Cannabis and Cognitive Function

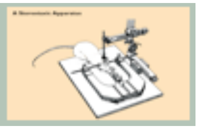
Dr Nadia Solowij

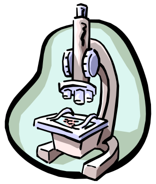
School of Psychology and Illawarra Health and Medical Research Institute,
University of Wollongong

Schizophrenia Research Institute Affiliated Scientist

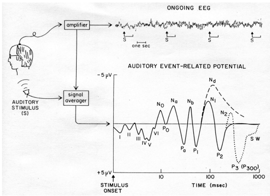
Sydney Australia

Cannabis - the most popular illicit drug





- Acute intoxication impairs cognitive processes and psychomotor function
- Long term consequences?
- Many confounds in previous studies



- Access to populations with greater exposure to cannabis over many years
- Advances in study of cognition
- Improved methodology
- Memory / attentional mechanisms

STUDIES OF CHRONIC CANNABIS USERS

- Long term vs short term or
  heavy vs light vs non-user controls
  → memory and attention

- Matched with non-users on :
  age, sex, IQ, education, alcohol and other substance use, personality measures

- Groups differ on level of cannabis use

STUDIES OF CHRONIC CANNABIS USERS

- Tested in the unintoxicated state
- Psychophysiological (brain electrical activity), neuropsychological and neuroimaging techniques to assess cognition and brain structure/function in cannabis users

Long term or heavy cannabis use results in cognitive dysfunction that persists beyond the period of intoxication

- Cognitive impairment
  - may last for hours, days or months
  - is related to frequency, quantity, duration of cannabis use, age of onset
- Recovery of function?
  - uncertain but probable
- Nature of cognitive deficits?
  - memory, attention, executive or higher cognitive functions
  - similar to deficits in schizophrenia

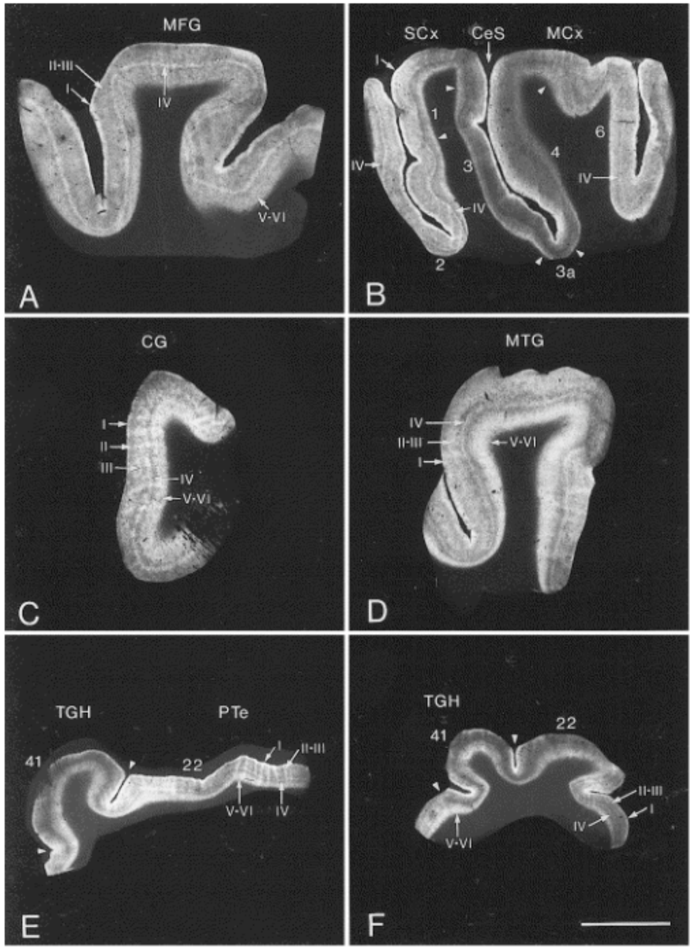
Table 1: Summary of the evidence linking cannabinoid function and effects to schizophrenia endophenotypes

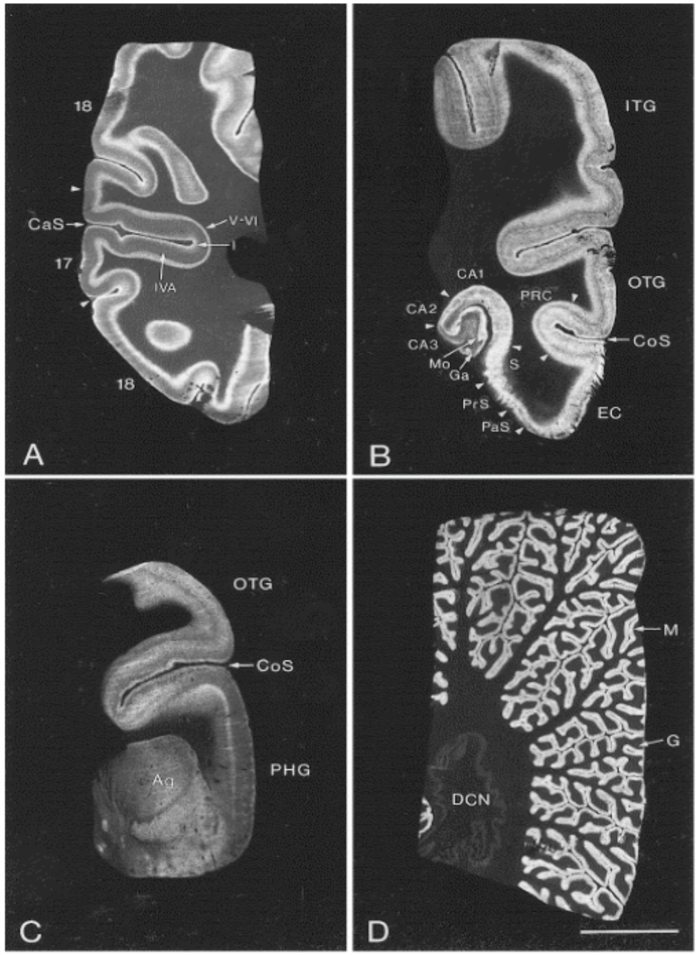
Cognitive endophenotypes of schizophrenia	Measures	Evidence for impaired functioning in cannabis users?	Evidence for direct involvement of the eCB system from animal studies?	Neural substrates interacting with eCB system?
Pre-attentive or automatic	P50, PPI, MMN	P50, yes PPI, mixed MMN, NA	P50, NA PPI, yes MMN, NA	Yes (α-7-nicotinic receptor, NMDA, PFC, hippocampus)
Inhibition	Response inhibition	Yes	NA	Yes (PFC, anterior cingulate, cerebellum)
Attention/working memory/ dysexecutive	Sustained attention, working memory, executive function	Yes	Yes (includes interaction with dopamine and GABA)	Yes (PFC, anterior cingulate, orbitofrontal cortex, hippocampus, cerebellum)
Verbal memory	Verbal learning, declarative memory	Yes	NA	Yes (PFC, medial temporal cortex, hippocampus, cerebellum)
Eye movement control	Smooth pursuit, antisaccade, oculomotor disturbances	Mixed	NA	Yes (substantia nigra, PFC)

eCB = endogenous cannabinoid; GABA = gamma-aminobutyric acid; MMN = mismatch negativity; NA = not applicable or not available; NMDA = N-methyl-D-aspartate; PFC = prefrontal cortex; PPI = pre-pulse inhibition.

