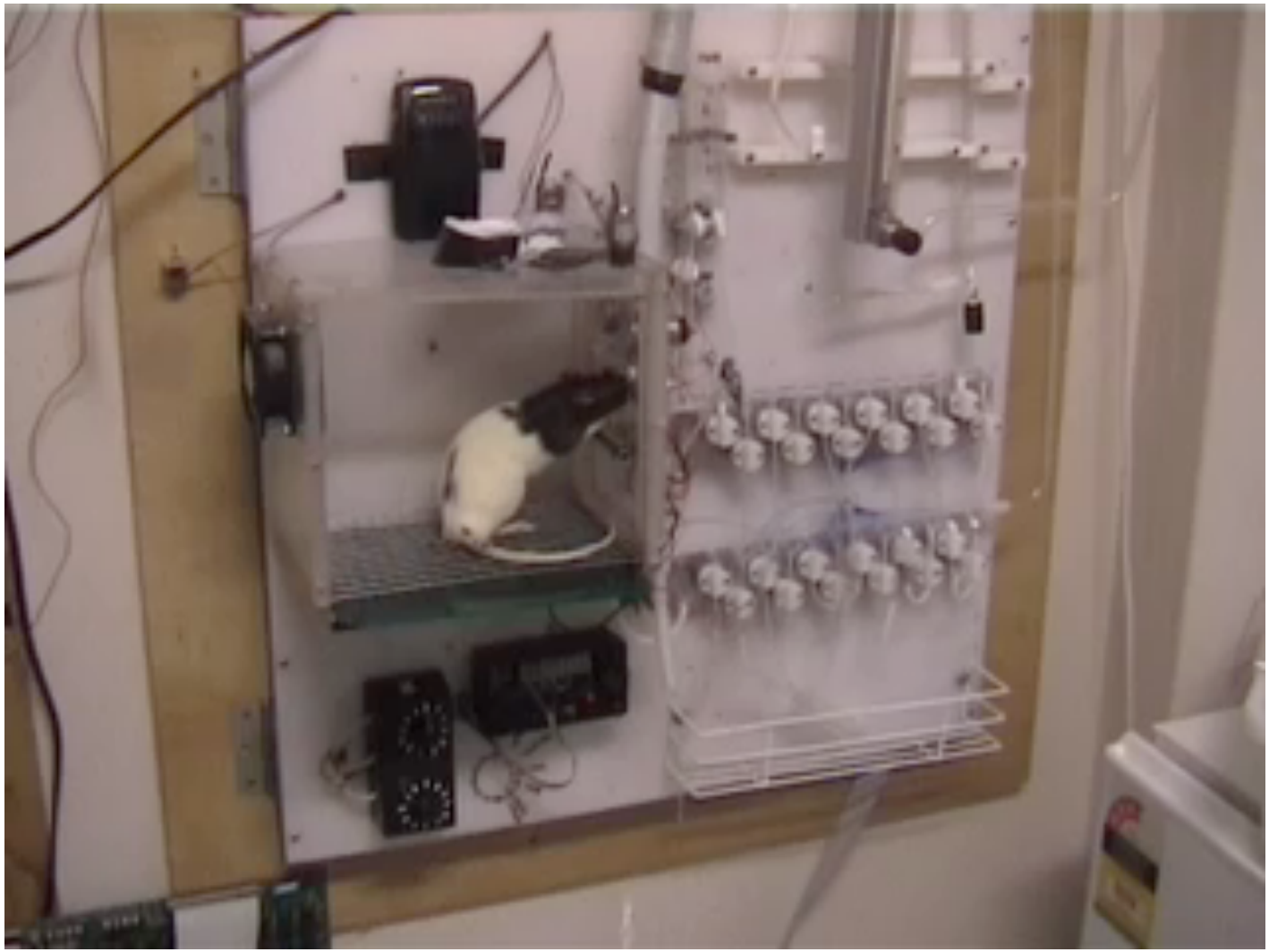


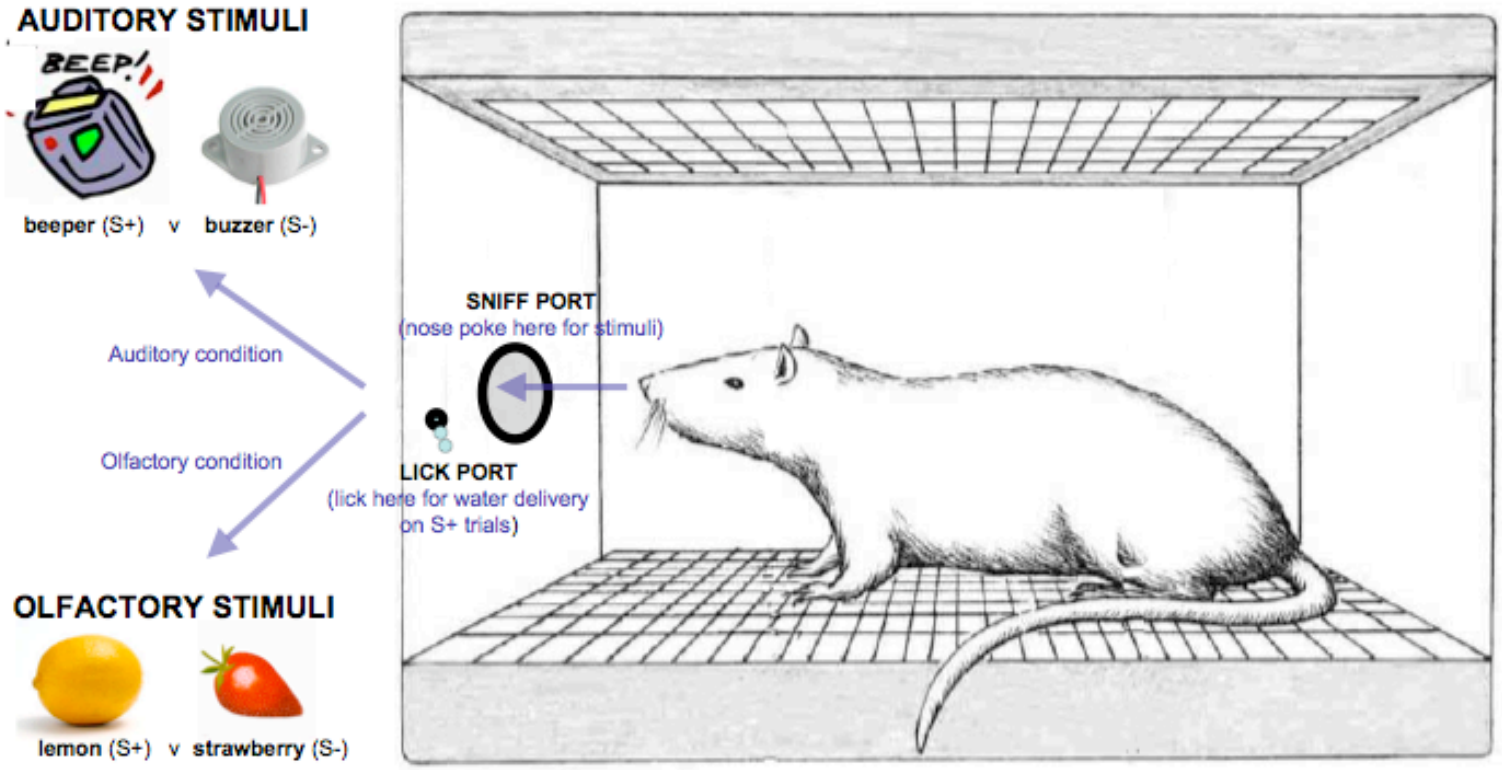
Figure 1: **Mean harm scores for 20 substances**
Classification under the Misuse of Drugs Act, where appropriate, is shown by the colour of each bar.

High dose THC effects in a rat: catalepsy

Subtle low dose effects:
olfactory go/no-go discrimination task

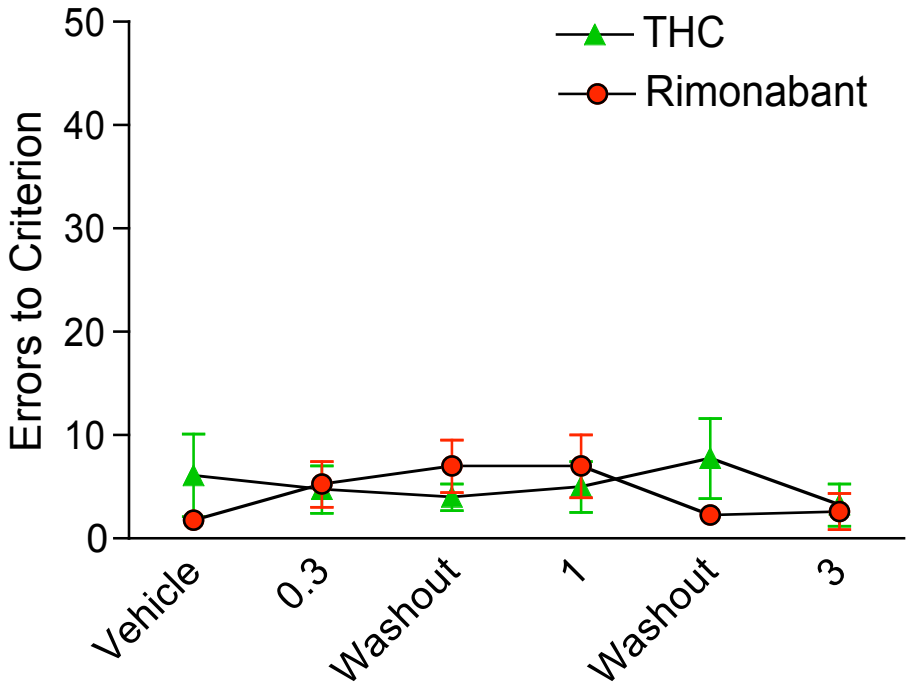


Olfactory and auditory discrimination paradigms



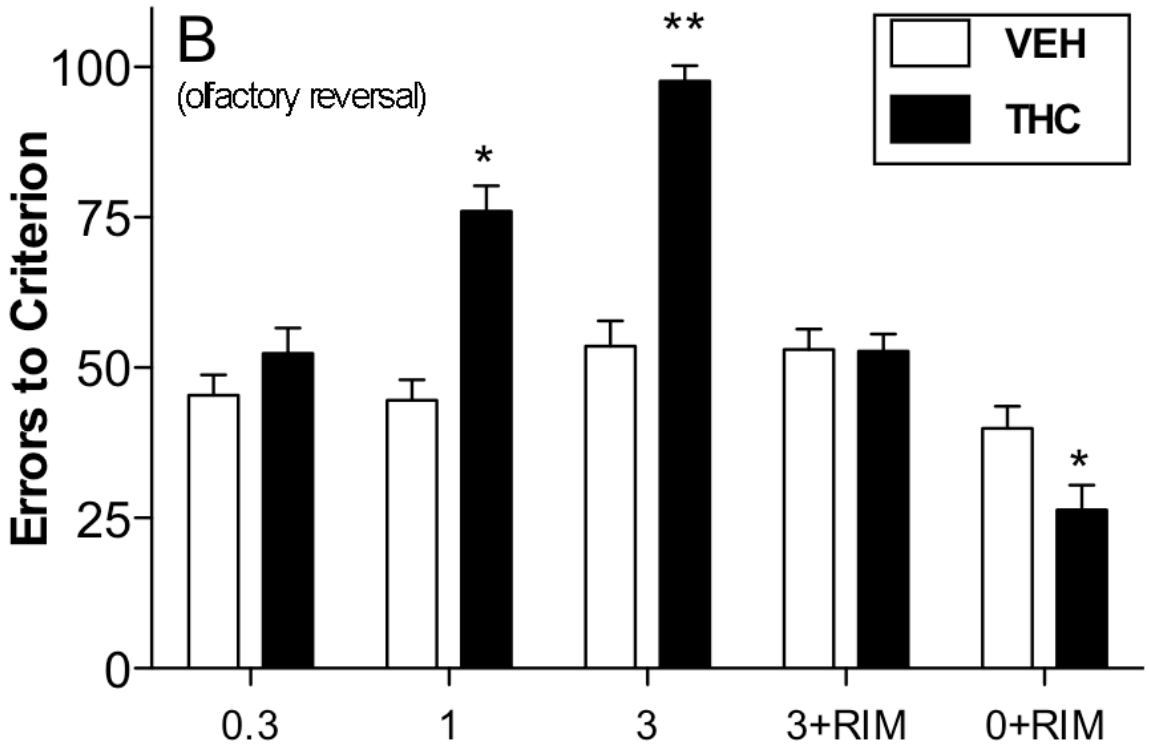
Sokolic, Long, Callaghan, McGregor (manuscript under review)

