The Chronic Effects of Cannabis on Memory in Humans: A Review

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Abstract: Memory problems are frequently associated with cannabis use, in both the short- and long-term. To date, reviews on the long-term cognitive sequelae of cannabis use have examined a broad range of cognitive functions, with none specifically focused on memory. Consequently, this review sought to examine the literature specific to memory function in cannabis users in the unintoxicated state with the aim of identifying the existence and nature of memory impairment in cannabis users and appraising potentially related mediators or moderators. Literature searches were conducted to extract well-controlled studies that investigated memory function in cannabis users outside of the acute intoxication period, with a focus on reviewing studies published within the past 10 years. Most recent studies have examined working memory and verbal episodic memory and cumulatively, the evidence suggests impaired encoding, storage, manipulation and retrieval mechanisms in long-term or heavy cannabis users. These impairments are not dissimilar to those associated with acute intoxication and have been related to the duration, frequency, dose and age of onset of cannabis use. We consider the impact of not only specific parameters of cannabis use in the manifestation of memory dysfunction, but also such factors as age, neurodevelopmental stage, IQ, gender, various vulnerabilities and other substance-use interactions, in the context of neural efficiency and compensatory mechanisms. The precise nature of memory deficits in cannabis users, their neural substrates and manifestation requires much further exploration through a variety of behavioural, functional brain imaging, prospective and genetic studies.

Keywords: Cannabis, memory, long-term effects, cognition, human.

INTRODUCTION

Short-term memory problems are among the most frequently self-reported consequences of cannabis use by individuals who use the drug and are commonly reported reasons for seeking to quit or reduce cannabis use. The perception that cannabis impairs short-term memory has become ingrained in the general community and in popular culture and lay literature. Even where a perception exists that cannabis is a relatively benign drug, when asked whether it might have any deleterious effects, short-term memory will often be the first thing that comes to mind in the average person asked on the street, and memory problems are the butt of numerous jokes and anecdotes about cannabis users. Together with amotivation or apathy, (and perhaps paranoia), memory problems define the prototypical and caricatured image of the chronic cannabis user.

In the general scientific literature, impairment of memory is often cited in association with cannabis use. Over the years since cannabis rose to become the most widely used illicit drug in the developed world, general memory function has been investigated in acute administration studies of cannabis to humans and animals, and in studies of long term cannabis users. Despite the apparent prominence of potential memory deficits in cannabis users, a search of the literature revealed that no reviews *specific* to this topic have been published, other than a recent welcome review of the acute effects of cannabis on memory in humans by Ranganathan and D'Souza [1] and an examination of the acute effects of cannabis on verbal and episodic memory in relation to schizophrenia by Fletcher and Honey [2]. Reviews of the general literature on cognitive functioning in long term cannabis users have included studies of memory among many other cognitive functions assessed but no reviews have focused exclusively on memory or attempted to unravel the complexity of understanding the nature of memory deficits, if they exist. Further, the most recent of any such reviews were published some time ago (e.g., [3, 4]) and hence mostly reflect the literature prior to the late 1990s. Other recent reviews have examined cognitive deficits only within a specific context (e.g., similarity to schizophrenia [5]). A meta-analysis of a small number of studies of cognitive function in cannabis users suggested that if any deficits exist in this population beyond the acute intoxication period, they are most likely to occur in the domain of learning and retrieval of information [6]. This overall state of affairs prompted us to undertake to examine the recent literature toward the compilation of this review of the long-term effects of cannabis on memory in humans.

Ranganathan and D'Souza [1] found in their review that acute administration of cannabis impairs immediate and delayed free recall of information, while Fletcher and Honey [2] also cite evidence for difficulties in manipulating the contents of working memory, failure to use semantic processing and organisation to optimise episodic memory encoding, and impaired retrieval performance. We sought to examine the extent to which similar (or other) memory dysfunction was apparent in chronic cannabis users in the unintoxicated state and to discern whether impairment may be associated with specific parameters of cannabis use, such as duration, frequency, dose or age of onset of cannabis use. We defined "unintoxicated state" for the purposes of this review as the period beyond the several hours of acute intoxication that immediately follows can-

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nabis use. Thus, this state may reflect subacute intoxication and residual effects, as discussed further below, and may extend to truly long-term effects following substantial abstinence periods. Literature searches were conducted from the period January 2000 – June 2007 using the broad search terms : cannabis (or synonyms) and memory using Web of Science. This strategy returned more than 250 papers of which abstracts were examined to identify studies that investigated memory function in human cannabis users in the unintoxicated state. Surprisingly few studies from this date range have examined memory function in long-term cannabis users; as a result, we also cite within this review select studies prior to 2000 that investigated memory function and were well-controlled. The primary studies that were considered in this review are listed in Table **1** where details are provided regarding the nature of the samples recruited, cannabis use measures and major findings pertinent to memory. Animal literature will not be covered in this review, other than brief reference in support of specific concepts. Reviews of preclinical findings pertinent to memory may be found in Egerton *et al*. [7] and Solowij & Michie [5] and clearly demonstrate deficits in short-term and working memory and reversal-learning after acute and chronic administration of cannabinoids to rodents and monkeys, implicating hippocampal and prefrontal cortical dysfunction. Studies where cannabis users formed a control group within an investigation of effects of other substances (e.g., MDMA) were considered separately to the primary literature, as were studies of prenatal exposure in humans. We have organised this review into sections addressing working memory, verbal episodic memory and other general memory processes, reflecting the focus of the recent literature.

While cannabis users, as well as the average person on the street, may not have the necessary insight, knowledge or vocabulary to describe their perceived memory problems to any degree of precision, it was our aim in conducting this review to enable us, as researchers, and the scientific community to better define the nature of memory deficits in cannabis users.

THE ENDOGENOUS CANNABINOID SYSTEM AND MEMORY

Before proceeding with our review of the literature, it is important to introduce the involvement of the endogenous cannabinoid system (eCB) in functions pertinent to memory. Notably, cannabinoid (CB1) receptors occur in high density in brain regions critically involved in memory functions and cannabinoids profoundly affect synaptic plasticity underlying learning and memory [8], disrupting long-term potentiation in the hippocampus [9-11]. Even a single exposure abolishes retrograde signalling [12] and can induce lasting deficits in spatial learning and memory in mice 3-4 weeks and 4 months after exposure [13].