Solowij and Michie (2007) Journal of Psychiatry and Neuroscience

Distribution of cannabinoid receptors in adult human brain





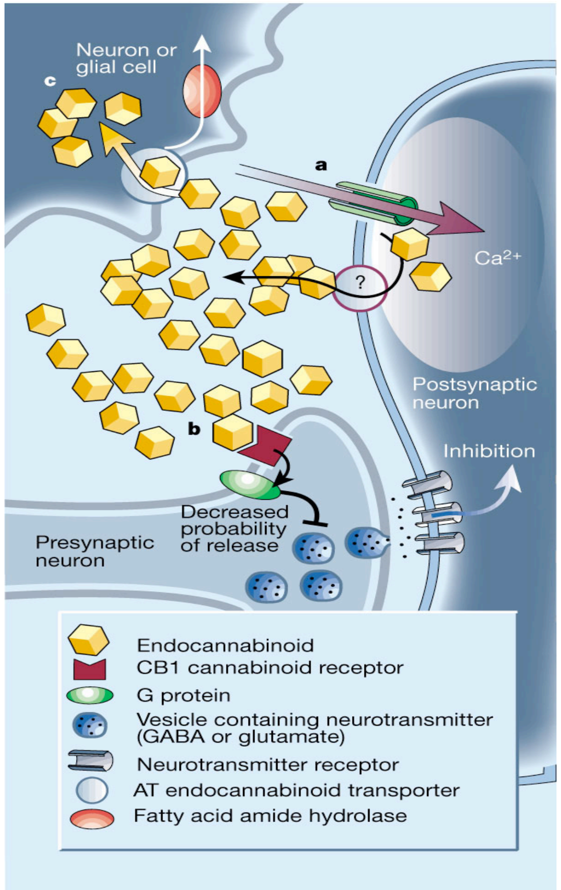
Cerebral cortex

Occipital cortex, temporal lobe, cerebellum

Dense binding in hippocampal region and forebrain areas associated with higher cognitive functioning

Glass, Dragunow & Faull (1997) Neuroscience, 77, 299-318.

Endogenous cannabinoid signalling



Christie & Vaughan (2001) Nature, 410, 527-530

Endogenous cannabinoids

- retrograde messengers within the brai
- regulate ion channel selectivity and neurotransmitter release.

Cannabinoids inhibit the release of GABA, glutamate, acetylcholine, noradrenaline and serotonin release in hippocampus, prefrontal cortex and cerebellum.

Acute cannabinoid administration increases frontal and ***striatal*** dopamine metabolism and release.

Chronic administration leads to a persistent reduction in prefrontal cortical dopamine turnover.

Wilson & Nicoll (2001) Nature, 410, 588-592.
Ohno-Shosaku et al, (2001) Neuron, 29, 729-738.
Kreitzer & Regehr (2001) Neuron, 29, 717-727.
Verrico, Jentsch & Roth (2003) Synapse, 49, 61-66.
Gessa et al (1998) Eur J Pharmacol, 35, 119-124.
Katona et al (2000) Neurosci, 100, 797-804.

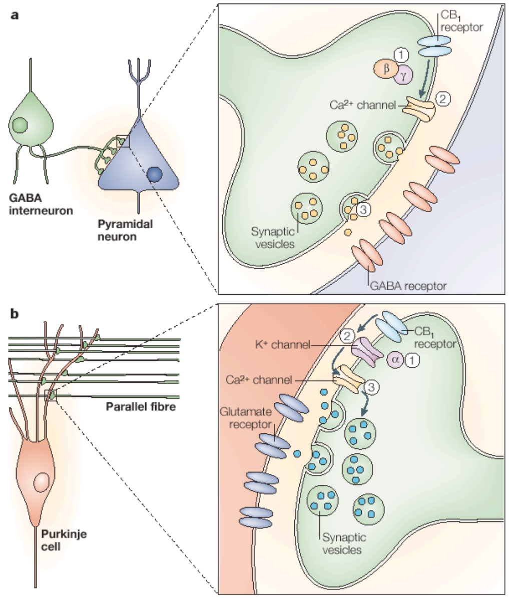


Figure 7 | Regulation of presynaptic ion channel activities by CB_1 cannabinoid receptors.

Piomelli (2003) Nat Rev Neurosci, 4, 873-884.

Reduced hippocampal spike timing coordination and theta, gamma and ripple oscillations may be responsible for cannabis-induced memory deficits.

Robbe et al (2006) Nature Neurosci, 9, 1526-1533.

- Fine tuning role of the endogenous cannabinoid system may be deregulated by the potent and less selective bombardment by THC acutely.

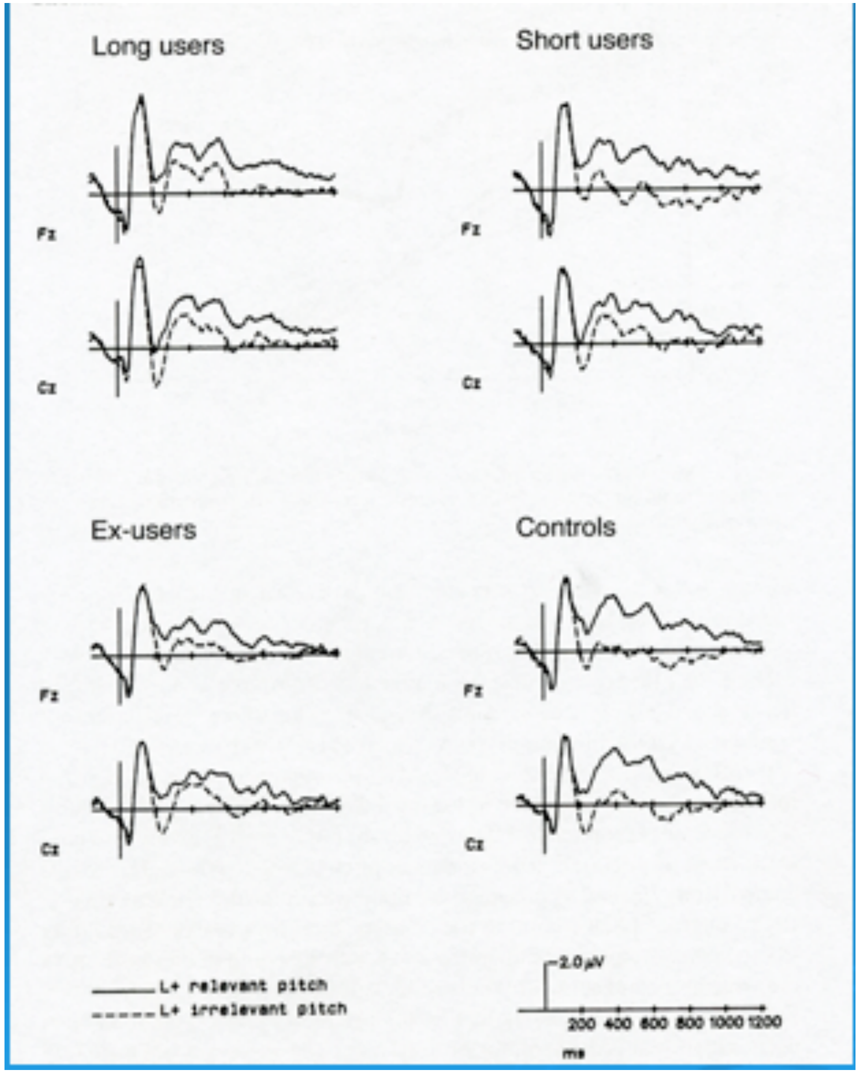
- Acute intoxication - cognitive impairments, mild hallucinations, delusions, perceptual distortions.