THC and rimonabant do not affect olfactory discrimination performance in rats

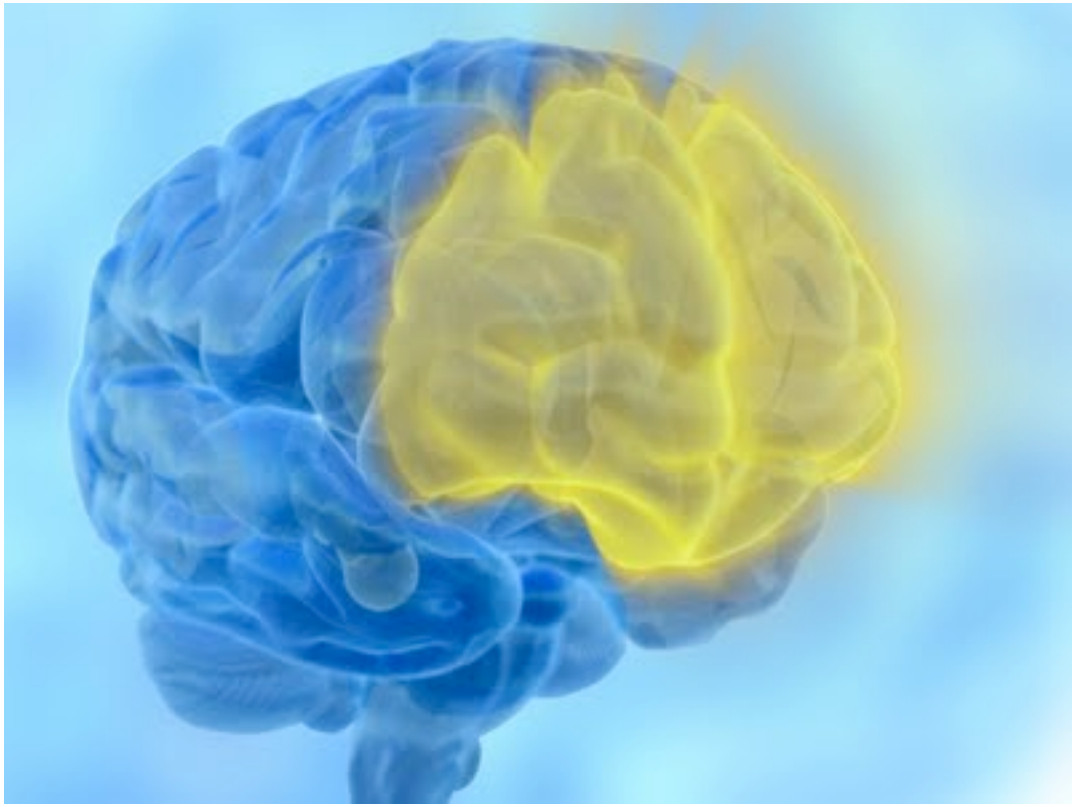


Sokolic, Long, Callaghan, McGregor (manuscript under review)

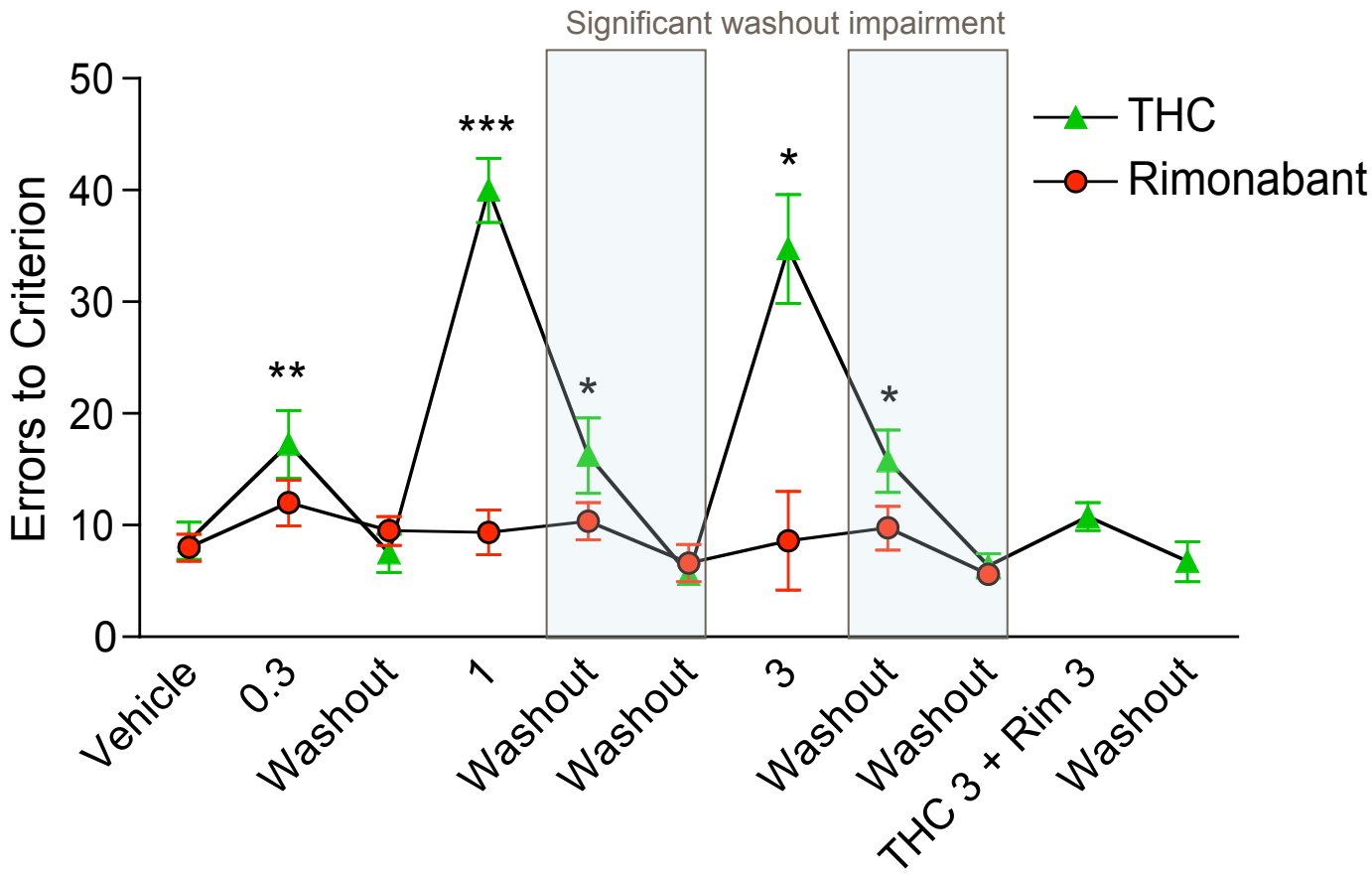
THC impairs *reversal* of olfactory discriminations: loss of cognitive flexibility



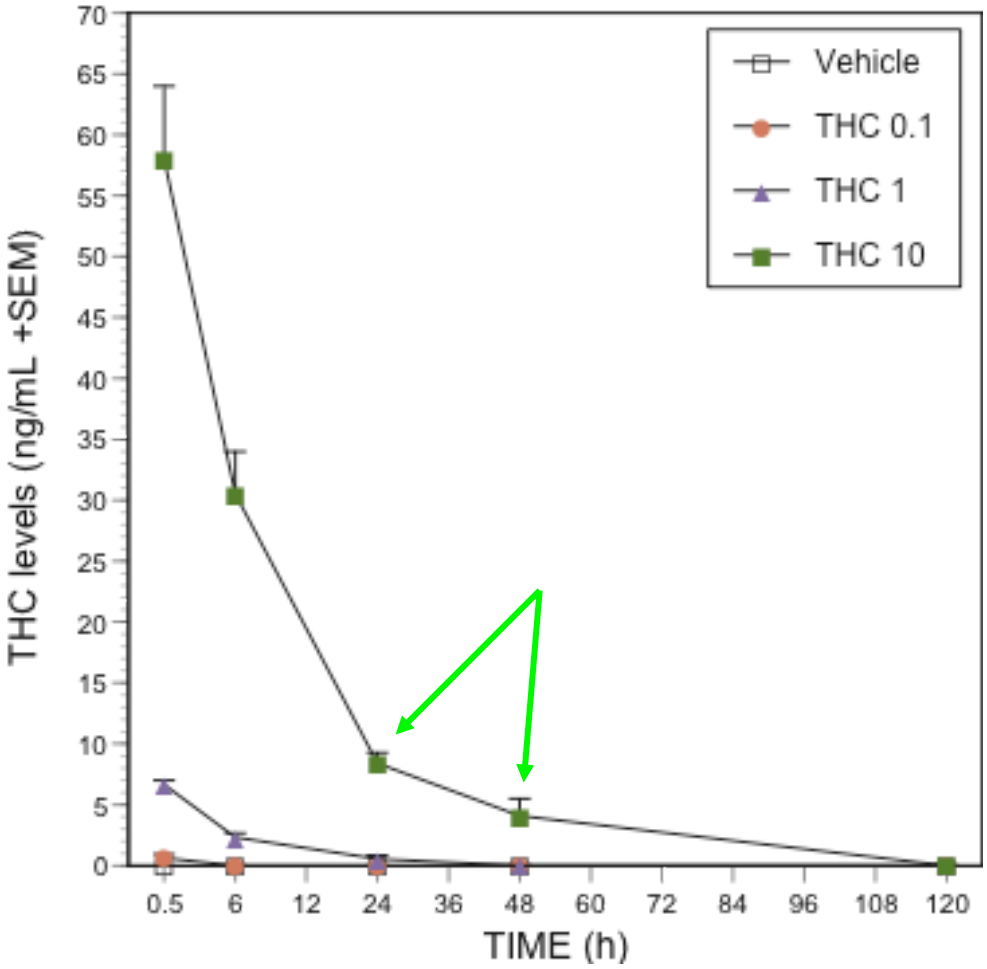
Impairment of reversal learning may involve prefrontal cortex



THC impairs auditory discrimination performance in rats: cannabis impairs auditory more than olfactory performance