CB1 receptors are the most abundant metabotropic receptors in the brain and are involved in multiple important physiological and behavioural events [8, 14]. They reside on presynaptic terminals in regions involved in cognition, particularly learning and memory, critically in hippocampus, prefrontal cortex (PFC), anterior cingulate, basal ganglia and cerebellum. The eCB system, *via* its endogenous ligands anandamide and 2-arachidonoyl-glycerol (2-AG), mediates the flow of information in the brain through retrograde signalling, modulating inhibitory and excitatory neurotransmitter release crucial for synaptic plasticity, depolarisation-induced suppression of inhibition or excitation, long term potentiation, and hence learning, memory and other higher cognitive functions [8, 9, 15, 16]. eCBs are synthesised on demand through cleavage of membrane precursors and are involved in various short-range signalling processes [16]. Research has demonstrated alterations in the functioning of the brain in CB1 rich regions and in cognitively-relevant neuromodulator systems (e.g.,, dopaminergic, cholinergic, serotonergic, GABAergic, glutamatergic) as a result of exposure to cannabinoids [3, 9, 16]. Alterations in the functionality of the eCB system, such as receptor downregulation, desensitisation and downstream effector changes accompanying the development of tolerance, dependence and resultant regional neuroadaptations, occur following chronic administration of cannabinoids [11, 17]. Neurobiological studies have uncovered mechanisms involving the eCB system (too complex and detailed to review here) that may inform the neural substrates underlying persistent deficits in cognition following repeated exposure to cannabis (see [1, 5, 7]).

STRUCTURAL BRAIN ALTERATIONS ASSOCIATED WITH CHRONIC CANNABIS USE

Evidence for structural brain changes in cannabis users has been lacking from most studies undertaken to date. Some recent studies have found no global or regional changes in brain tissue volume or composition [18-20], while others have found grey and white matter density changes globally [21] or in parahippocampal areas [22]. Using more sensitive measures and assessing cannabis users with far greater exposure to cannabis than previous studies, we have recently reported significant reduction of hippocampal and amygdala volumes in long-term very heavy cannabis users (mean age 40, mean duration of use 20 years) [23]. Hippocampal volumetric reduction was dose-related, correlating with current daily dose, and cumulatively. It may be that only excessive daily doses of cannabis, over a prolonged period of time, will result in structural brain changes. Age of onset of cannabis use may also be a critical factor, with potentially greater deleterious effects to the brain when cannabis use is commenced during significant periods of neurodevelopment, such as adolescence. Early onset cannabis users (before age 17) were found to have smaller whole brain volumes, lower percent cortical grey matter, higher percent white matter and increased resting cerebral blood flow compared to later onset users [21].

Recent evidence of diminished neuronal and axonal integrity in the dorsolateral prefrontal cortex (DLPFC) indicated by magnetic resonance spectroscopic markers of metabolism (the ratio NAA/tCr) was reported by Hermann *et al*. [24]. Dose-related changes in this study were also found in anterior cingulate and putamen/globus pallidum, but not in hippocampus. Strong evidence for cumulative dose-related neuronal damage, however, comes from the animal literature where chronic cannabinoid administration has been shown to induce neurotoxic changes within the hippocampus, including decreases in neuronal volume, neuronal and synaptic density, and dendritic length of CA3 pyramidal neurons [25-28]. Since functional impairment is likely to precede major

Table 1. List of Studies Reviewed with Use Parameters, Abstinence Period, Estimated IQ, Tests Used and Memory Findings

Author(s)	Groups (n/Mean Age)	Cannabis Use Parameters	Abstinence Period	Estimated IQ (Mean)	Memory (& Imaging) Tests	Memory Findings
Working Memory						
Jacobsen *et al*. (2004)	CAN(7/17.4); TOB(7/17.1); CON(7/16.8)	CAN(24-1460 days of use; Mean 282.8); TOB(0-1; Mean 0.6); CON(nil)	CAN(1.5-24 mo; Mean 10)	CAN(97); TOB(91.4); CON(103.2)	n-back WM task with Selective Attention Task Load; CPT; fMRI	CAN<CON on accuracy WM; Can<CON on % correct CPT; CAN<CON & CAN<TOB in deactivation of right hippocampus
Kanayama *et al*. (2004)	CAN(12/37.9); CON(10/27.8)	CAN(5100-54000 occasions; Mean 19200); CON(no history of abuse/dependence)	CAN(6-36 hrs)	na	SWM - perception & short-delay; PET	CAN<CON on accuracy ns; CAN>CON activation in PFC/ACC/Basal Ganglia
Jager *et al*. (2006)	CAN(10/22.7); CON(10/22.8)	CAN(mean 7.1 yrs; 2-17 j/wk); CON(0-15 life j)	CAN/CON (Min 1 wk)	CAN(104.9); CON(106.1)	Sternberg; fMRI	No group differences on Sternberg; CAN>CON for activation in SPC
Harvey *et al*. (2007)	CAN(34/16.1); CON(36/16.4)	Over 28-days: CAN(2.2-84.8 j; Med 11.3; 1st use age 7-16); CON(0-6 j; Med 0; 1st use age 5-17)	Min 12 hrs	CAN(95.9); CON(103.4)	CANTAB - RVIP, SWM, PAL, Spatial Span; RAVLT; Digit Span	CAN>CON on RVIP, SWM errors; CAN<CON on SWM strategy use; CAN<CON on RAVLT Total Words Recall
Jacobsen *et al*. (2007)	CAN(20/17.1); TOB(25/17)	CAN(62-2799 life use; Med 351); TOB(0-40 life use; Med 6)	CAN(0.5-24 mo; Mean 4.8 mo); TOB(1-40 mo; Mean 9.2 mo)	CAN(92.6); TOB(95.1)	n-back WM task with Selective Attention Task Load; HVLT-R	CAN<TOB on Delayed Recall during nicotine withdrawal; CAN>TOB in PC activation; disrupted F-P connectivity for CAN
Verbal Episodic Memory						
Fletcher *et al*. (1996)	O(17/45.31); O(30/45.64); YCAN(37/29.29); YCON(49/27.28)	OCAN(Mean 34 yrs; 5.2 j/day, 2-7 times/wk); YCAN(Mean 8 yrs; 3.8 j/day, 2-7 times/wk)	72 hrs	OCAN(110.33); OCON(115.50); YCAN(113.78); YCAN(115.33)	12-trial Spanish SRT + Free Recall; Sorting task; Story Episodic Memory	OCAN<OCON on SRT Accuracy & Free Recall
Pope & Yurgelun-Todd (1996)	HVY(65/Median 20); LGT(64/Median 21)	HVY(22-30 days/mo); LGT(0-9 days/mo)	Min 19 hrs	HVY(100.6); LGT(104.8)	WMS, CVLT, ROCF	HVY<LGT on Imm Recall, Total Recall, Post-Interference, & Delayed Recall (ns)
Pope *et al*. (2001)	CAN(63/36); EX-CAN(45/41); CON(72/39.5)	CAN(15-24 yrs; 11700-27000 eps; Mean 11700); EX-CAN(11-19 yrs; 8400-16000 eps; Mean 11000) CON(5-25 eps; Mean 5)	0, 1, 7 & 28 days	CAN(106); EXCAN(115); CON(115)	Assessed repeatedly over 3-4 days: BSRT; Benton Revised Visual Retention Test; WMS	After IQ-adjustment, CAN<CON on Day 7 Total Recall & Consistent Long-Term Retrieval
Pope *et al*. (2002)	CAN(77/36); CON(87/40)	CAN(Min 5000 times; current daily); CON(1-50 times)	0, 1, 7 & 28 days	CAN(108); CON(115)	Assessed repeatedly over 3-4 days: BSRT; Benton Revised Visual Retention Test; WMS	After IQ-adjustment, CAN<CON on Day 7 Consistent Long-Term Retrieval
Bolla *et al*. (2002)	HVY(7/20.7); MOD(8/21.9); LGT(7/24.6)	HVY(3-10 yrs; 78-117 j/wk); MOD(2-15 yrs; 18-70 j/wk); LGT(2-6 yrs; 2-14 j/wk)	HVY/MOD/LGT(28 days)	HVY(91); MOD(95); LGT(101.9)	RAVLT; Logical Mem (WMS-R); Rey Osterreith Complex Figure; Symbol Digit PAL	-ve *r* with RAVLT Delayed Recall & Symbol Digit PAL