- Long term exposure may result in lasting dysfunction of the endogenous cannabinoid system, schizophrenia-like neurotransmitter conditions, desynchronised neural networks, psychotic symptomatology and cognitive impairment (primarily attention, learning, memory and executive functions)

Cohen, Solowij & Carr (2008) Aust NZ J Psychiatry

Solowij et al (2009) In M. Ritsner (Ed) Neuropsychiatric Biomarkers, Endophenotypes, and Genes: Promises, Advances, and Challenges

Selective attention: Difficulty in filtering out irrelevant information

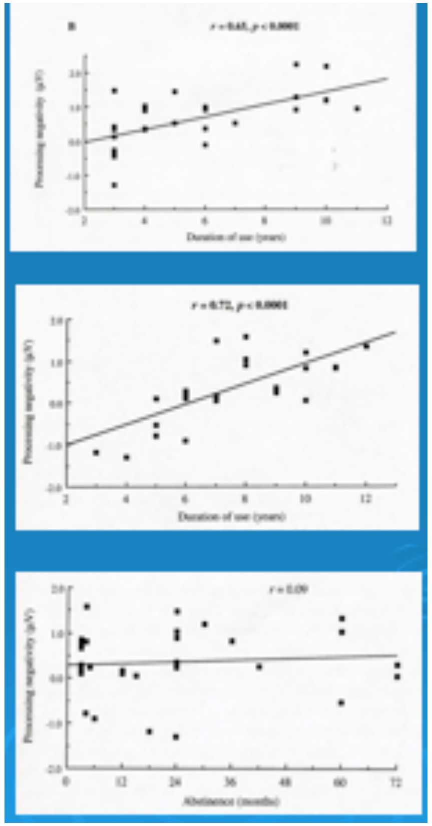


- worsens with increasing duration of cannabis use
- an enduring impairment

Correlates with increasing years of cannabis use in CURRENT USERS
r=0.65, p<0.0001

and in EX-USERS
r=0.72, p<0.0001

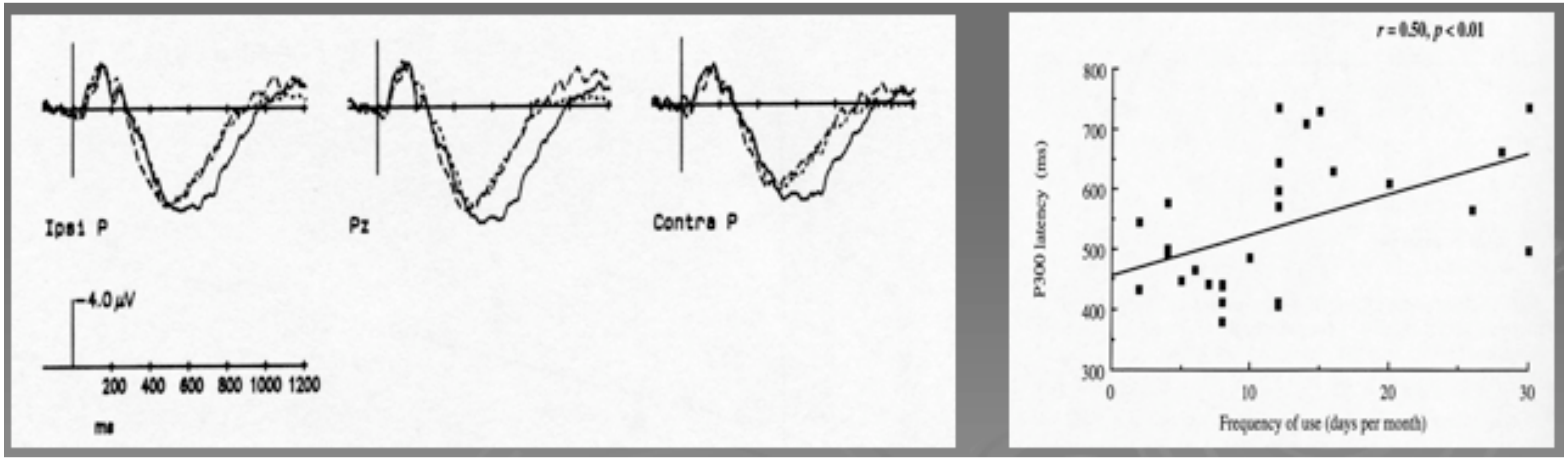
but no decline with increasing months of abstinence



Solowij et al, 1995; Solowij 1995; 1998

Slowed information processing associated with frequency of cannabis use

- a shorter lasting effect that dissipates with reduction or cessation of cannabis use



Solowij et al, 1995; Solowij 1995; 1998

- Impaired performance on selective, divided and sustained attention tasks, acutely and in chronic users associated with duration, frequency and age of onset (Fletcher et al, 1996; Pope et al, 1996; Ehrenreich et al, 1999; Pope et al, 2001; Skosnik et al, 2001; Ilan et al, 2004; Jacobsen et al, 2004)
- Evidence for impaired attentional processing from multiple animal studies (Presburger et al, 1999; Mishima et al, 2002; Arguello et al, 2004; Verrico et al, 2003;2004)