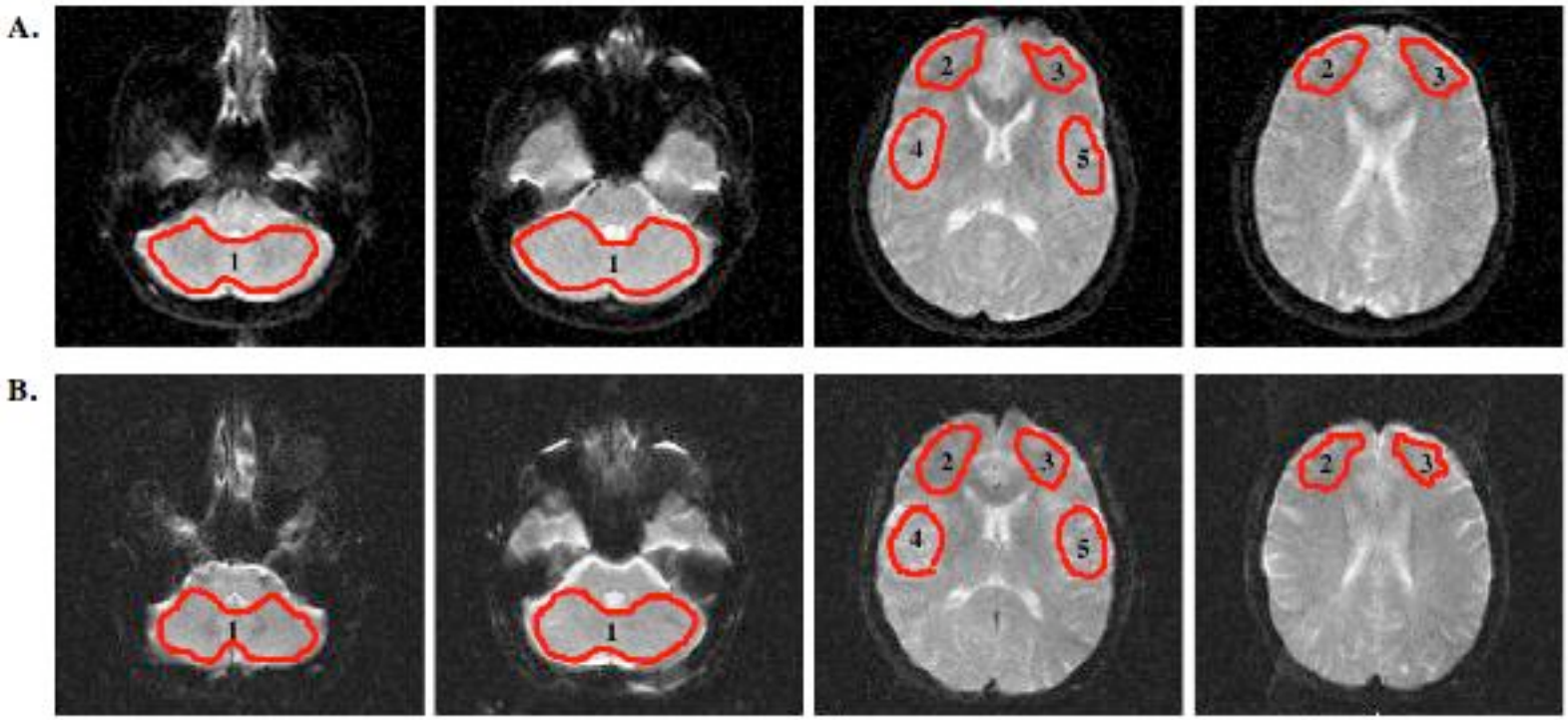


Significant THC blood levels on the days following THC 10 mg/kg in rats



Arnold, Long, Surgeon, McGregor (unpublsihed data)

Temporal lobe shows increased regional blood flow in heavy cannabis users, even after 28 days of abstinence



Differences in Regional Blood Volume During a 28-Day Period of Abstinence in Chronic Cannabis Smokers

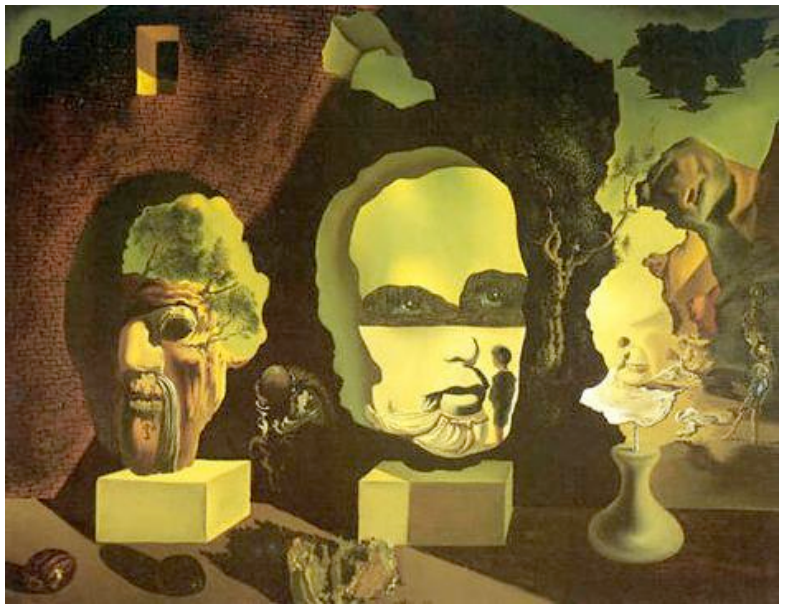
Sneider et al Eur Neuropsychopharm (2008) 18: 612-619

3. Residual cannabis harms: animal models

Adolescent behaviours

"from dependence to independence"

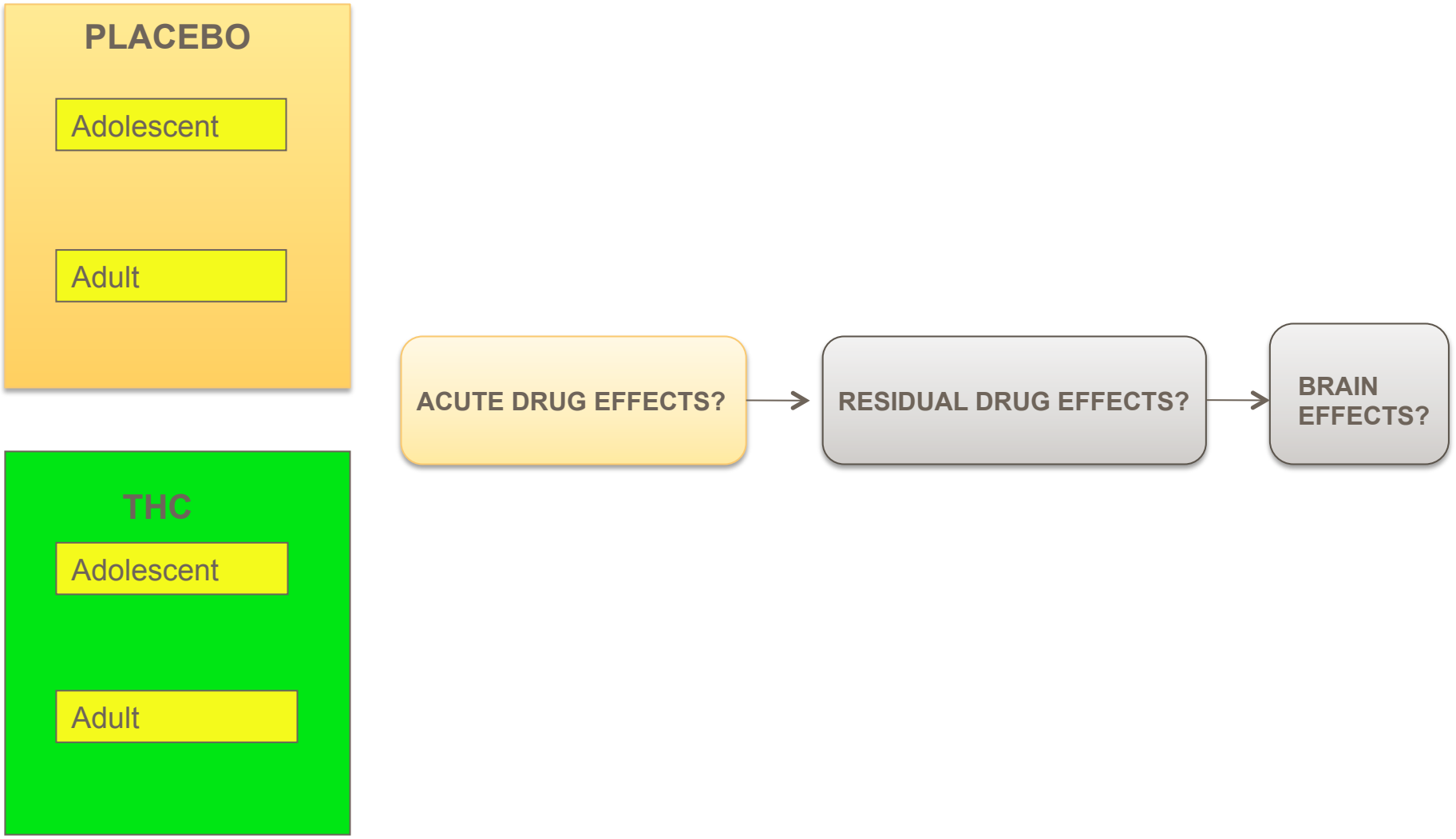
- Novelty seeking
- Risk taking and impulsivity
- Peer to peer social networking
- Sexual awakening
- Abstract reasoning