(Table 1) contd…..

Author(s)	Groups (n/Mean Age)	Cannabis Use Parameters	Abstinence Period	Estimated IQ (Mean)	Memory (& Imaging) Tests	Memory Findings
Block *et al*. (2002)	CAN(18/na); CON(13/na)	CAN(2+ yrs, Mean3.9 yrs; 7+ times/week); CON(0-2 life use)	CAN(Min 26 hrs; Mean 27.8 hrs)	na	BSRT; Novel Word List; PET	CAN<CON on learning/relearning in BSRT; CAN>CON for word recency in Novel list; CAN<CON for middle list words in Novel list; CAN<CON in PFC activation; CAN had absence of hippocampal lateralization
Solowij *et al*. (2002)	LT(51/42.1); ST(51/28.7); CON(33/34.8)	LT(17.3+ yrs/Med 27.9 days/mo); ST(2.7-17 yrs/Med 28.3 d/mo); CON(limited history)	LT/ST(7-240 hrs; Med 17 hrs)	LT(105.7); ST(105.1); CON(107.9)	RAVLT; Omitted Numbers	LT<ST/CON on Total Recall; LT<Con on RecogA/B; LT/ST<CON on RecogA/B
Lyons *et al*. (2004)	Twins: CAN/CON(54/46.3)	CAN(Mean 5.8 yrs; Mean 916 days)	CAN(Mean 20 yrs; 1 yr Min)	CAN(107.98); CON(108.13)	WMS-R; CVLT; ROCF	CAN<CON on CVLT long delay free recall & long delay cued recall (ns)
Wadsworth *et al*. (2006)	CAN(34/24.03); CON(85/26.79)	CAN(Mean 7.63 yrs, 3.35 days/wk)	na - implied heavier use on weekends	CAN(113.28); CON(113.22)	Imm/Delayed Free Recall; Delayed Recog; Verbal Reasoning; Semantic Processing	CAN<CON on Verbal Reasoning & Delayed Recall pre-work day 1
Medina *et al*. (2007)	CAN(31/18.07); CON(34/17.86)	CAN(Mean 2.91 yrs; Mean 540.64 life use); CON(<5 life use)	CAN(Min 28 days)	Vocab. *T*: CAN(55.7); CON(57.3)	CVLT; ROCF; Logical Mem (WMS-III)	CAN<CON on CVLT Trial 1 & Verbal Story Mem composite score, WMS-III Logical Mem measures
Other Memory Processes						
Hermann *et al*. (2007)	CAN(13/22); CON(13/23)	CAN(Mean 719 g/day for 5.6 yrs; Mean 25 days/mo); CON(nil)	CAN(3-84 hrs; Mean 29); Hair Analysis	CAN(124); CON(124)	HAWIE-F/B; TME, BVRT; MRS	CAN<CON in BVRT STM Accuracy; CAN>CON in errors for BVRT, TME & Errors; CAN<CON on neuronal & axonal integrity in DLPFC
Jager *et al*. (2007)	CAN(20/24.5); CON(20/23.6)	CAN(Med 1900 life j; Med 332.5 j last yr); CON(Med 0 life j; Med 0 j last yr)	1 wk	CAN(107); CON(103)	Pictorial Memory paradigm; fMRI	-ve *r* for Recall Accuracy with extent of last yr & life cannabis use; CAN<CON brain activation in bilateral parahippocampal & right DLPFC
Cannabis Comparison Group Studies						
Rodgers *et al*. (2000)	MDMA/CAN(15/31); CAN(15/30); CON(15/32)	MDMA/CAN(Mean 4 days/wk over 10 yrs); CAN(Mean 4 days/wk over 11yrs); CON(nil history)	1 mo	na	WMS-R	MDMA/CAN & CAN<CON on Logical Mem I/II; MDMA/CAN<CAN & CON on Verbal/Visual Paired Assoc. II
Croft *et al*. (2001)	CAN(18); MDMA/CAN(11); CON(31)	CAN(7762.4 life Mean); MDMA/CAN(10964.9 life Mean); CON(0.5 life use)	48 hours	CAN(115.2); MDMA/CAN(116.2); CON(115.2)	Warrington Recog Mem Test; F/B-DS; Coughlan List & Design Learning	CAN & MDMA/CAN<CON on Coughlan Total Recall & F/B-DS

(Table 1) contd…..