Inhibitory processing

- Altered inhibitory processing on Stroop task, Go/NoGo and decision making tasks requiring response selection and inhibition (eg. Bolla et al, 2002; Solowij et al, 2002; neuroimaging studies: Eldreth et al 2004; Porrino et al, 2004; Smith et al, 2004; Bolla et al, 2005; Gruber et al, 2005)
- Acute intoxication increases impulsive responding in various tasks (eg. Hart et al, 2001; McDonald et al, 2003) and long term effects in adolescent cannabis users – impulsivity, impaired inhibitory control and risky decision making (Solowij et al, 2009)
- Related to frequency, dose, duration, age of onset of cannabis use

Working memory and executive function

- Multiple animal studies show unequivocal role for the endogenous cannabinoid system in working memory and impaired performance following acute and chronic cannabinoid administration (eg. radial arm, Morris water maze, DMTS)
- Various executive tasks impaired by cannabis acutely and in chronic users (eg. verbal fluency, WCST, Ravens, TOL) (eg. Pope et al, 1996; 2001; 2003; Bolla et al, 2002; Solowij et al, 2002; Solowij et al, in progress)

Working Memory

Table 2. Performance measures on CANTAB visuospatial memory tests: mean (SD) or median [range], *p*

		Cannabis users	Controls	*p*
PRM	% correct	87.5 [54.2-100]	91.7 [70.8-100]	0.024*
	mean latency (ms)	2091 (469)	1967 (463)	0.192
SRM	% correct	84.3 (9.5)	88.3 (7.3)	0.022*
	mean latency (ms)	2342 (811)	2002 (363)	0.01*
SSP	length[a]	6.2 (1.5)	6.9 (1.4)	0.024*
	total errors	12 [4-30]	11 [0-43]	0.11
	usage errors	6 [0-27]	3 [0-41]	0.042*
SWM	total errors	26.5 (17.3)	14.8 (12.7)	< 0.001*
	between errors	25.3 (16.9)	14.2 (12.4)	< 0.001*
	between errors, 6 boxes	5 [0-27]	1 [0-22]	0.001*
	between errors, 8 boxes	18.2 (10.6)	10.1 (9)	< 0.001*
	within errors	1 [0-15]	1 [0-11]	0.061
	within errors, 8 boxes	1 [0-11]	0 [0-11]	0.017*
	strategy	33 (4.2)	28.9 (6.3)	< 0.001*
PAL	total errors	8 [0-60]	7 [0-63]	0.02*
	total errors, 6 shapes	3 [0-19]	2 [0-18]	0.202
	total errors, 8 shapes	5 [0-55]	3 [0-44]	0.042*
	total trials	12.4 (4)	11.2 (2.7)	0.007*
	total trials, 6 shapes	2 [1-8]	2 [1-8]	0.286
	total trials, 8 shapes	2 [1-10]	2 [1-10]	0.11
	stages completed on 1st trial	6.1 (1)	6.2 (0.8)	0.628
	1st trial memory score	17.1 (5.4)	18.1 (4.9)	0.35
	mean errors to success	1 [0-8.6]	0.88 [0-9]	0.027*
	mean trials to success	1.6 (0.5)	1.3 (0.2)	0.006*

[a] Significance lost after covarying for IQ

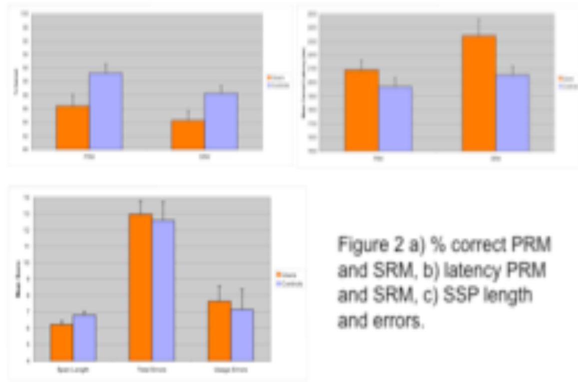


Figure 2 a) % correct PRM and SRM, b) latency PRM and SRM, c) SSP length and errors.

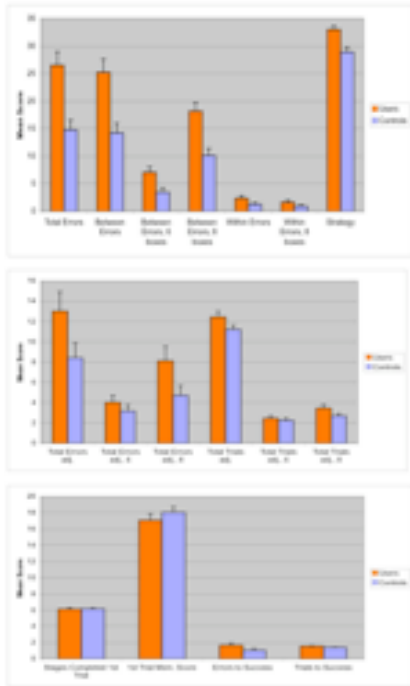
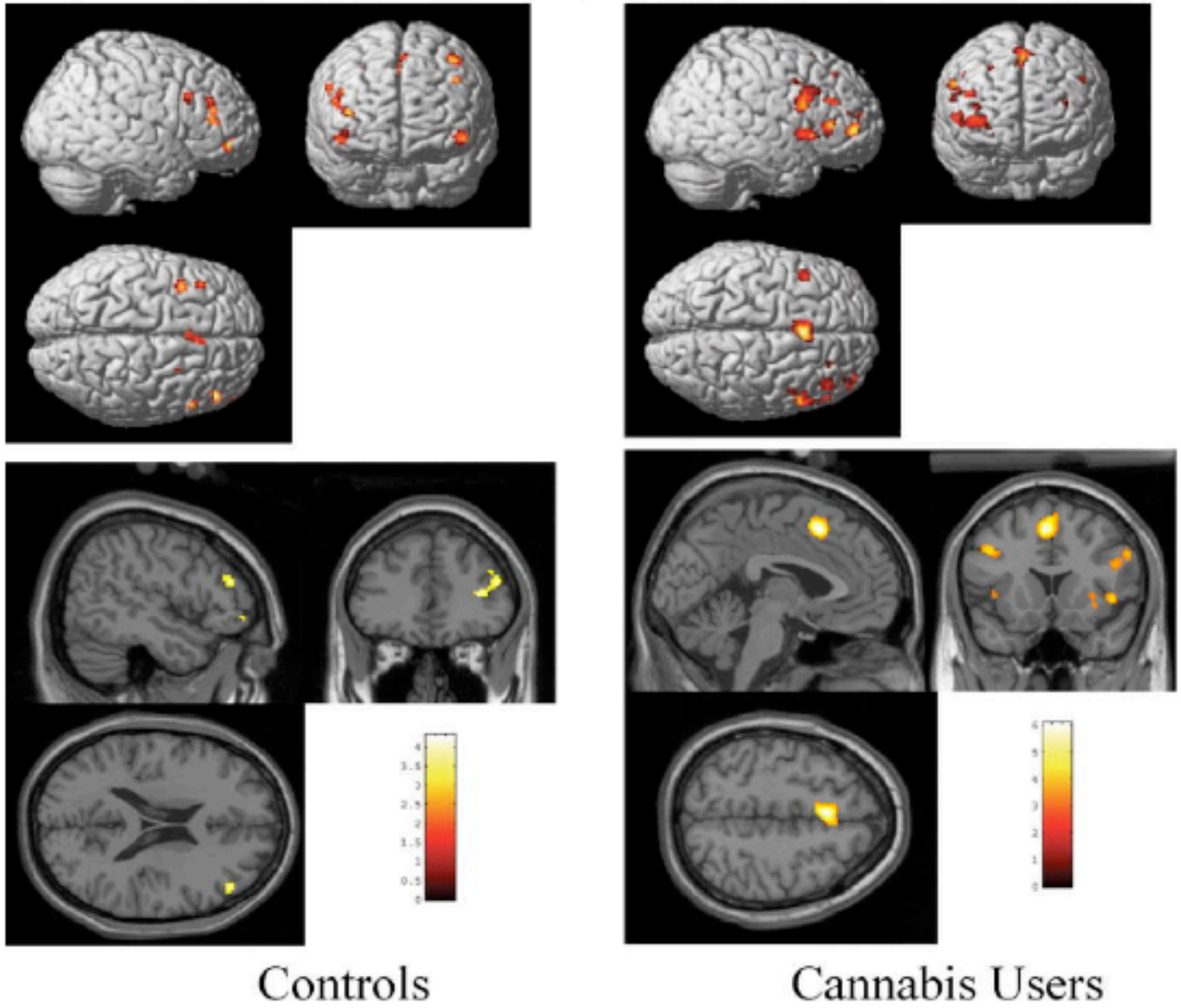