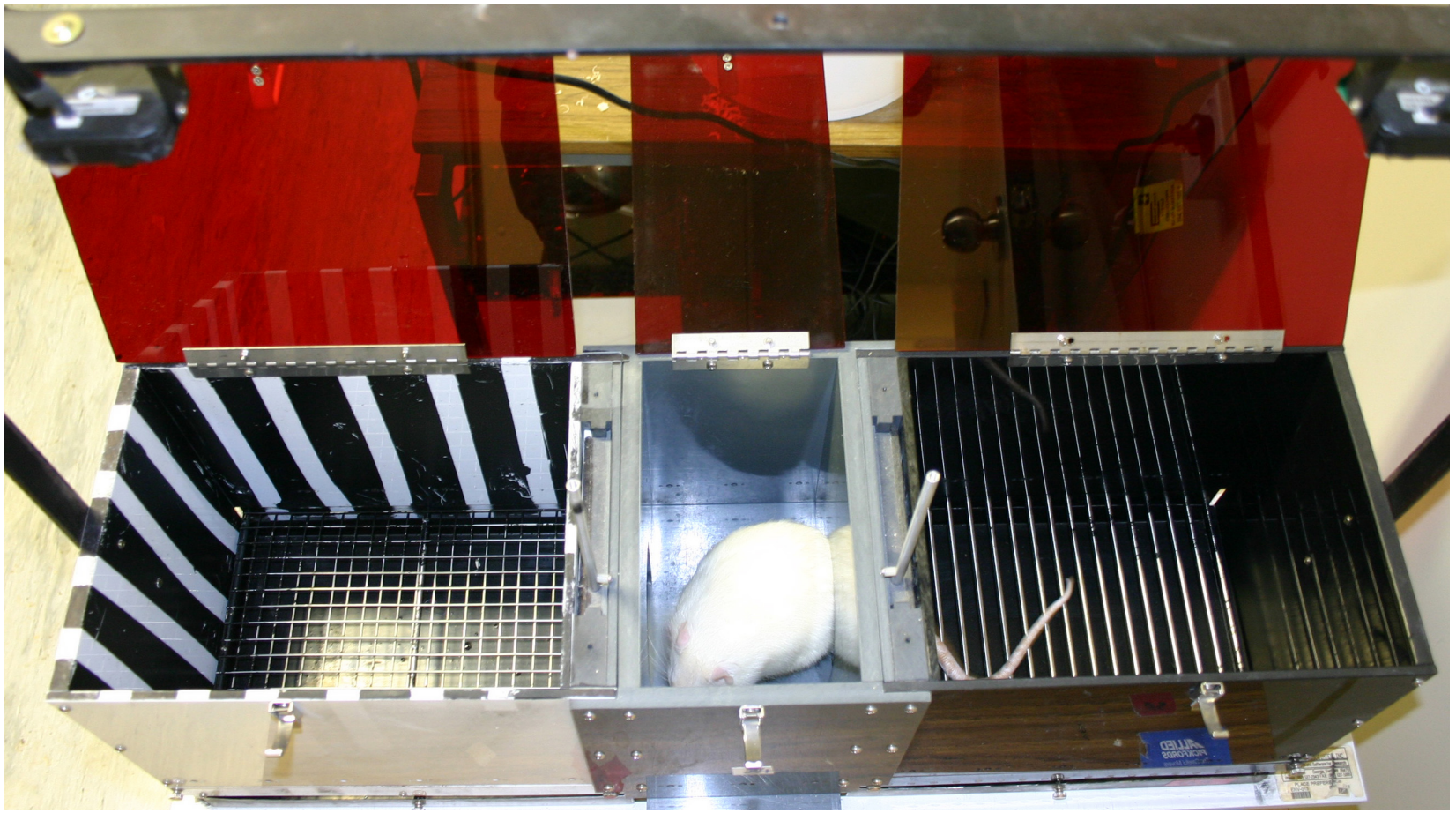
Salvador Dali. Old age, Adolescence, Infancy (The Three Ages) (1940)

Developmental stages in rats

Adolescent drug effects: standard experimental design



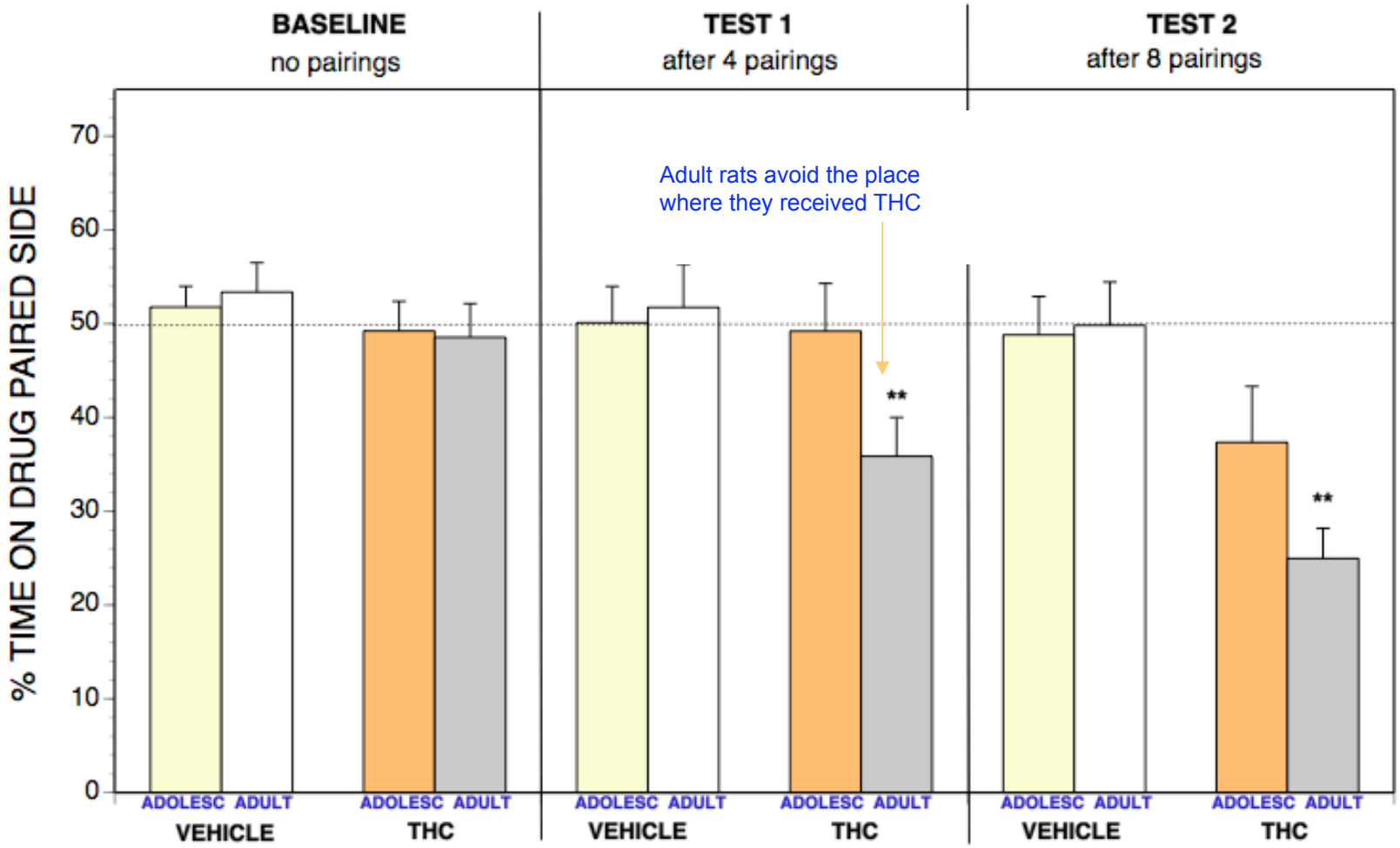
Conditioned place preference apparatus: do you like the drug or not?



Drug paired side

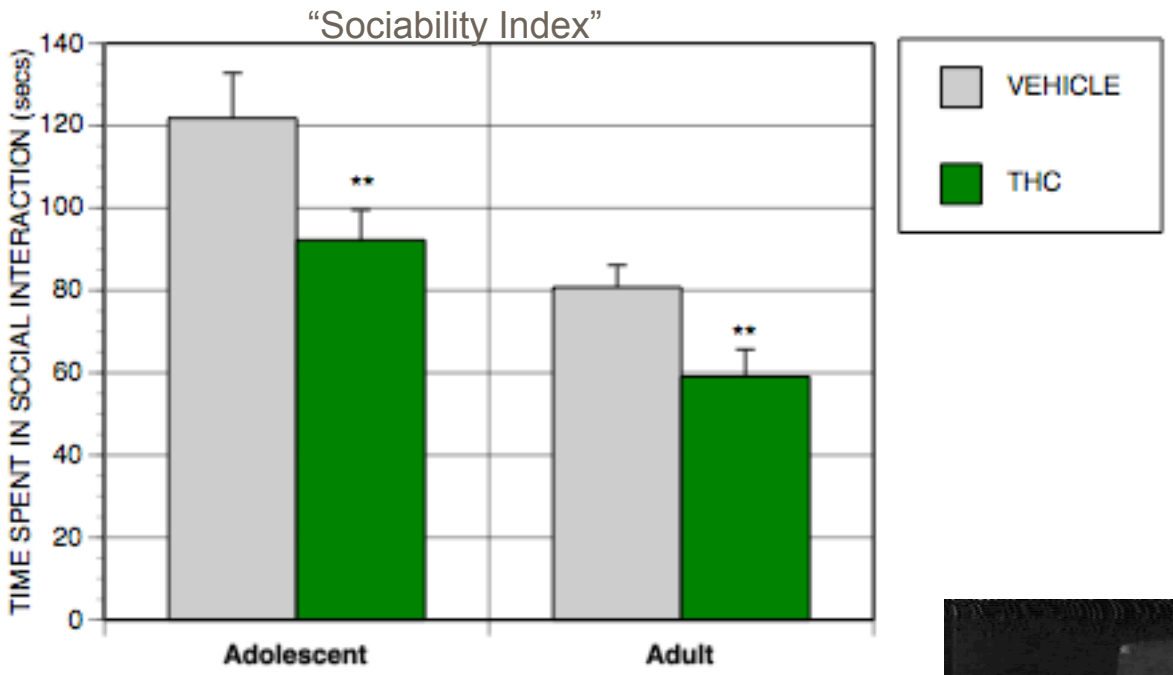
Placebo paired side

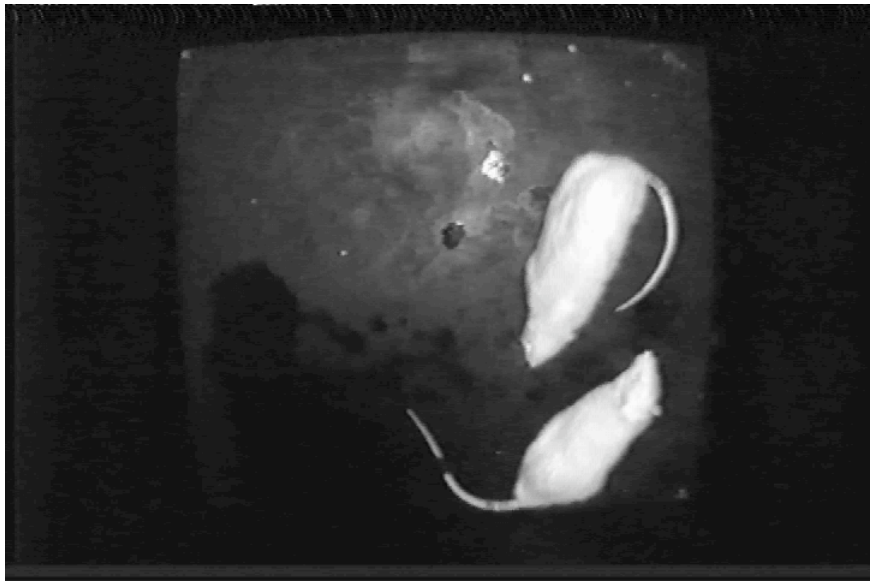
Conditioned Place Preference Results



Quinn H.R., et al & **McGregor IS** (2008). Adolescent rats find repeated delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology*. **33**, 1113-1126.