Author(s)	Groups (n/Mean Age)	Cannabis Use Parameters	Abstinence Period	Estimated IQ (Mean)	Memory (& Imaging) Tests	Memory Findings
Rodgers *et al*., (2001)	MDMA/CAN & CON(488/21-25 Modal Age)	MDMA/CAN(1-4, 5-20, or 20+ times/mo)	na	na	EMQ, PMQ, UEL	+ve *r* for level of cannabis use with errors in EMQ, PMQ short-term & PMQ internally cued
Simon & Mattick (2002)	MDMA/CAN (40/25.3); CAN(37/23.2)	MDMA/CAN(Mean 67.9 j/mo; n=25 regular use); CAN(Mean 62.6 j/mo)	Minimum 24 hours	MDMA/CAN(105.6); CAN(107.6)	WMS-III	No group differences. Frequency of use (ns) predicting visual memory performance
Schweinsburg *et al*. (2005)	CANALC(15/16.91); ALC(15/16.77); CON(19/16.50)	CANALC(Mean 3.37 yrs; Mean 309.87 life eps); ALC(Mean 3.03 yrs; Mean 11.33 life eps); CON(Mean 1.46 yrs; Mean 1.47 life eps)	CANALC(Mean 7.64 days); ALC(Mean 79.67 days); CON(Mean 145 days)	Vocab. Scaled: CANALC(11.77); ALC(12.53); CON(12.21)	SWM; fMRI	No differences on SWM; CANALC>CON for activation in DLPFC; CANALC<CON for activation in inferior frontal & temporal regions; CANALC<ALC in activation in inferior frontal & temporal regions; CANALC>ALC in activation in medial frontal area
Quednow *et al*. (2006)	CAN(19/25.42); MDMA(19/24.21); CON(19/23.42)	CAN(Mean 6.55 yrs; Mean 3.89 times/wk); MDMA(Mean 3.95 yrs; Mean 1.63 times/wk); CON(nil)	Minimum 3 days: CAN(Mean 7.1); MDMA(Mean 11.1)	CAN(109.7); MDMA(100.6); CON(105.7)	RAVLT	MDMA<CON on Imm Recall, Total Recall, Retroactive Interference, Delayed Recall, Recog
Medina *et al*. (2007)	CANALC(26/17.6); ALC(16/16.9); CON(21/17.5)	CANALC(Mean 402.3 life eps; Mean 14.2 days/mo over last 3 mo); ALC(Mean 11.9 life eps; Mean 0.8 days/mo over last 3 mo); CON(nil)	CANALC(Mean 31.4 days; Min 2); ALC(419.9); CON(951.9)	Vocab. *T*: CANALC(55.3); ALC(59.2); CON(56.7)	CVLT; structural MRI	No CVLT or hippocampal volume group differences. Hippocampal asymmetry correlated with CVLT performance in CON; abnormal in CANALC and ALC

ACC - Anterior Cingulate Cortex, *ALC* - Alcohol only group, *BSRT* - Buschke's Selective Reminding Task, *BVRT* - Benton Visual Retention Test, *CAN* - Cannabis group, CANALC – Cannabis and alcohol group, *CON* - Control group, *CPT* - Continuous Performance Task, *DLPFC* - Dorsolateral Prefrontal Cortex, *eps* – Episodes, *EXCAN* - Formerly Heavy Ex-Cannabis User group, *F/B-DS* - Forward/Backwards Digit Span, *EMQ* – Everyday Memory Questionnaire, *fMRI* – Functional magnetic resonance imaging, *F-P* – Fronto-Parietal, *HAWIE* – Hamburg Wechsler Intelligenztest für Erwachsene, *hrs* – Hours, *HVY* – Heavy User group, *IED* – Intra/Extra Dimensional Shift, *Imm* – Immediate, *LGT* – Light User group, *LT* – Long-Term User group, *MDMA* – MDMA/Ecstasy group, *Med* – Median, *Min* – Minimum, *mo* – Month(s), *MOD* – Moderate User group, *MRI* – Magnetic resonance imaging, *MRS* – Magnetic resonance spectroscopy, *na* – Not Available, *ns* – Non-Significant, *OCAN* – Older Cannabis User group, *OCON* – Older Non-Users group, *PAL* – Paired Associates Learning, *PC* – Posterior Cortex, *PFC* – Prefrontal Cortex, *PMQ* – Prospective Memory Questionnaire, *RAVLT* – Rey Auditory Verbal Learning Test, *Recog* – Recognition, *ROCF* – Rey-Osterreith Complex Figure Test, *RVIP* – Rapid Visual Information Processing, *SRT* – Selective Reminding Task, *ST* – Short-Term User group, *SWM* – Spatial Working Memory, *TME* – Tempoleistung und MerkFähigkeit Erwachsener, *TOB* – Tobacco User group, *wk* – Week(s), *WM* – Working Memory, *WMS* – Wechsler Memory Scale, *YCAN* – Younger Cannabis User group, *YCON* – Younger Control group.

structural alterations in the brain, or to manifest concomitant to more minor neural alterations, there is, therefore, good reason to suspect long-term effects of cannabis use on memory function.

STUDIES OF MEMORY IN CHRONIC CANNABIS USERS

Working Memory

Working memory is disrupted by acute cannabis use [29], including spatial n-back [30] and delayed matching to sample (DMTS) tasks [31]. There is a substantial animal literature reporting impaired working memory following acute and chronic administration of cannabinoids (see [5, 7]), including an impaired DMTS task performance that resembles lesions or removal of the hippocampus [10]. A general paucity of studies investigating working memory and related functions in chronic cannabis users in the unintoxicated state is now being rectified with a growing recent literature.

Kanayama *et al*. [32] used functional magnetic resonance imaging (fMRI) to investigate spatial working memory in long-term heavy cannabis users employing a relatively simple task. Users made nonsignificantly more errors on the task, although very few errors in both groups reflected the simplicity of the task and it has been suggested that performance deficits in chronic cannabis users are more likely to be elicited in complex tasks (e.g., [4]) or tasks with a greater memory load [33]. However, greater and more widespread brain activation was displayed by cannabis users in Kanayama *et al*.'s study, with increased activation of regions typically used in spatial working memory tasks, such as prefrontal cortex and anterior cingulate, and additional recruitment of areas not typically used in such tasks, such as basal ganglia regions. The authors interpreted their findings in terms of cannabis users experiencing subtle neurophysiological deficits for which they compensate by working harder and calling upon additional brain regions to meet the demands of the task. Increased activation of the anterior cingulate in particular was thought to reflect an increased effort

to overcome cannabis-induced attentional impairments and to coordinate activity from the wide range of regions recruited to perform the task.

An fMRI study of a small sample of adolescent cannabis users performing an n-back working memory task with additional selective attention load focused analyses on the hippocampus [34]. Despite a mean abstinence of 10 months, the cannabis users performed less accurately on the task overall compared to non-smokers and on some measures compared to tobacco smokers, with poorest performance on the most difficult condition (selective attention load) but with no additional decrement as a function of memory load. Further, users failed to deactivate the right hippocampus across task conditions in contrast to both control groups, which the authors suggested may reflect a dysfunction of inhibitory hippocampal interneurons.