Figure 3 a) SWM performance measures b) and c) PAL performance measures

Solowij et al (2008) Int J Neuropsychopharmacology

Brain Activity in Short-Delay Response minus Perception



Kanayama et al (2004) Psychopharmacology

Verbal memory

- One of the most consistent deficits associated with acute (eg. Curran et al, 2002; D'Souza et al, 2004; Ilan et al, 2004) and chronic cannabis use (Solowij, 1998; Grant et al, 2003) [and one of the most impaired cognitive domains in schizophrenia]

- Multiple studies of long term or heavy cannabis users show impaired performance on list learning tasks (RAVLT, CVLT, Buschke Selective Reminding) (eg. Fletcher et al, 1996; Pope et al, 1996; 2001; 2002; Bolla et al, 2002; Solowij et al, 2002; Messinis et al, 2006) and functional impairment in neuroimaging studies (eg. Block et al, 2002; Solowij et al, 2004)

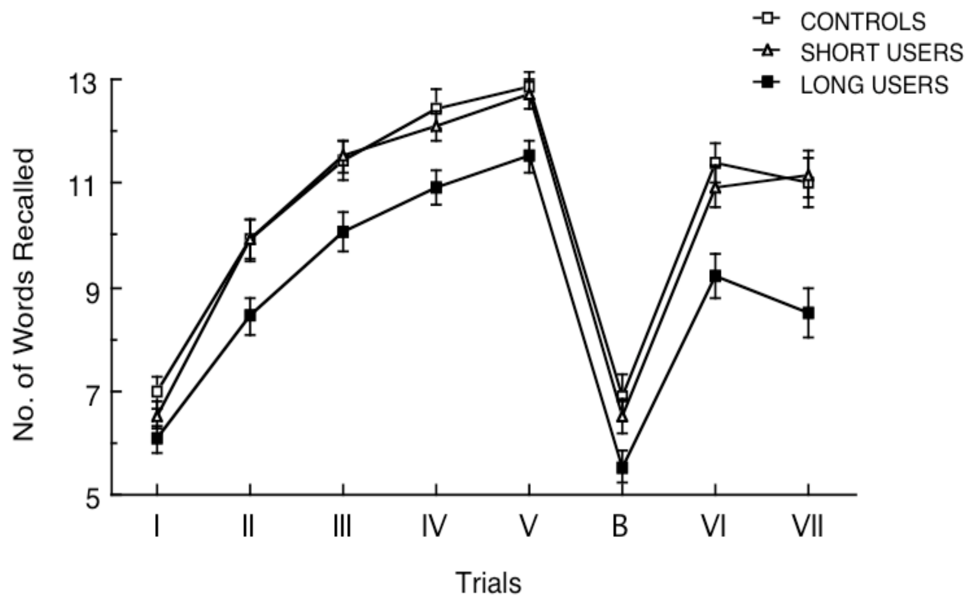
- The evidence suggests impaired encoding, storage, manipulation and retrieval mechanisms in long-term or heavy cannabis users

Solowij and Battisti (2008) Current Drug Abuse Reviews

Verbal learning and memory studies of cannabis users

- Pope et al (1996; 2001; 2002) frequency (heavy vs light); recovery after 28 days, less apparent when age of onset prior to 17 years*
- Solowij et al (2002) duration of use (very long term vs shorter); partial recovery with cessation / reduction
- Bolla et al (2002) persistent dose-related impairments (joints / week) after 28 days abstinence
- Messinis et al (2006) duration of use