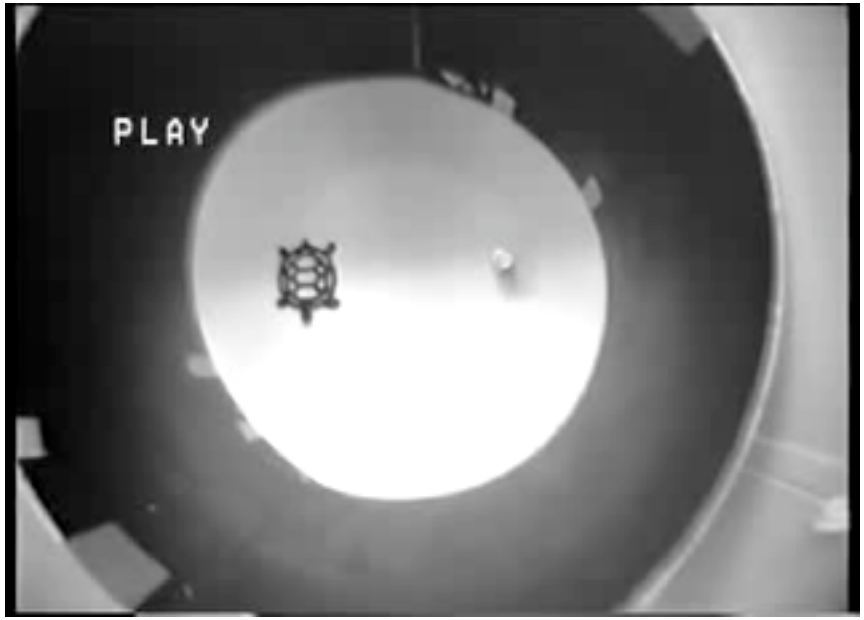
Residual deficits in social interaction in THC pre-exposed adult and adolescent rats



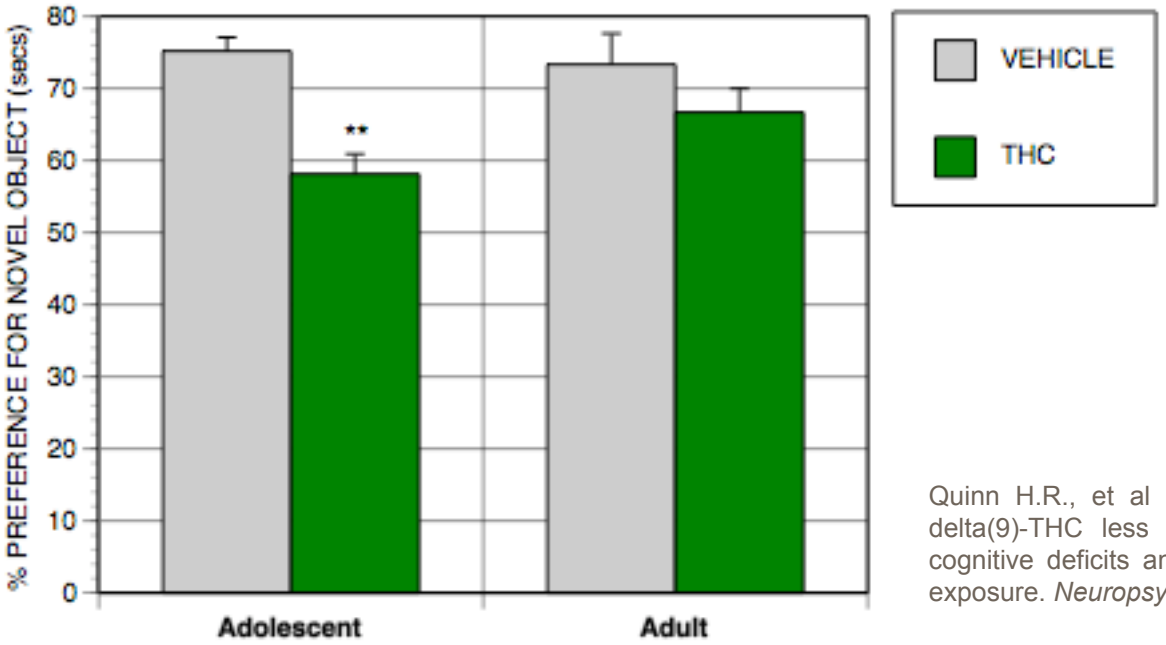


Quinn H.R., et al & **McGregor IS** (2008). Adolescent rats find repeated delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology*. **33**, 1113-1126.

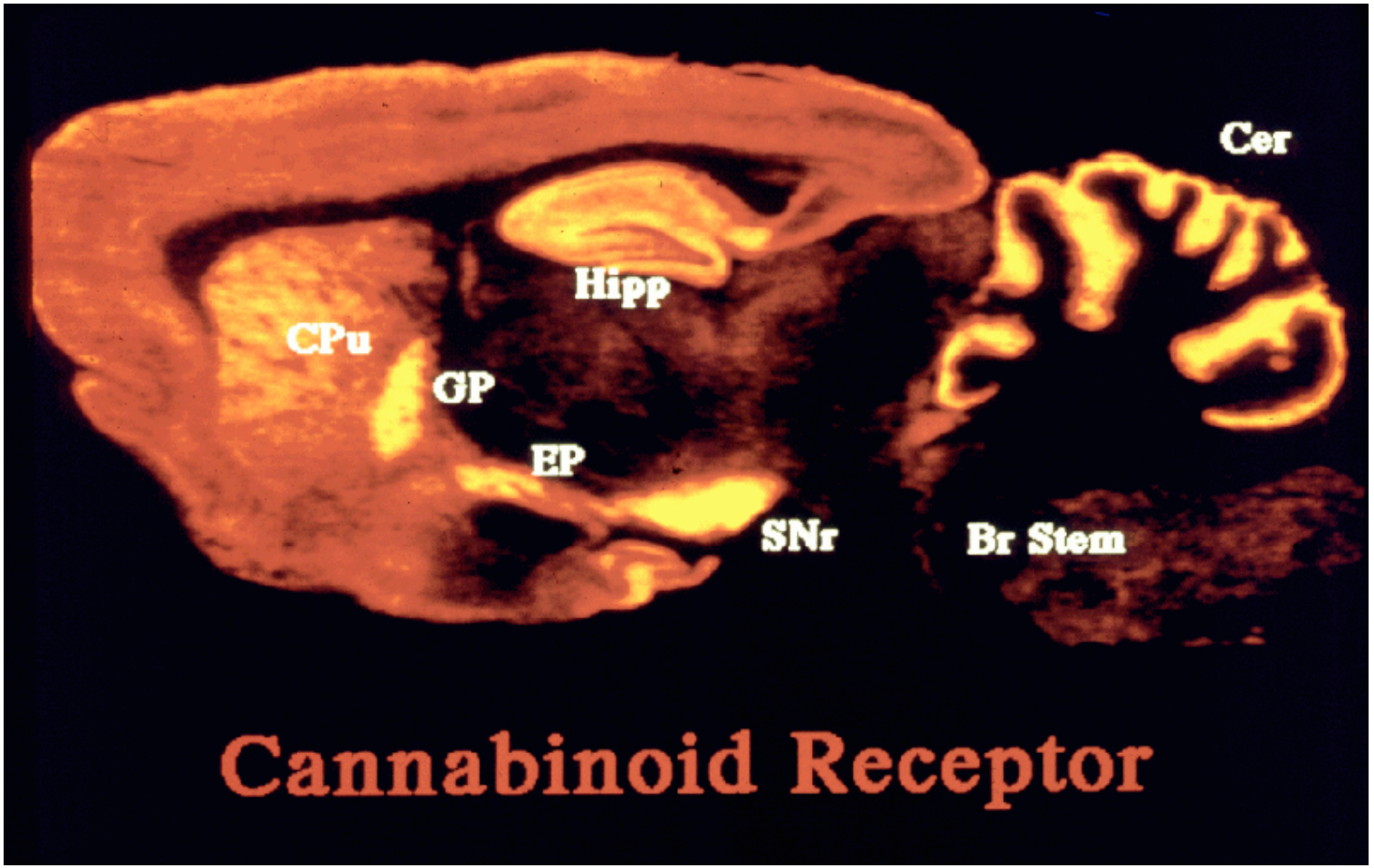
Residual deficits in object recognition memory in THC pre-exposed adolescent rats



"Memory Index"



Quinn H.R., et al & **McGregor IS** (2008). Adolescent rats find repeated delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology*. **33**, 1113-1126.


Cer
Hipp
CPu
GP
EP
SNr
Br Stem
Cannabinoid Receptor

Numerous significant hippocampal protein changes in THC pre-exposed adolescent rats

Table 6 Differentially Expressed Proteins in the Hippocampus of Adolescent Δ^9-THC-Treated Rats

Spot	Identified protein name	pI	MW	No. of mass values matched	Sequence coverage (%)	Mowse score	Accession number	Fold change
Oxidative stress/mitochondrial function								
129	Stress-70 protein, mitochondrial precursor (GRP 75)	5.97	73798	18	28	148	P48721	−1.83
527	Glutathione transferase ω-1	6.25	27651	10	48	87	Q9Z339	−1.80
137	Heat shock cognate 71 kDa protein	5.37	70872	28	38	155	P63018	−1.62
601	Protein DJ-1	6.32	19961	13	48	106	O88767	−1.42
584	Peroxiredoxin-6	5.65	24672	8	48	56	O35244	−1.21
217	60kDa heat shock protein	5.91	60917	14	31	158	P63039	−1.19
Cytoskeletal								
616	Transgelin-3 (NP25)	6.53	24696	12	48	120	P37805	−1.51
239	Tubulin α-2 chain	4.94	50120	29	57	78	Q6P9V9	−1.48
239	Tubulin β-3 chain	4.82	50386	25	42	135	Q4QRB4	−1.48
Signaling								
494	Annexin A3	6.05	36169	19	57	183	P14669	−1.84
545	14-3-3 protein ζ/δ	4.73	27754	20	51	137	P63102	1.65
Metabolic proteins								
554	Phosphoglycerate mutase 1	6.21	28497	7	33	59	P25113	−1.62
558	Phosphoglycerate mutase 1	6.21	28497	18	56	111	P25113	−1.56
550	Phosphoglycerate mutase 1	6.21	28497	17	53	84	P25113	−1.46
551	Phosphoglycerate mutase 1	6.21	28497	22	58	76	P25113	−1.22
665	Ubiquitin-conjugating enzyme E2 variant 2	8.05	16211	6	24	50	Q7M767	−1.47
652	Nucleoside diphosphate kinase B	6.92	17272	10	75	131	P19804	−1.08
Other								
633	Myelin basic protein S	11.25	21358	13	59	99	P02688	1.72
604	Ras-related protein Rab-1A	5.93	22532	6	38	85	Q6NYB7	1.56
439	NAD-dependent deacetylase sirtuin-2	6.67	39294	10	33	84	Q5RJQ4	−1.51

Quinn H.R., et al & **McGregor IS** (2008). Adolescent rats find repeated delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology*. **33**, 1113-1126.

Fewer significant hippocampal protein changes in THC pre-exposed adult rats

Table 7 Differentially Expressed Proteins in the Hippocampus of Adult Δ^9-THC-Treated Rats

Spot number	Identified protein name	pI	MW	No. of mass values matched	Sequence coverage (%)	Mowse score	Accession number	Fold change
Metabolic proteins								
100	Aconitate hydratase, mitochondrial precursor	7.87	85380	44	54	259	Q9ER34	1.73
447	Glyceraldehyde-3-phosphate dehydrogenase	8.44	35682	20	52	104	P04797	−1.51
149	Succinate dehydrogenase (ubiquinone) flavoprotein subunit	6.75	71570	26	43	206	Q920L2	−1.51
572	Triosephosphate isomerase	6.51	26773	22	72	171	P48500	−1.50
Signaling								
495	Annexin A5	4.93	35591	13	39	90	P14668	−2.32
522	14-3-3 protein ε	4.63	29155	29	71	104	P62260	−1.12
Oxidative stress								
576	Glutathione S-transferase Yb-3	7.27	25533	16	42	126	P08009	−1.69
Other								
211	Serine/threonine-protein phosphatase 2B catalytic subunit α isoform	5.58	58606	13	20	88	P63329	−1.68
447	NAD-dependent deacetylase sirtuin-2	6.67	39294	12	42	56	Q5RJQ4	−1.51

Quinn H.R., et al & **McGregor IS** (2008). Adolescent rats find repeated delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology*. **33**, 1113-1126.