In a further study of abstinent adolescent (aged 13-18) cannabis and tobacco smokers compared to tobacco only smokers, this group [35] found fMRI evidence of altered neurocircuitry during the performance of an n-back auditory working memory task in the cannabis group, but only during nicotine withdrawal. Subjects were tested twice, once during an ad libitum cigarette smoking condition and again after 24 hours abstinence from tobacco, and cannabis users were abstinent from cannabis for at least 2 weeks prior to testing. In the tobacco abstinence condition, cannabis users showed increased task-related activation of posterior cortical regions and disrupted frontoparietal connectivity during a high verbal working memory load. Performance on the n-back task deteriorated with memory load in cannabis users in both smoking and abstinence from tobacco conditions, whereas poorer retention on the HVLT-R (outside of the scanner) was only evident in cannabis users during withdrawal from nicotine. Interestingly, the changes present during nicotine withdrawal were apparent solely in cannabis users, not in tobacco smokers, and were in spite of a limited history of cannabis use and a substantial abstention period (mean 4.8 months, range 0.5 - 24). The authors suggested that nicotine use may mask the effects of cannabis, protecting against some of its cognitive impact in correcting performance and neural activity. Increased regional activation in cannabis users during nicotine withdrawal may reflect compensatory processes that are engaged in an (unsuccessful) attempt to achieve satisfactory task performance, in accord with the Kanayama *et al*. [32] study.

In a Sternberg-type working memory task administered in an fMRI study, Jager and colleagues [33] found no performance deficits among moderately frequent young adult cannabis users after one week of abstinence. Few overall regional brain activation differences were found between users and controls, but users showed a smaller decrease in activity in the left superior parietal cortex in response to a decrease in memory load than did controls, and this correlated significantly with past year exposure to cannabis. This region is known to be involved in short-term storage and retrieval of verbal information. The authors interpreted these findings as reflecting similar activation of working memory systems between cannabis users and controls, but with cannabis users requiring greater activation to achieve similar performance, which may be insufficient with more challenging tasks.

Using a very different 'real-world functioning' approach, one study examined mood and cognitive performance in a sample of workers with and without recent cannabis use, before and after work at the start and end of the working week [36]. Details regarding levels of cannabis use in the sample were scant and preclude firm conclusions. A verbal reasoning task was employed to measure "working memory". Other memory tasks included immediate and delayed free recall and recognition of 20 words presented on a computer screen and a semantic processing task measuring speed of retrieval of knowledge from general memory. Poorer performance in verbal reasoning was apparent in cannabis users at the start of the working week and correlated with frequency of cannabis use. This effect was interpreted as a 'hangover' from weekend use of cannabis. Poorer performance in delayed recall was found in cannabis users pre-work at the end of the working week and was correlated with duration of cannabis use. Cannabis users also showed slower response organisation and lower alertness than non-users generally, and slower psychomotor speed toward the end of the week, reflecting a lack of improvement in speed over the working week in contrast to controls, rather than a progressive slowing by cannabis users. The findings of this study suggest that impaired performance in cannabis users may only manifest under certain conditions, for example when tired or under a heavy cognitive load, and the results are informative with regard to hangover effects and impacts on real world work performance.

A recent paper by Harvey *et al*. [37] reported an investigation of working memory and other executive and attentional functions in adolescent cannabis users using select tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB). Memory-related subtests included: Rapid Visual Information Processing (RVIP) – a test of sustained attention with a working memory component; Spatial Working Memory (SWM) – assessing strategy use and memory updating ability for different spatial locations; Paired Associates Learning (PAL) – testing associative learning of patterns and spatial locations of increasing difficulty; and, Spatial Span – spatial memory span for order and location. Additional CANTAB subtests included Motor Screening and Intra/Extra Dimensional Shift (IED) – measures of visual and motor problems, and attention and cognitive flexibility, respectively. Participants also completed the Rey Auditory Verbal Learning Test (RAVLT), measuring verbal memory encoding, storage and retrieval, Digit Span to assess attention and working memory, and the Symbol Digit Modalities Test for sustained attention. Regular cannabis users differed significantly from non-regular users on RVIP errors, SWM total errors and strategy use, and on total words recalled on trials 1 to 5 of the RAVLT. Cannabis use was a significant independent predictor of SWM and RAVLT performance. No significant differences were found on PAL, Spatial or Digit Span, Symbol Digit Modalities, or the additional, non-memory related, CANTAB subtests. The findings of this study provide further evidence for a potentially greater impact of cannabis upon certain aspects of memory function in the developing adolescent brain, given the substantially more limited exposure to cannabis in this young sample.

We have preliminary data from adult long-term heavy cannabis users and matched non-user controls on several

measures from the CANTAB [38]. We found that cannabis users' performance was poorer than non-users on most measures but differed significantly only on SWM errors and strategy, spatial recognition memory and the IED, which requires shifting of attention and reversal learning. Performance on SWM worsened as a function of the duration of cannabis use. Further analyses of these data are in progress and will enable a better comparison of similarities and differences between our findings in adult long-term heavy cannabis users and those in the adolescent cohort reported by Harvey and colleagues [37].

Verbal Episodic Memory

Verbal learning and memory have been, perhaps, the most consistently impaired cognitive functions in studies of acute cannabis administration as well as in chronic cannabis users. In acute studies, poorer performance has been observed in immediate and delayed recall of words [29], greater intrusion errors [30] and, at high doses, no learning whatsoever occurring over trials [39]. A reduced brain event-related potential (ERP) difference between previously studied words and new distracter words was observed in subjects most affected subjectively by the acute intoxication, suggesting disruption of neural mechanisms underlying memory for recent study episodes [30]. Impairment on word list learning tasks has been consistently demonstrated in recent neuropsychological studies of heavy or long-term cannabis users in the unintoxicated state.

Word list learning tasks, such as the RAVLT, California Verbal Learning Test (CVLT), Hopkins Verbal Learning Test Revised (HVLT-R), Buschke's Selective Reminding Task (BSRT) and variants (henceforth collectively referred to as verbal learning tasks (VLTs)), require learning and recalling a supra-span list of words (12-16) over a series of trials (usually 3 – 6) and sometimes following an interference trial. Words can be presented from semantic categories (as in the CVLT), which enables the use of organisational strategies to facilitate efficient encoding. Recall and recognition memory may also be assessed after a delay (e.g., 20-30 minutes). Thus, VLTs measure the ability to encode, consolidate, store and retrieve verbal episodic information and are highly sensitive to neurological impairment [40], though age, intelligence and educational experience also impact upon performance [41]. Deficits in cannabis users have been demonstrated in all VLT task measures and have variously been attributed to duration of cannabis use [42, 43], frequency of cannabis use [44, 45] or cumulative dosage effects [46]. Generally, long-term heavy cannabis users learn fewer words on each trial and overall, recall fewer words and forget more words following interference or a delay than short-term or light cannabis users or non-user controls. Recognition performance may also be poor, albeit less consistently, while intrusion errors may be present but are not routinely monitored or reported in studies.