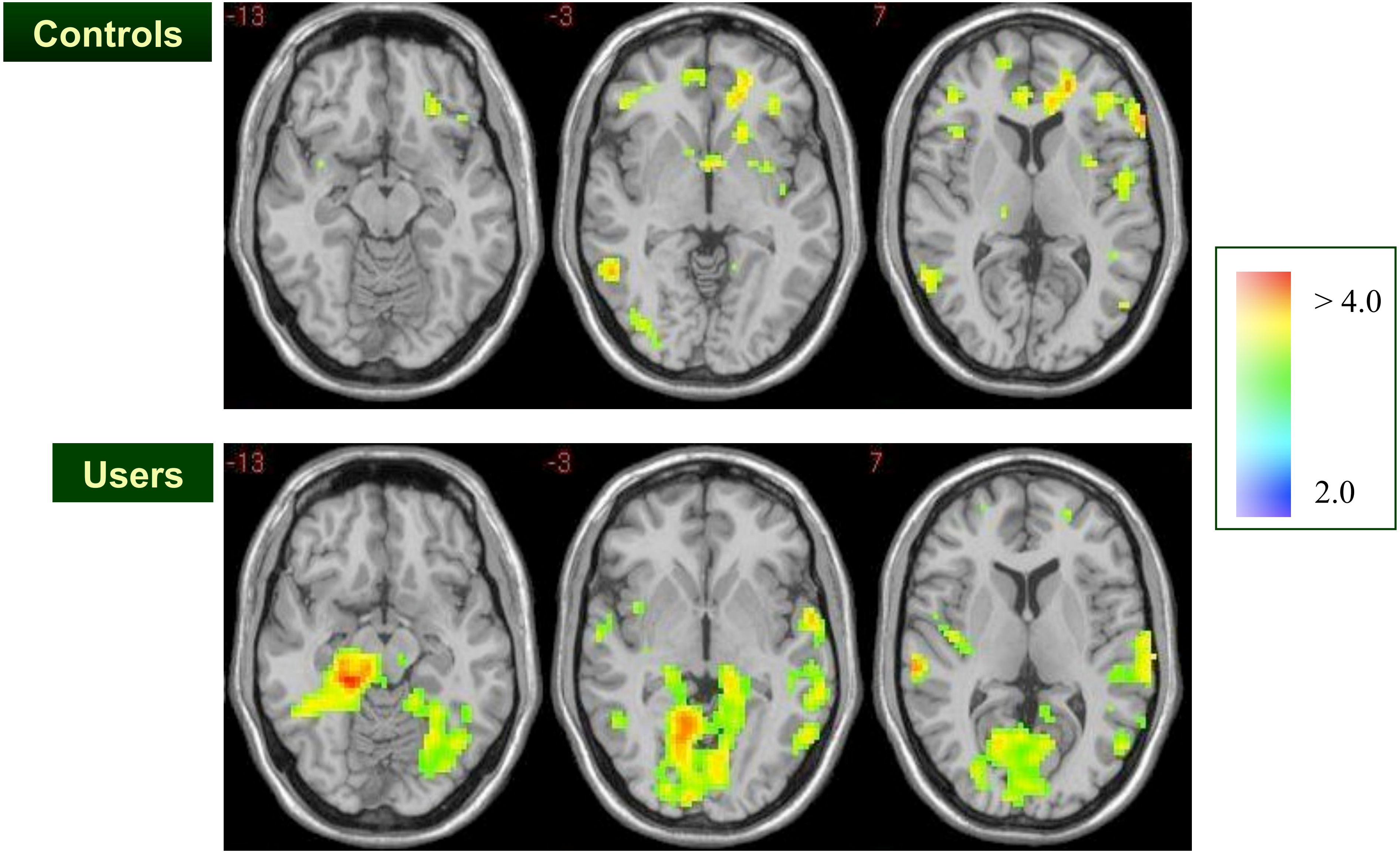
Performance on the RAVLT by long term cannabis users, short term cannabis users and controls



Solowij et al (2002) JAMA, 287, 1123-1131

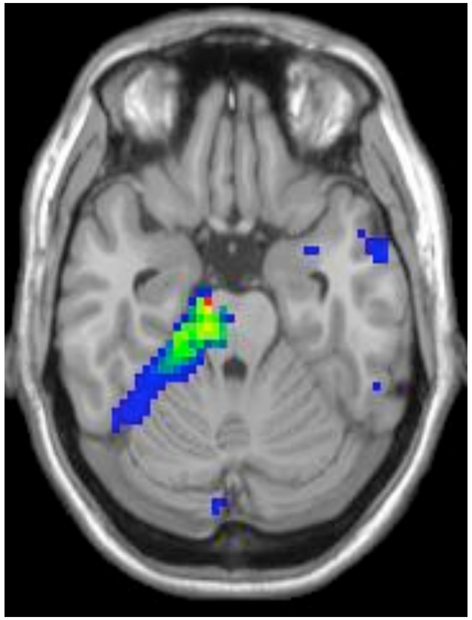
*Ehrenreich et al, 1999; Wilson et al, 2000; Huestegge et al, 2004 also demonstrate adverse effects among those commencing cannabis use prior to age 17