Female rats may be more vulnerable to adverse effects?

Original Papers

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Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats

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Iain S. McGregor *School of Psychology, Sydney University, New South Wales, Australia.*
Paul E. Mallet *School of Psychology, University of New England, Armidale, New South Wales, Australia.*

Abstract

Although many studies have examined the acute behavioural effects of cannabinoids in rodents, few have examined the lasting effects of cannabinoids at different developmental ages. This study compared lasting effects of cannabinoid exposure occurring in adolescence to that occurring in early adulthood. Forty, 30-day old (adolescent) and 18, 56-day old (adult) female albino Wistar rats were injected with vehicle or incremental doses of the cannabinoid receptor agonist (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl) cyclohexanol (CP 55,940) once per day for 21 consecutive days (150, 200 and 300 μg/kg i.p. for 3, 8 and 10 days, respectively). Following a 21-day drug-free period, working memory was assessed using an object recognition task. Locomotor activity was also measured in the object recognition apparatus via a ceiling-mounted passive infrared sensor. Three days later, anxiety was assessed using a social interaction test. In the object recognition task, significantly poorer working memory was observed in the adolescent but not adult CP 55,940-treated rats. Adolescent, but not adult CP 55,940-treated rats, also exhibited a significant decrease in social interaction with a novel conspecific. These results suggest that chronic exposure to a cannabinoid receptor agonist well after the immediate postnatal period, but before reaching sexual maturity, can lead to increased anxiety and a lasting impairment of working memory.

Keywords
adolescent, anxiety, cannabinoid, CP 55,940, memory, object recognition, rat, social interaction

Introduction

Cannabis sativa has been used for thousands of years for both recreational and medical purposes but, despite this long history, very little is known about the long-lasting neurobehavioural effects of chronic cannabis use. The residual effects of cannabinoids, defined as the effects that persist long after the drug has left the central nervous system (CNS) (Pope *et al*., 1995), have received only sparse research interest. In particular, the effects of cannabis initiation occurring in and around the adolescent period remains relatively unknown. Human cannabis use is commonly initiated in adolescence (Scallet, 1991), which coincides with major neuronal changes in the CNS (Ehrenreich *et al*., 1999). Furthermore, in recent years, the age of initiation of cannabis use is becoming earlier in life. For example, a survey conducted in 1998 found that over 78% of adolescents had reported cannabis initiation at 14 years or younger compared to previous findings of 64% in 1992 (McCreary Centre Society, 1999). It is therefore of interest to determine whether adolescent cannabis use can produce lasting effects on cognitive function and emotion.

In the rat, adolescence can be defined as the period just before reaching sexual maturity (6–8 weeks; Fallon, 1995). Major changes in neuronal structure occur at this age, and the administration of cannabinoids at this time may produce marked changes in neuronal function (Rodríguez de Fonseca *et al*., 1991). A few studies on rats corresponding to the same age (30–40 days old) have addressed the residual effects of cannabinoids on learning (Fehr *et al*., 1976; Stiglick and Kalant, 1982, 1983). In these studies, varying doses of Δ^9-tetrahydrocannabinol (THC) were administered to 30-day old rats for 1–6 months, followed by a

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4. Cannabis withdrawal: lithium and oxytocin as therapeutics

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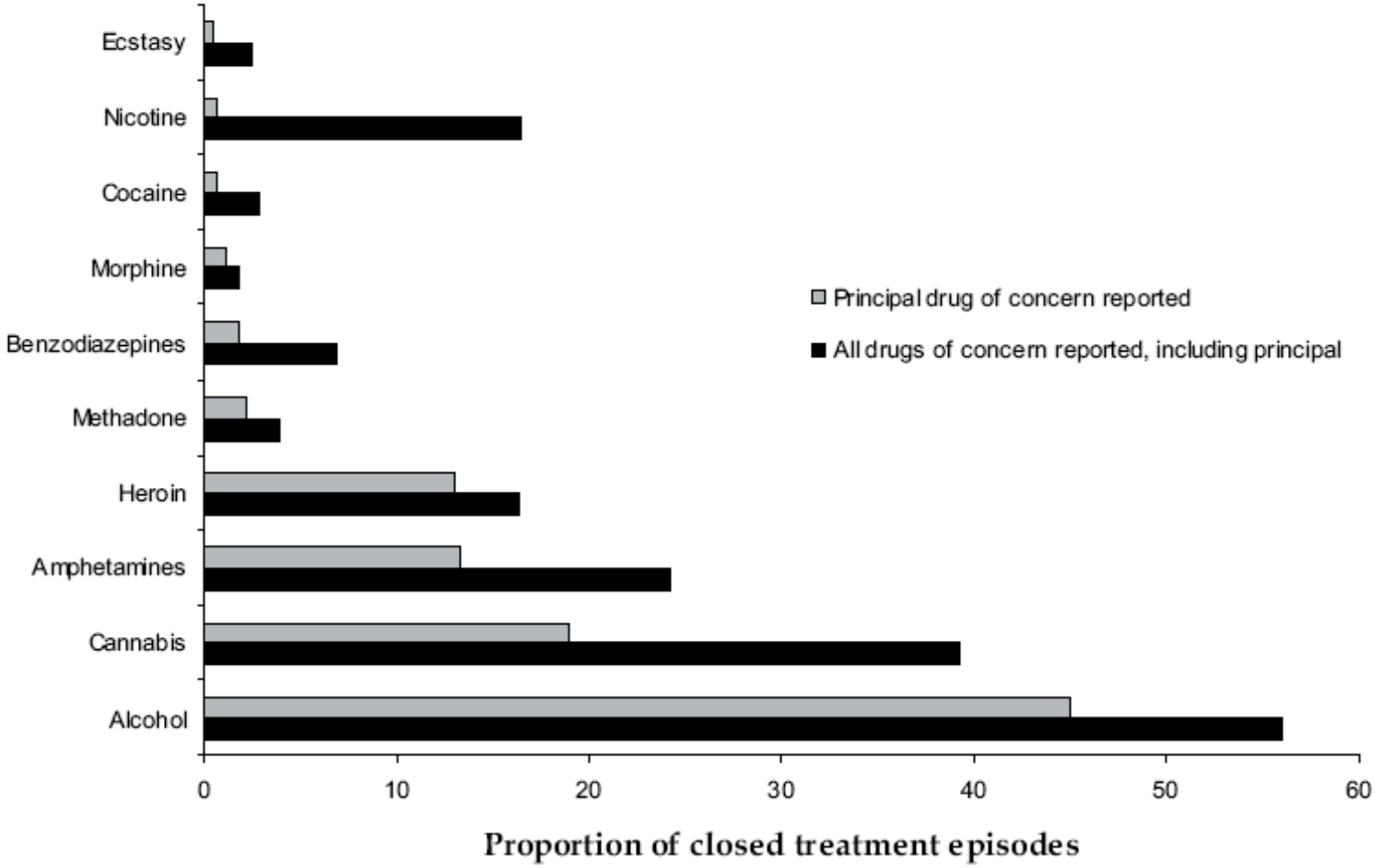
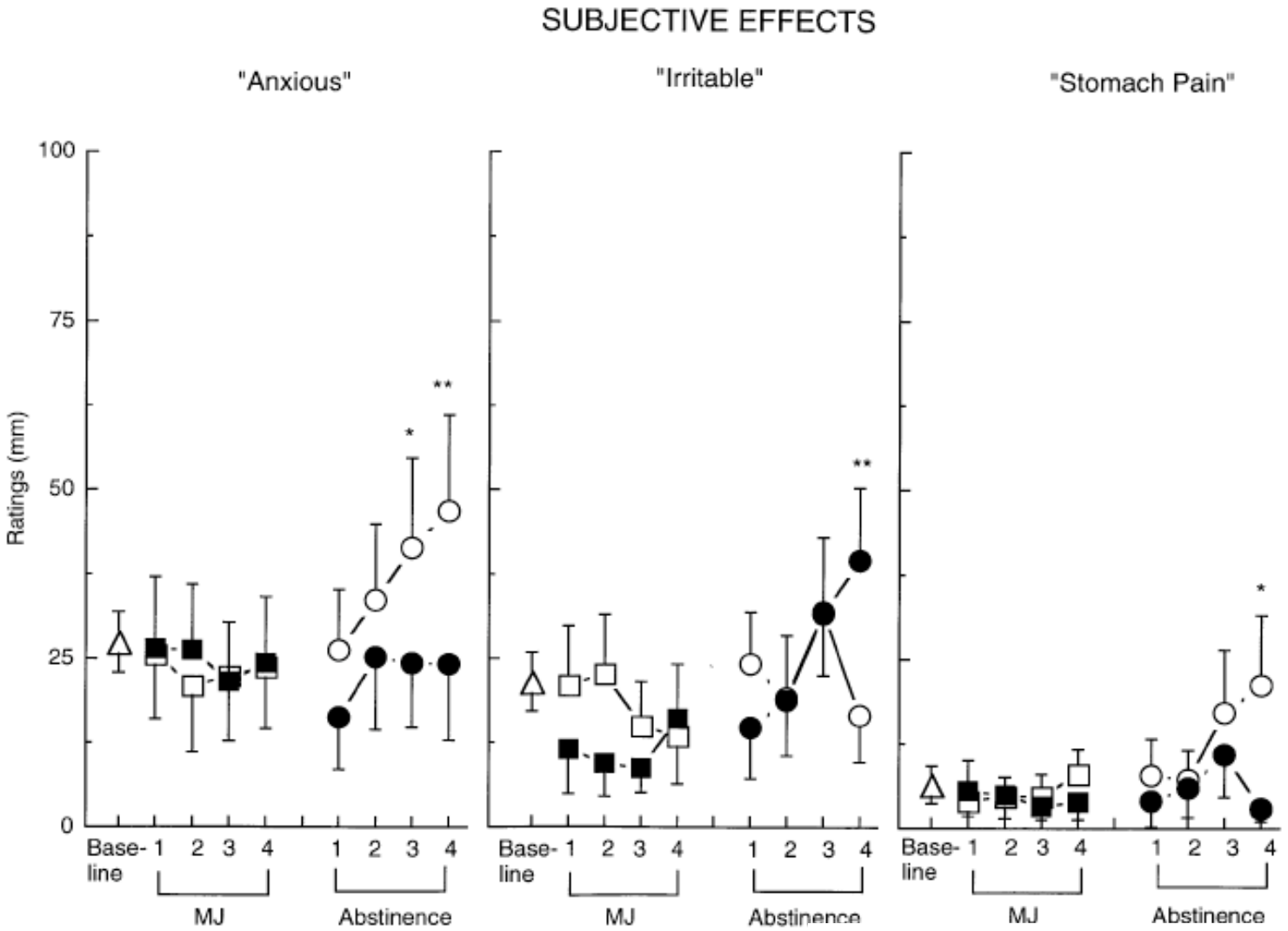


Figure 1: Closed treatment episodes by principal drug of concern and all drugs of concern, NSW, 2006–07

Anxiety and irritability during cannabis withdrawal



Margaret Haney · Amie S. Ward · Sandra D. Comer
Richard W. Foltin · Marian W. Fischman