Pope and Yurgelun-Todd [45] compared performance on the CVLT of heavy (≥ 22 days use in the past month, median 30 days) and light (< 9 days in the past month, median 2 days) users of cannabis, following at least 19 hours of supervised abstinence. The duration of use of the sample was not reported, although the median age of 20-21 suggests limited years of use. Heavy and light users differed significantly, with poorer performance by heavy users in the number of words recalled on almost every trial, in the sum of all five trials, following the presentation of an interference list, following cueing and in delayed recall (40 minutes later), but there was no temporal decay of recall in either heavy or light users. These results suggested reduced learning in heavy cannabis users, but the ability to retain newly learned information after a delay appeared to remain relatively intact. In a 17 year follow-up of chronic users, Fletcher *et al.* [47] found that only older long-term cannabis users differed from controls in list learning, while young users were unaffected.

More recent studies have replicated impairment in learning, recall and delayed recall, with some evidence of decay. We found that 17-hour abstinent long-term heavy (near daily) cannabis users (mean 24 years of use) recalled fewer words than shorter-term heavy users (mean 10 years of use) and non-user controls over all learning trials of the RAVLT and lost significantly more words following a 20 minute delay [43]. Recognition performance was also significantly poorer in long-term users and measures of recall and recognition correlated significantly and inversely with the years of cannabis use, after controlling for age and IQ. Despite near daily use also in the shorter-term users, they did not differ from controls, supporting a greater impact of long duration of cannabis use rather than frequency of use. Long-term users also showed a smaller primacy effect, but groups did not differ in recency or words recalled from the middle of the list. Messinis *et al*. [42] essentially replicated these findings in a sample of long-term (10 or more years of use) and short-term (5-10 years of use) cannabis users with a substantially longer duration of abstinence prior to testing (a mean 122.8 hours), compared to controls (with a very limited history of use). They found poorer performance by long-term users on most trials of the RAVLT and on delayed recall and recognition. In this study, however, the short-term users' performance was also significantly poorer than controls on trials 5, 6, delayed recall and recognition, whereas in our study short-term users did not differ from controls on any measure from the RAVLT. Both long- and short-term users in the Messinis *et al*., study differed from controls on the Trail Making Test Part A (processing speed) and Part B (executive functioning including working memory). Multiple measures from the RAVLT were also found to correlate inversely with the duration of cannabis use. The authors interpreted these findings as indicative of a generalised memory deficit, as verbal learning, retention and retrieval were all impaired.

Both our study [43] and that of Messinis *et al*., [42] employed rigorous criteria for inclusion of cannabis users in the study to eliminate potential confounds. While most results from these two studies are consistent and show that long-term heavy use of cannabis impairs verbal learning and memory, it is not clear why differences were found with regard to short-term cannabis users. The larger sample size (n=51 *vs* n=20), relatively greater duration (mean 10.2 *vs* 6.95 years) and frequency (28.3 *vs* 20.7 days/month) of cannabis use in our short-term users cohort, as well as the significantly shorter period of abstinence prior to testing (median 17 hours *vs* mean 122.8 hours), might have predicted a greater probability of cognitive deficits occurring in the short-term users of our study. Further, our cohort may have used a significantly greater quantity of cannabis per day (an average 2 joints), whereas Messinis *et al*.'s threshold for

entry to the study was 4 joints per week, but actual quantities used were not reported. The only other differences between the two cohorts were that Messinis *et al.*'s subjects were slightly younger (24.25 *vs* 28.7 years) and less educated (10.8 *vs* 14.1 years), with several points lower IQ (101.1 *vs* 105.1). Perhaps this combination of factors confers a greater vulnerability to cognitive deficits following heavy cannabis use.

Other studies have investigated the persistence of cognitive deficits or recovery of function following much longer periods of abstinence from cannabis. Bolla and colleagues [46] found a significant dose-related response on delayed recall from the RAVLT in 28-day abstinent former heavy cannabis users: the number of words recalled diminished as a function of the number of joints smoked per week but performance was unrelated to duration of cannabis use. The mean duration of use in the sample, however, was only 4.8 years (range 2 – 15 years). Heavy users were not impaired in recognition performance in contrast to light users, leading the authors to speculate that heavy cannabis use is associated with difficulty in recalling information, rather than with acquisition or retention of information. However the sample size of this otherwise well-controlled study was exceedingly small (n=22 users in total, only 7 classified as heavy (mean 94 joints per week)), which may have lead to insufficient power to detect recognition deficits. Alternatively, recognition performance may be more amenable to recovery following abstinence. Despite the small sample size, the strength of this study is in its assessment of cognition beyond the washout period for the majority of cannabinoid residues, with cannabis users residing on an inpatient clinical research ward for 28 days. This may rule out the attribution of any deficits found to the residual effects of acute cannabis intoxication (although up to 4 months abstinence may be required to eliminate all remaining accumulated cannabinoid metabolites in some users). Bolla and colleagues showed a trend toward persistent poorer performance by heavy users than light users on all measures of verbal learning and memory in their study (including Logical Memory and Digit-Symbol Paired Associate Learning which also showed a dose-related decrement), with a large magnitude of difference between heavy users and light users (1.0 – 3.3 SD units) and poorer performance than age-matched norms on some tests (e.g., Rey Complex Figure Copy and Delayed Recall). They suggested that the pattern of results was characteristic of subcortical, prefrontal involvement and normal aging, implying that heavy use of cannabis may result in premature cognitive decline. Further, they also found that IQ interacted with dose on several measures (e.g., Symbol-Digit Paired Associate Learning, but not RAVLT performance) whereby lower IQ individuals were significantly more impaired with increasing number of joints smoked per week. This suggests that perhaps higher IQ individuals are better able to compensate for cannabis-related cognitive impairment.

Similar deficits in recall of word lists from the BSRT was found by Pope and colleagues [44] in heavy cannabis users (at least 7 uses per week and at least 5000 lifetime episodes of use) who were abstinent for 0, 1 or 7 days at testing, but these deficits appeared to recover after 28 days of supervised abstinence with no significant differences evident between former heavy users or controls at that time. Performance on delayed recall was significantly worse in heavy users still on day 28, but not after controlling for IQ. No associations were found between performance on day 28 of abstinence and lifetime episodes of cannabis use, but some association was apparent with levels of the urinary cannabinoid metabolite taken at baseline (day 0). The authors interpreted their data to suggest that cannabis-associated memory deficits may be reversible phenomena associated with recent drug exposure. This contrasts with our analyses [43] showing that impaired performance was not a consequence of recent use prior to testing (hours of abstinence) or cannabinoid residues (urinary cannabinoid metabolite level on the day of testing), and while recency of use was also a predictor of performance, duration of use was generally a superior predictor.