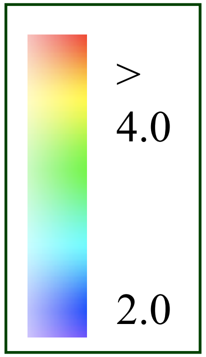
Main effects of encoding at Trial 4

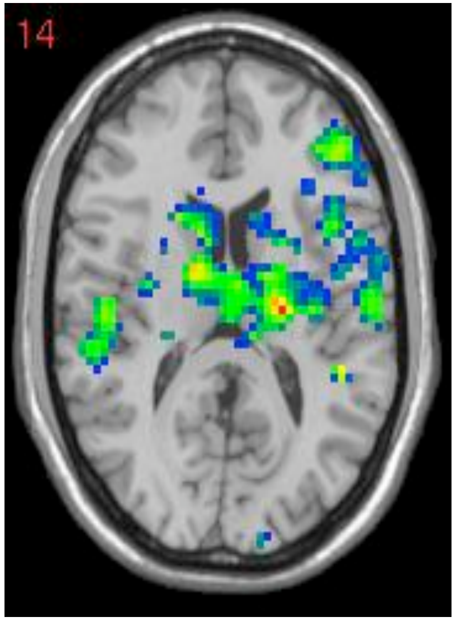


Correlations with duration of cannabis use

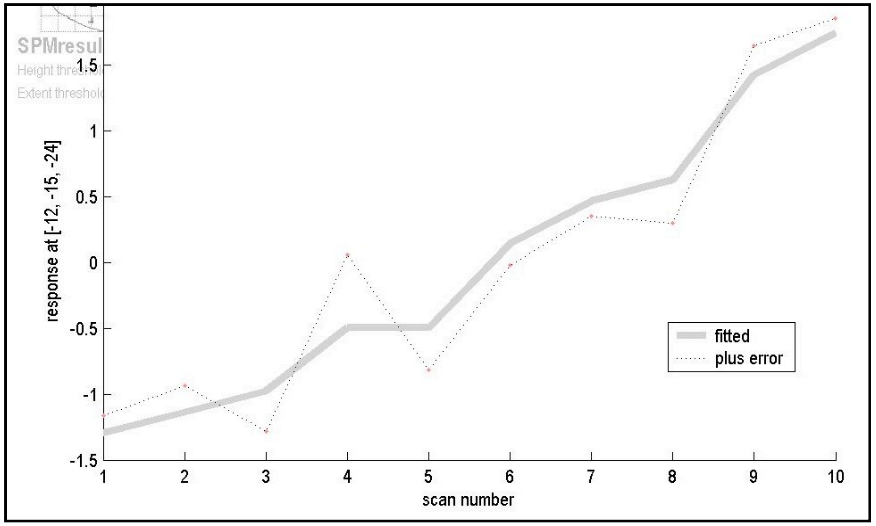
Trial 1

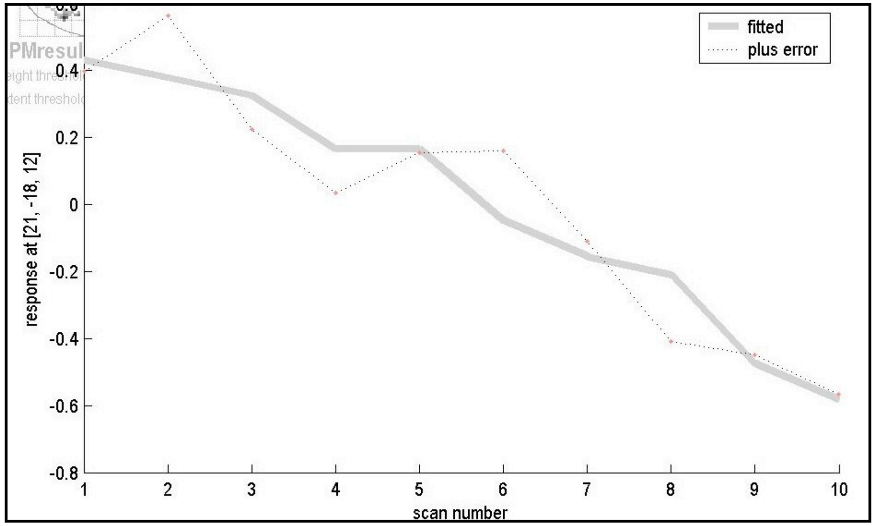






Trial 4

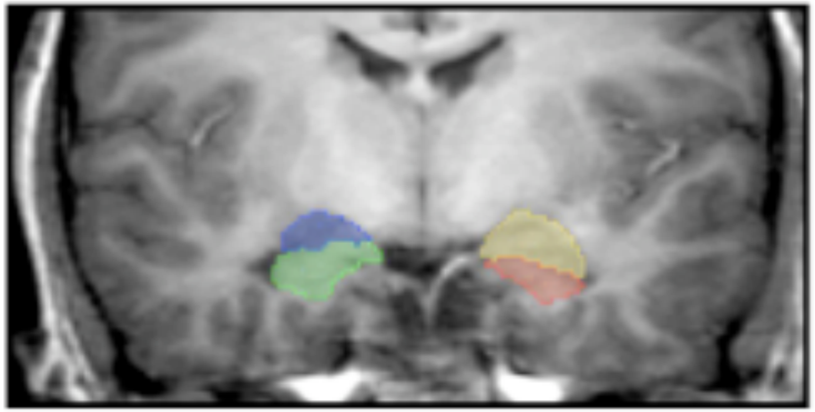




Positive correlations -
Increasing years cannabis use

Negative correlations -
Increasing years cannabis use

Dose-related reduction in hippocampal and amygdala volumes in long-term heavy cannabis users



Tracings of the left (red) and right (green) hippocampus, and left (yellow) and right (blue) amygdala.

Left hippocampal reduction correlated with cumulative dose of cannabis exposure (r -0.62, p=0.01)

Age, gender, IQ matched groups.
Duration cannabis use = 20 yrs, daily, approx 7 joints/day

Yücel, Solowij, Respondek et al (2008) Arch Gen Psychiatry

Hippocampal volumes were markedly reduced bilaterally in cannabis users compared to non-user controls
(L_Hipp = 12.1%, R_Hipp = 11.9%)
Effect size 1.22

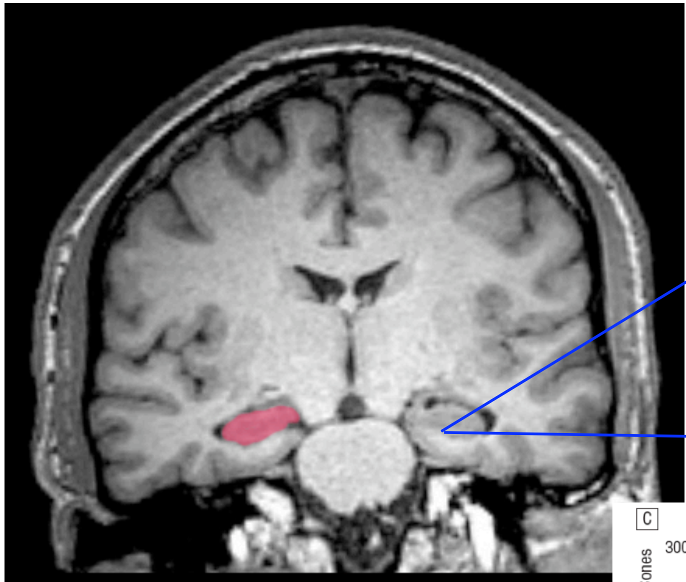
Amygdala volume also reduced bilaterally (≈7.1%).

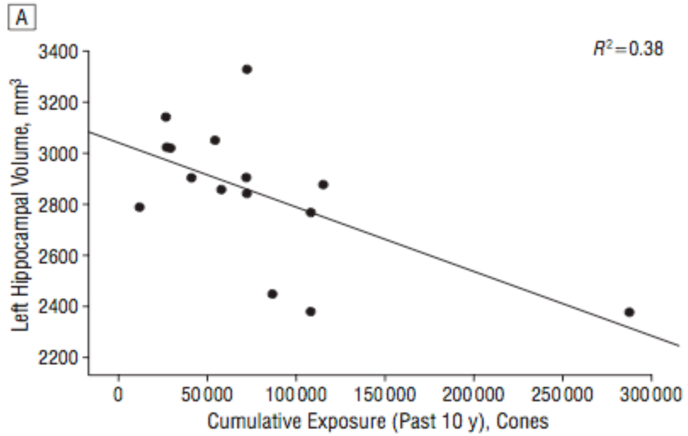
Reflects findings of neurotoxicity in animal studies which suggest cannabis is harmful *precisely* in the hippocampal region

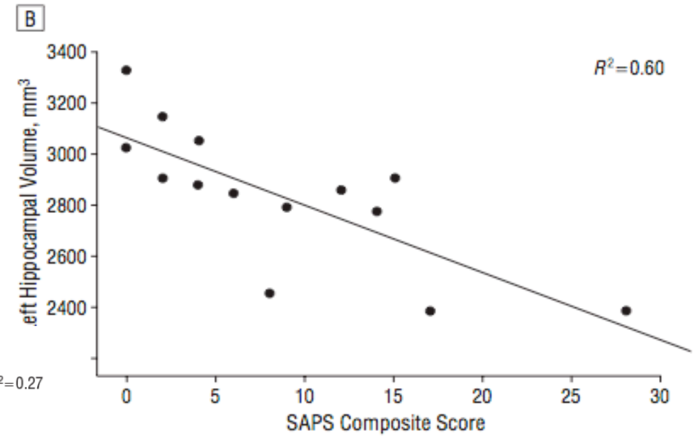
Scallet et al., Brain Res, 1987; Chan et al., J Neurosci 1998; Landfield et al., Brain Res, 1998; Lawston et al., Brain Res, 2000