Psychopharmacology (1999) 141 : 395–404

Cannabis withdrawal

Table 2. Signs of the cannabinoid withdrawal syndrome

Counted signs	Observed signs
Wet-dog shakes	Piloerection
Rearing	Hunting position
Forelimb tremor	
Penile licking	
Mastication	
Scratch sequence	

Lithium and IP oxytocin attenuate cannabis withdrawal in rats

9874 J. Neurosci., December 15, 2001, 21(24):9867–9876

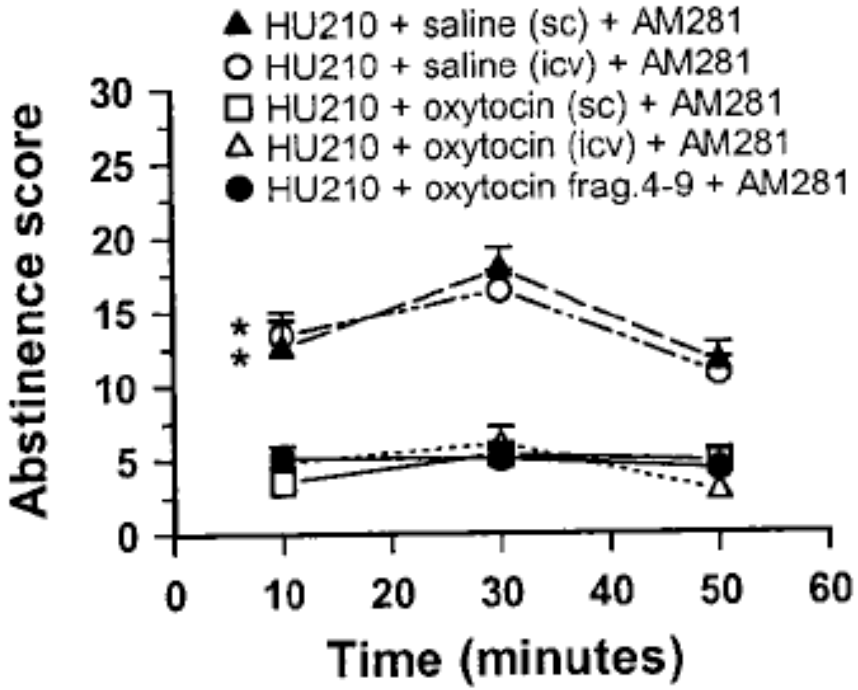


Figure 7. Effects of oxytocin on the cannabinoid withdrawal syndrome after different treatments ($n = 6$ per group) (see Table 1 and Materials and Methods for treatment protocols). *Indicates a significant difference ($p < 0.001$) in comparison with each of the other three groups without the label *.

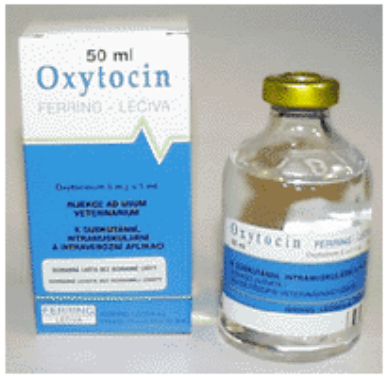
Shu-Sen Cui,[1] Rudy C. Bowen,[1] Gui-Bao Gu,[2] Darren K. Hannesson,[1] Peter H. Yu,[1] and Xia Zhang[1]

Dr Adam Guastella
BMRI

Intranasal oxytocin for:

- Autism
- Prader-Willi syndrome
- Social Anxiety disorder
- Schizophrenia
- Addictions?

Methamphetamine
Alcohol
Cannabis



British Journal of Pharmacology (2008) 154, 358–368

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REVIEW

From ultrasocial to antisocial: a role for oxytocin in the acute reinforcing effects and long-term adverse consequences of drug use?

IS McGregor[1], PD Callaghan[1] and GE Hunt[2]

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Addictive drugs can profoundly affect social behaviour both acutely and in the long-term. Effects range from the artificial sociability imbued by various intoxicating agents to the depressed and socially withdrawn state frequently observed in chronic drug users. Understanding such effects is of great potential significance in addiction neurobiology. In this review we focus on the 'social neuropeptide' oxytocin and its possible role in acute and long-term effects of commonly used drugs. Oxytocin regulates social affiliation and social recognition in many species and modulates anxiety, mood and aggression. Recent evidence suggests that popular party drugs such as MDMA and gamma-hydroxybutyrate (GHB) may preferentially activate brain oxytocin systems to produce their characteristic prosocial and prosexual effects. Oxytocin interacts with the mesolimbic dopamine system to facilitate sexual and social behaviour, and this oxytocin-dopamine interaction may also influence the acquisition and expression of drug-seeking behaviour. An increasing body of evidence from animal models suggests that even brief exposure to drugs such as MDMA, cannabinoids, methamphetamine and phencyclidine can cause long lasting deficits in social behaviour. We discuss preliminary evidence that these adverse effects may reflect long-term neuroadaptations in brain oxytocin systems. Laboratory studies and preliminary clinical studies also indicate that raising brain oxytocin levels may ameliorate acute drug withdrawal symptoms. It is concluded that oxytocin may play an important, yet largely unexplored, role in drug addiction. Greater understanding of this role may ultimately lead to novel therapeutics for addiction that can improve mood and facilitate the recovery of persons with drug use disorders.
British Journal of Pharmacology (2008) **154**, 358–368; doi:10.1038/bjp.2008.132

Keywords: addiction; antisocial; anxiety; cannabinoid; GHB; MDMA; methamphetamine; oxytocin; social; vasopressin

Abbreviations: AVP, arginine vasopressin; GHB, gamma-hydroxybutyrate; L-368,899, (2S)-2-Amino-*N*-[(1S,2S,4R)-7,7-dimethyl-1-[[[4-(2-methy lphenyl)-1-piperazinyl]sulphonyl]methyl]bicyclo[2.2.1]he pt-2-yl]-4-(methylsulfonyl)butanamide; MDMA, 3,4,-methylenedioxymethamphetamine; NAS, nucleus accumbens; OT, oxytocin; PVN, paraventricular nucleus of the hypothalamus; SON, supraoptic nucleus; THC, delta-9-tetrahydrocannabinol; TOC, tocinoic acid; WAY 100,635, *N*-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2 pyridinylcyclohexanecarboxamide maleate salt; VTA, ventral tegmental area; 8-OH-DPAT, 8-hydroxy-2-(di-n-propylamino)-tetraline

Introduction

The social causes and social consequences of drug use, and their underlying neural correlates, are important but as yet understudied areas in the study of addiction. Even the most cursory reflection on human drug use suggests that the motivation to consume drugs is inextricably linked to the social context. Obvious examples are the widespread use of alcohol for 'social lubrication', the popular use of 'party drugs' such as 3,4-methylenedioxymethamphetamine (MDMA) (Ecstasy) and gamma-hydroxybutyrate (GHB) for their prosocial and prosexual effects, and drug initiation in adolescence as a result of 'peer pressure'. Drug use may even define social groups, with the psychedelic movement of the 1960s and rave phenomenon of the late 1980s and 1990s seeing entire subcultures identified by their drug choice and drug-induced behaviours.

The adverse consequences of drug use are often expressed in terms of costs to society; encapsulating the idea that repeated drug use entails profound social costs. Familiar examples include the random violence inflicted by intoxicated pub patrons, the aggressive psychosis and paranoia

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NHMRC funded project: RCT of Lithium/oxytocin for cannabis withdrawal (2009-2010)

Nick Lintzeris, Adam Winstock, Adam Guastella, Iain McGregor

Methodological overview of a randomised controlled trial of lithium carbonate for the management of cannabis withdrawal

Adam Winstock[1], Nicholas Lintzeris[2,3], Iain McGregor[2], Adam Guastella[2]
[1]National Addiction Centre, King's College London, [2]University of Sydney, [3]Sydney South West Area Health Service

Background

50-75% of regular cannabis users report cannabis withdrawal symptoms on cessation of regular use. Withdrawal symptoms can be a barrier to achieving abstinence.

Currently there are no evidence-based pharmacotherapies for the management of cannabis withdrawal.

Pre-clinical research suggests that lithium moderates cannabis withdrawal symptoms and is associated with an increase in oxytocin levels (Cui et al., 2001).

Human pilot trial of lithium carbonate

Winstock, Lea & Copeland, 2009

Open-label, inpatient trial of lithium for cannabis withdrawal with 20 cannabis dependent adults. Dose: 500mg b.d. for 7 days. Twelve participants completed treatment (60%).

Self-reported cannabis withdrawal was of generally low severity. Participants endorsed a mean of 4.75 symptoms of at least mild severity during treatment.

Objectives of current trial

1.Determine the efficacy of lithium compared to placebo in reducing the severity of cannabis withdrawal.

3. Compare detoxification completion rates between treatment conditions.

4. Compare adverse events during detoxification between treatment conditions.

5. Determine whether provision of lithium is associated with a reduction in cannabis use during a 3-month follow-up period.

6. Examine the potential role of oxytocin in mediating the effects of lithium on cannabis withdrawal.

Trial design

Phase III, multi-site, double-blind, placebo controlled trial.

Participants will be 120 treatment-seeking, cannabis dependent adults.

Participants will be admitted for 7 days, with block randomisation stratified by trial site.

Lithium dose: 500mg b.d. for 7 days.

Recruitment will take place over 15 months at two inpatient drug treatment facilities located in Lismore (Riverlands Drug and Alcohol Centre) and Sydney (Fairfield Drug Health Services).

Research follow-up interviews will occur at 30, 60 and 90 days following discharge from the inpatient unit. Urine and blood samples will be taken at these interviews to corroborate self-reported cannabis use, and to determine the long-term effects of lithium on oxytocin, vasopressin and cortisol levels.

Measures

Cannabis withdrawal symptoms and adverse effects will be assessed daily during treatment via self-report (Marijuana Withdrawal Checklist) and clinician assessment, respectively.

Urinalysis will be conducted on day 1 and 7 to confirm abstinence from cannabis during treatment.

Plasma oxytocin levels will be assessed on day 1, 4, and 7. Serum lithium levels will be assessed on day 4 and 7.

The first 30 participants will undergo additional oxytocin and lithium sampling on day 4 and 7 with post-dose measurements at 60, 90, 240 and 480 minutes (cannulated). This will determine the optimal timing of plasma oxytocin assays following lithium administration in humans.

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Need a job?

Senior Research Officer / Trial Coordinator - BMRI

Senior Research Officer/Trial Coordinator
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The Faculty of Medicine is part of the University of Sydney's Faculties of Health, the largest and most comprehensive grouping of health and medical education and research in the Asia Pacific region. It conducts cutting-edge research and provides medical education and training in more than 100 associated teaching hospitals and research institutes and centres.

The Faculty's Central Clinical School is currently seeking to employ a Senior Research Officer/ Trial Coordinator to oversee the operations of a clinical trial investigating the safety and efficacy of lithium carbonate for the management of cannabis withdrawal in humans. The trial is being conducted at two inpatient drug treatment facilities located on the NSW North Coast (Lismore) and in Sydney. The position will be based in Lismore. The trial is being conducted in conjunction with the Brain & Mind Research Institute (BMRI).

You will be responsible for the day-to-day management of the trial, ensuring that the research protocol, reporting systems, and budgetary procedures are operating effectively. You will also be responsible for the supervision of Research Assistants involved in the study. The position is based in Lismore, and will involve periodic travel to Sydney to meet with investigators and to monitor the conduct of the trial at the Sydney site.