Pope *et al.*'s [44] findings also contrast with Bolla *et al.*'s [46] with regard to the persistence of cannabis-related effects after 28 days of abstinence. It is possible that the repeat-measures, and hence practice, inherent in Pope *et al.*'s study enabled cannabis users to overcome persistent deficits, particularly since they were of a significantly higher IQ than the users of Bolla *et al.*'s study, but they were also significantly older (36 *vs* 20 years) and may have consumed less cannabis over time than did those of Bolla *et al.*'s study. Pope *et al.*, report a median 18,720 lifetime episodes of cannabis use (episodes being separated by at least one hour) but no quantity measures are provided and less than one joint may be used per episode. Bolla *et al.*'s heavy users were using approximately 94 joints per week at the time of admission to the study and had used cannabis for a mean 5.3 years, which could extrapolate to 25,906 lifetime joints, although this heavy pattern of use may well have not been consistent over the duration of their lifetime cannabis use. Nevertheless, it would appear that four critical factors could explain the persistence of deficits in Bolla and colleagues' study in contrast to that of Pope and colleagues: a significantly greater amount of cannabis was consumed by Bolla *et al.*'s sample over a significantly shorter period of time by significantly younger users of significantly lower IQ. Thus, excessively heavy use in young adults of lower IQ may result in persistent impairment of memory (and other cognitive functions) that may require a much longer period of abstinence to recover. This is in line also with our findings of structural brain alterations in excessively heavy users (albeit in much older users) and earlier work of ours showing greater cognitive impairment in lower IQ users [4]. The young age of Bolla *et al.*'s sample also raises concern regarding possibly greater deleterious effects in the young adult or adolescent brain: age of onset was not reported but can be calculated as being 14 – 15 years in the heavy users.

Interestingly, in a re-analysis of their data, Pope's group found that deficits on the BSRT, and in particular on 30 minute delayed recall, were more likely to persist after 28 days abstinence among those who had commenced cannabis use prior to age 17 [48]. Although the authors sought to explain this in terms of potential "cultural divergence", the finding accords with several other studies that have also found evidence for greater adverse effects among those commencing cannabis use earlier during adolescence as opposed to young adulthood, most often before versus after the age of 17. Early onset cannabis use was shown to impair attentional processes measured by reaction time during visual scanning [49], visual search and short-term memory [50, 51], and result in the most reduced P300 amplitudes in an

attention task [52]. Early onset effects on brain volume, grey and white matter, and cerebral blood flow [21] were reported above. That the adolescent brain may be more vulnerable to the impairing effects of cannabis on memory (among other attentional and executive functions) is evident from the few studies that have now been conducted on adolescent samples of cannabis users. Attention to this specific population has been slow to translate into the research arena; Schwartz *et al*. [53] were the first to observe persistent short-term visual memory impairment in 6-week abstinent adolescent cannabis users. The study by Harvey *et al*. [37] discussed above, shows evidence of impaired performance on the RAVLT in regular adolescent cannabis users (mean age 16.1, range 13-18), with additional evidence for impaired working memory in adolescents in this study and the fMRI studies of Jacobsen *et al*. [34, 35] (mean age around 17 years; age of onset around 13.6 years). Recently, Medina and colleagues [54] reported poorer story memory (Logical Memory from the Wechsler Memory Scale III (WMS-III)), as well as poorer planning and sequencing ability, complex attention and slower psychomotor speed in a neuropsychological study of adolescent cannabis users after a minimum 23 days monitored abstinence. These measures were significantly associated with lifetime episodes of cannabis use after controlling for lifetime alcohol use. Lifetime cannabis use was marginally associated with CVLT performance, although this did not differ markedly from controls. Several other studies of adolescent cannabis users are further discussed below [55-57].

A further investigation of the potential persistence of cognitive deficits in cannabis users comes from a study of monozygotic twins discordant for cannabis use. Lyons and coauthors [58] administered an extensive neuropsychological test battery assessing a broad range of cognitive functions. The cannabis-using twins had not used cannabis for at least one year, but the last regular cannabis use had occurred almost 20 years ago in this cohort. The mean age of participants at the time of testing was 46.3, the mean age of last regular use of cannabis was 27.1, the mean age of initiation 21.3 and the mean duration of use was 5.8 years, with an estimated mean 916 days of use over the lifetime. Memory assessments included the CVLT, subtests of the WMS–Revised (WMS-R), and the Rey-Osterrieth Complex Figure Test. Cannabis-using twins differed significantly in general intelligence and not in the composite scores across the memory domain. However, long delay free recall on the CVLT was significantly poorer in the cannabis users in univariate tests, with a trend apparent also for long delay cued recall, and these measures together with Block Design and non-dominant Finger Tapping were the only significant findings from the entire battery, with the largest effect sizes. There was no relation between performance and lifetime days of cannabis use. The authors downplayed their findings, concluding that their study did not support the existence of meaningful long-term effects of previous cannabis use in long-abstinent individuals, and reasoned that the CVLT findings would have been more meaningful had there been evidence of similar trends toward impairment on the other CVLT measures and on the Logical Memory subtest of the WMS. It should be noted that the minimal extent and duration of cannabis use in this sample, and commencement of use at a relatively older age, may have lessened the extent of development of memory impairment in contrast to other studies, but indices of deficient memory functioning were nevertheless detected 20 years after regular cannabis use. Poorer performance on precisely the measures that other studies of both current and abstinent cannabis users have found to be impaired, and in general intelligence, in otherwise genetically- and environmentally-matched twins speaks to cannabis-related effects and further prospective studies of much heavier cannabis users, perhaps who had commenced at an early age, with similarly long abstinence periods would be informative.

One study has used functional brain imaging to investigate verbal memory processes in cannabis users. Block and colleagues [59] used positron emission tomography (PET) to examine memory-related regional cerebral blood flow in frequent users after a minimum 26 hours supervised abstinence. Subjects learned a list of words (from the RAVLT) over multiple trials to a criterion of two perfect recalls, using Buschke's selective reminding technique, one day prior to the scanning session. Cannabis users required significantly more trials than controls to achieve the learning criterion but then performed the task in the scanner as well as controls. However, upon introduction of a novel list of words, users showed an increased recency effect, recalling more words than controls from the end of the word list and fewer from the middle, suggesting a greater reliance on short-term or working memory and poorer encoding ability. This pattern of altered distribution of memory processes would contribute to poor list learning over trials. Cannabis users showed decreased memory-related blood flow in the PFC, increased flow in memory-relevant regions of the cerebellum, and altered lateralisation in the hippocampus relative to controls, with the greatest differences apparent in episodic encoding during new list learning (ie. differences in brain activation were less evident for the well-learned list than for the novel one).