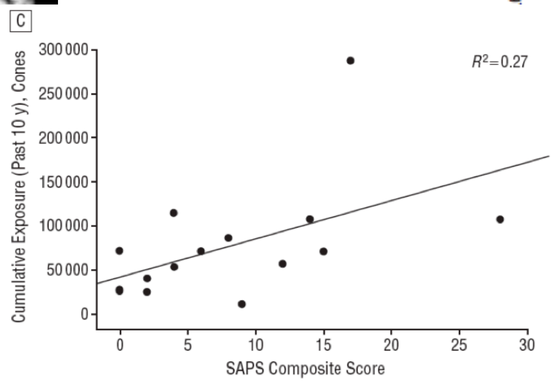
Measure	Long-term Cannabis Users (n=15)	Nonusing Control Subjects (n=16)	*P* Value[a]
RAVLT score, mean (SD)			
Sum of 5 learning trials	43.8 (8.8)	57.4 (10.1)	<.001
20-min delay	8.9 (4.1)	12.3 (3.7)	.009[b]

While cannabis users were impaired in verbal memory, it was not associated with changes in hippocampal volume









Reduced hippocampal volume associated with the development of subclinical positive psychotic symptoms

Issues Raised

- Carefully screened for psychotic disorders, yet developed memory deficits, brain changes, and subclinical positive symptoms similar to schizophrenia

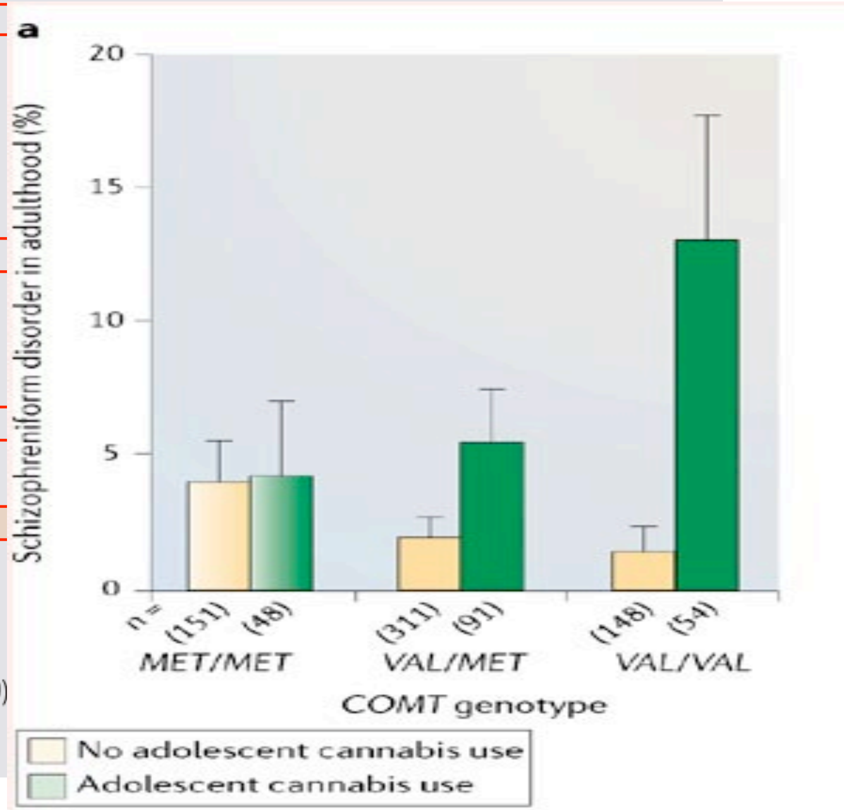
- Also developed significant subthreshold negative psychotic symptoms and elevated depressive symptoms, but neither of these were related to hippocampal volumetric reductions

- Mean age (39.8) suggests that they were not in a prodromal state

- Why did they not develop psychosis early in their cannabis using career?

Why didn't they develop psychosis?

Measure	Long-term Cannabis Users (n=15)	Nonusing Control Subjects (n=16)	*P* Value[a]
Age, mean (SD), y	39.8 (8.9)		
IQ, mean (SD)	109.2 (6.3)		
RAVLT score, mean (SD)			
Sum of 5 learning trials	43.8 (8.8)		
20-min delay	8.9 (4.1)		
Educational level, mean (SD), y	13.4 (3.2)		
GAF scale score, mean (SD)	72.0 (11.2)		
HAM-D score, mean (SD)	5.87 (3.2)		
STAI, mean (SD)			
State anxiety	34.3 (9.8)		
Trait anxiety	39.3 (9.7)		
SAPS score, mean (SD)	8.1 (7.9)		
SANS score, mean (SD)	11.7 (8.5)		
Cannabis use			
Duration of regular use, mean (SD) [range], y[c]	19.7 (7.3) [10-32]		
Age started regular use, mean (SD) [range], y[c]	20.1 (6.9) [12-34]		
Current use, mean (SD), d/mo[d]	28 (4.6)		
Current use, mean (SD), cones/mo[d,e]	636 (565)		
Cumulative exposure, past 10 y, mean (SD)[f]	77 816 (66 542)		
Cumulative exposure, lifetime, mean (SD)[f]	186 184 (210 022)		
Estimated episodes of use, median (range)	62 000 (4600-288 000)		
Alcohol use, mean (SD), standard drinks/wk	9.6 (6.1)		
Tobacco use, mean (SD), cigarettes/d	16.5 (8.9)		



(Caspi et al., 2005)

Everyone is vulnerable to the adverse mental and cognitive effects of cannabis?

- Long term very heavy cannabis use leads to cognitive deficits, brain structural changes and subclinical psychotic symptoms that resemble schizophrenia

- Everyone is vulnerable to these adverse effects if cannabis is used heavily enough for many years

- The adolescent brain may be more vulnerable – a critical period of neurodevelopment

- Rob Battisti, Susie Gordon, Sharon Monterrubio, Colleen Respondek; Sasha Davis, Megan Rozman, Dr Katy Jones, AProf Joseph Ciarrochi, Prof Patrick Heaven, School of Psychology, University of Wollongong
- AProf Murat Yücel, AProf Dan Lubman, Dr Marc Seal, Dr Alex Fornito, Dr Ben Harrison, Dr Sarah Whittle, Dr Michael Takagi, Valentina Lorenzetti, Ian Harding, Prof Christos Pantelis, Melbourne Neuropsychiatry Centre & ORYGEN Research Centre, University of Melbourne
- Prof Philip McGuire, Prof Robin Murray, Institute of Psychiatry, London
- Prof Dr Markus Leweke Universities of Cologne & Heidelberg
- Prof Pat Michie University of Newcastle
- Prof Wayne Hall University of Queensland
- AProf Philip Ward University of New South Wales
- AProf Brin Grenyer University of Wollongong
- Prof Roger Roffman, Dr Bob Stephens, Prof Tom Babor, US Collaborators

- National Health & Medical Research Council, Australia
- Clive and Vera Ramaciotti Foundation for Biomedical Research
- Schizophrenia Research Institute, Sydney
- Symbion Clinical and Research Imaging Centre
- Prince of Wales Medical Research Institute
- Illawarra Institute for Mental Health
- University of Wollongong
- Ian Potter Foundation