To be successful you will have postgraduate qualifications in psychology or the behavioural sciences or equivalent experience, coupled with experience in the management of clinical trials. Experience in data management, statistical analysis, and preparation of reports is essential. High-level organisational and communication skills are required, including the ability to manage a small team, and the ability to liaise effectively across professional groups.

The position is full-time fixed term for two years, subject to the completion of a satisfactory probation period for new appointees. There is the possibility of further offers of employment, subject to funding and need. Membership of a University approved superannuation scheme is a condition of employment for new appointees.

Appointment to this position is subject to the provisions of both Child Protection and Criminal Record clearances. Relevant criminal history, apprehended violence orders and prior employment checks, including relevant disciplinary proceedings, will be conducted on the preferred applicant.

Remuneration package: $79,753 - $86,884 p.a. (which includes a base salary Level 7 $67,392 - $73,419 p.a., leave loading and up to 17% employer's contribution to superannuation).

All applications must be submitted online. To be considered applicants must respond to selection criteria; to do so complete your responses on the online application form. The Selection Criteria can be found in the document attached at the bottom of the online advert.Please note that resumes need to include contact details of 2 referees.

Specific enquiries about the role can be directed to Nick Lintzeris on 0431 585 515. General enquiries can be directed to Julie Small on (02) 9036 7870.

5. “Reintoxication effects”: the curious case of cannabis flashbacks

Case study 1: anomalous post-mortem THC levels

DH and GF, known cannabis smokers, drown in an unfortunate accident at sea. It takes some 8 days for their bodies to be washed up. Post mortem analysis indicates the presence of alcohol and very high levels of THC (> 90 and 250 ng/ml) in both bodies. Blood levels of THC-COOH are negligible.

Possible explanation

"Death struggle" during drowning causes major lipolysis (fat metabolism) causing fat-stored THC to be released into blood.

Case from Collins et al (1997) J Analyical Toxicol 21, 538-542

Case study 2: death by dope…..or parachute?

JG, a novice parachuter, gets in a tangle with his chute and spends 2 minutes plummeting to his death at 200 km/h. Post mortem analysis shows high levels of THC in his bloodstream and cannabis intoxication is considered to be a possible contributing factor of the tragedy. However, friends accompanying him on the jump insist that he was not intoxicated at the time and his family know him as only an occasional cannabis smoker.

Possible explanation

The horror of impending death causes sympathetic activation (e.g. adrenaline and ACTH release), massive lipolysis and release of THC from fat into blood.

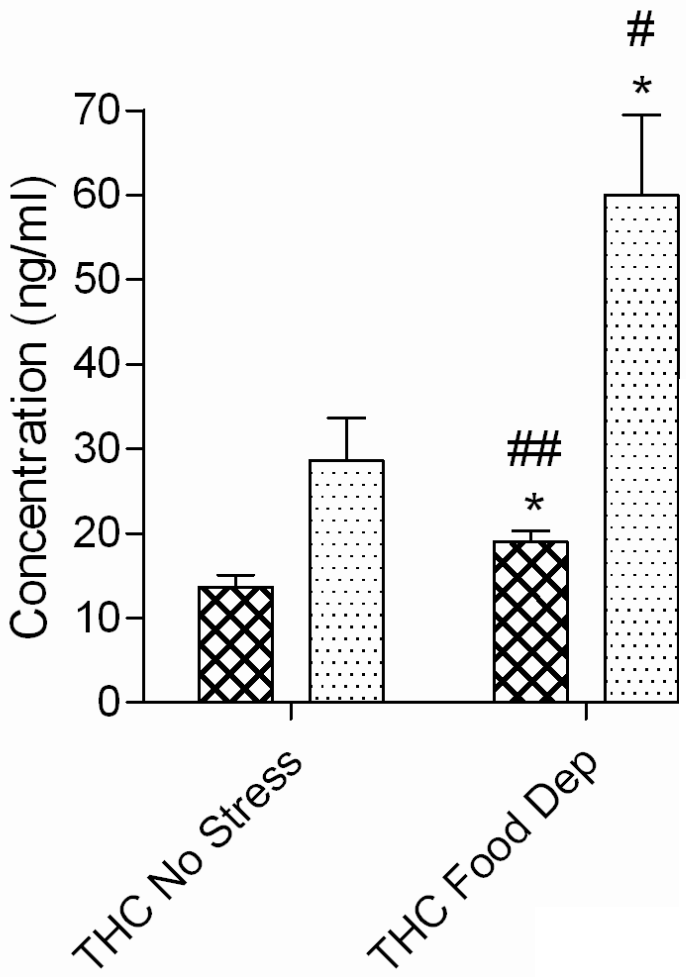
Case study 3: jockey returns THC-positive sample

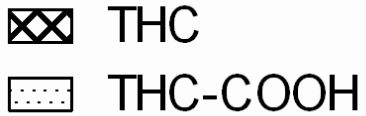
BB, an up-and-coming jockey and former cannabis smoker, returns a urine sample that is positive for THC-COOH after a major race. He admits to having been a former cannabis smoker but claims that he no longer indulges. He notes that in the week prior to the the race he was forced to lose 7 kilos of body weight. He did not eat for 5 days and undertook extensive gym workouts and saunas during that time.

Possible explanation

Again, major fat metabolism caused by starvation is liberating stores of THC from fat into blood causing the positive urine test for THC-COOH

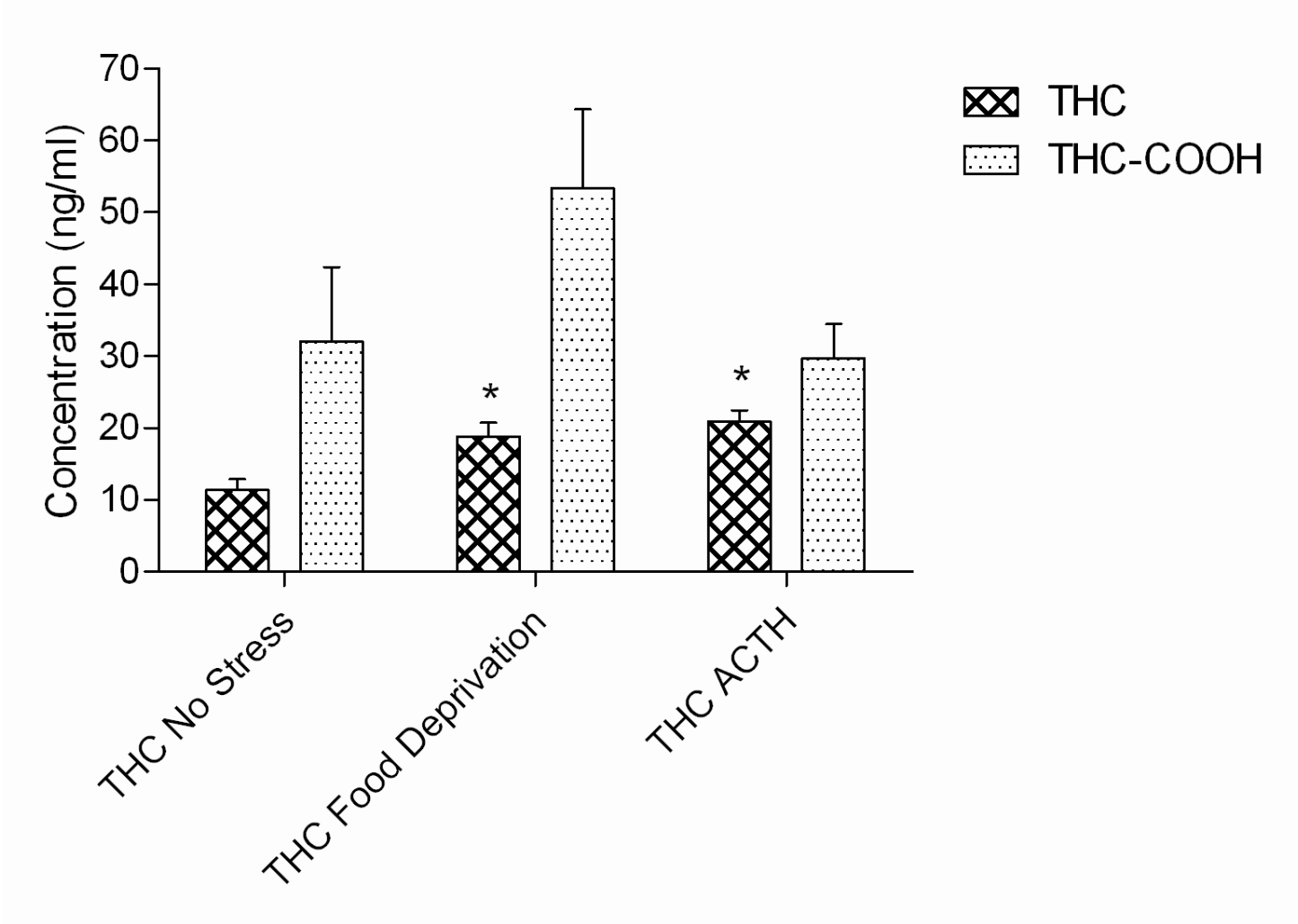
Food deprivation increases blood THC and THC-COOH levels in THC pre-exposed rats after 48 h washout





Gunasekaran, Long, Arnold, McGregor (2009) *British Journal of Pharmacology*

The stress hormone, ACTH, like food deprivation, increases blood THC levels in rats chronically pre-exposed to THC



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Dieting could lead to a positive test for cannabis

› 09 August 2009 by **Emma Young**
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CANNABIS smokers beware: stress or dieting might trigger "reintoxication", resulting in a positive drug test long after you last used the drug.

The main psychoactive ingredient of cannabis is tetrahydrocannabinol (THC), and once in the body it is readily absorbed into fat cells. Over the next few days it slowly diffuses back into the blood. Since THC is taken up by fat more readily than it diffuses out, continual intake means some THC can remain in the fat cells.

It has been suggested that stored THC can be released at a later date in situations where the body's fat is rapidly broken down. This is based on anecdotal reports of spikes in blood cannabinoid levels in people who have not taken the drug recently but have experienced extreme stress or rapid weight loss.

Jonathon Arnold at the University of Sydney, Australia, cites the example of an athlete who swore he hadn't smoked cannabis in months but who had rapidly lost 4 kilograms just before a positive drug test.

But I haven't smoked in months (Image: Rex Features)


FLASHBACK!
DRAWINGS & PHOTOGRAPHS
BY HOWARD CHRISTOPHERSON

Conclusions

- Massive breakthroughs are being made in our understanding of the role of endocannabinoids in brain and body function
- *Acute* THC effects are sometimes subtle: look out for reversal learning deficits and impairment of auditory discrimination
- *Chronic* THC appears to have greater adverse effects in adolescent than adult animals: look out for deficits in social behaviour and recognition memory
- Cannabis withdrawal and craving is only poorly understood in the brain: lithium and oxytocin hold out some promise as novel pharmacotherapies to assist withdrawal
- THC installs itself easily in fat: and might come out again under surprising circumstances

Thanks to my colleagues and students

- Nathan Gunasekaran
- Jonathan Arnold
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- Ljiljana Sokolic
- Kashem Abul
- Adam Guastella
- Alex Wong
- Dean Carson
- Adam Winstock
- Nick Lintzeris
- David Bosanquet
- Bina Sheriff
- Julia Surgeon
- Bronwyn Dawson
- Heidi Quinn

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