Other Memory Processes

Hippocampal-dependent associative memory has been assessed in an fMRI study of one week abstinent moderate cannabis users (median 1900 lifetime joints) compared to non-user controls using a pictorial memory task [19]. Performance on the task did not differ between groups but recall accuracy decreased as a function of past year and lifetime estimates of cannabis use. Decreased activation in cannabis users was observed in left and right parahippocampal regions and in the right DLPFC during associative learning, but no differences were apparent during recognition and activation differences did not correlate with cannabis use or voxel-based morphometric measures of parahippocampal volume. For this reason the authors surmised that lower brain activation may not reflect neurocognitive impairment but may be related to some other covariate of frequent cannabis use, but this is difficult to reconcile with their performance data indicating deterioration in recall accuracy to be progressive with extent of cannabis exposure. In contrast to other studies that found increased activation during memory-related tasks and interpreted these as compensatory mechanisms (reviewed above), this study found lowered activation, which accords with the hypoactivity observed in other studies that have utilised Stroop and decision-making tasks in fMRI studies of cannabis users [60, 61]. Results are likely to reflect differing

tasks, regions of brain activation investigated and methods of analysis, as well as differing extent of exposure to cannabis and abstinence periods.

Hermann *et al*. [24] found significant deficits in neuropsychological tests of visual short-term memory (Benton Visual Retention Test) and auditory verbal short-term memory in a small sample of near-daily cannabis users (mean age 22, duration of use around 5 years). Further, performance on the Wisconsin Card Sorting Test and Trail Making Test (both of which depend on efficient working memory) varied as a function of THC or cannabidiol detected in hair analysis, as did magnetic resonance spectroscopic metabolite ratios in anterior cingulate and putamen/globus pallidum, while, as reported above, a ratio indicative of diminished neuronal and axonal integrity in DLPFC was significantly lower in cannabis users.

STUDIES OF OTHER SUBSTANCE USERS WITH CANNABIS USERS AS A COMPARISON GROUP

Cannabis users often use other substances, most commonly alcohol and tobacco, but polydrug use of other illicit substances is also frequent. Most of the studies reviewed above have excluded other substance use as a confound and have sought to recruit cannabis users who are relatively free of regular use of illicit drugs in order to isolate effects associated with cannabis use itself. It is possible that the effects of smoking tobacco and drinking alcohol may be additive or synergistic with cannabis in the induction of memory or other cognitive impairment, and some studies have sought to examine these potential interactions (e.g., [35] as reviewed above, others below). Other studies have not sought specifically to investigate the cognitive effects of cannabis itself, but have employed cannabis users as control groups in investigations of the memory impairing effects of other substances (largely those investigating the effects of Ecstasy (3,4-methylenedioxymethamphetamine (MDMA)). Recent studies of these types, where some inferences may be made with regard to specific effects of cannabis, are reviewed in this section.

Schweinsburg *et al.* [57] used fMRI to compare SWM performance in adolescent (aged 15-17) cannabis and alcohol abusers, with solely alcohol abusers, and non-user controls. The cannabis users had been abstinent for approximately one week. There were no significant performance differences between any of the groups on the SWM task but brain activation differences were apparent between all three groups. The cannabis users showed lower activation in inferior frontal and temporal regions and greater activation in prefrontal regions than non-user controls. Lower inferior frontal and temporal, but greater medial frontal activation, was observed in the cannabis and alcohol user group compared to the alcohol abusers, which the authors interpreted as reflecting compensatory mechanisms. These observations were not present between the alcohol and non-user control groups. Given that the cannabis and alcohol groups were equivalent in alcohol, and other drug use history, differences were attributed to cannabis exposure, despite this being quite limited in this young sample.

Similar groups to those in the Schweinsburg *et al.* [57] study were recruited by Medina *et al*. [56] in a neuropsychological and structural MRI study. Examining the combined effects of alcohol and cannabis on cognitive function and hippocampal volume, cannabis and alcohol-abusing participants did not differ from alcohol only abusers or controls on assessments of vocabulary or verbal memory (CVLT). No overall group differences were found in hippocampal volumes, although cannabis and alcohol users had larger left than right hippocampal volumes, with the reverse for alcohol only users. A clear functional relationship between verbal learning and hippocampal asymmetry was found in non-user controls, but appeared abnormal in cannabis and alcohol users. Further investigation of brain function and morphology in adolescents, and adults, who use cannabis and alcohol is clearly warranted.

Ecstasy or MDMA is a popular recreational drug that produces feelings of euphoria and increased energy, with cannabis used frequently to offset withdrawal [62]. Cognitive deficits, and particularly memory impairment, are associated with ongoing use of MDMA [63, 64], and thus it may be reasoned that combined use with cannabis may result in further deficits. However, inconsistent findings within the literature suggest that the interaction is not straightforward, and indeed there have been suggestions that cannabis use may be neuroprotective against MDMA-related memory deficits due to differing actions acutely with regard to oxidative stress and other mechanisms (e.g., dopaminergic) [62, 63, 65].

Rodgers [64] compared the performance of MDMA/cannabis users and cannabis-only users with non-user controls on the WMS-R and found that both MDMA/cannabis and cannabis-only users performed worse than controls on the Logical Memory I and II subtests. Self-reported abstinence from cannabis was for 1 month (unverified). The authors posited that logical memory problems may have been associated more with cannabis use, whereas MDMA use impaired delayed recall and visual and verbal paired associate task performance. An additional study by Rodgers *et al*. [66] investigated memory problems associated with cannabis versus MDMA in a large sample of respondents (n=488) to a web-based assessment. Drug use was assessed by a web-modified-version of the University of East London Recreational Drug Use Questionnaire and memory was assessed by the Everyday Memory Questionnaire (EMQ) - a measure of common memory lapses, and the Prospective Memory Questionnaire (PMQ) - a measure of short-term habitual memory, episodic memory, internally cued memory, and strategies used to aid memory. The authors used regression techniques to isolate the contribution of each substance to variance in the cognitive measures and found a double-dissociation. Cannabis use was significantly and uniquely associated with everyday memory problems (as measured by the EMQ), and poorer short-term and internally cued memory (as measured by the PMQ), and these effects were dose-related, increasing with monthly frequency of cannabis use. Greater frequency of MDMA use, on the other hand, significantly and uniquely predicted long-term memory scores on the PMQ, relating to storage and retrieval mechanisms, and also predicted more errors in completing the online assessments. Use of strategic techniques to aid memory correlated negatively with use of both substances, but significantly more for cannabis. While there are limitations regarding validity and reliability in web-based research of this kind and the lack of objectivity of most of the meas-

ures, this study was the first to demonstrate a dissociation between self-reported memory effects associated with cannabis versus MDMA and has intrinsic value in quantifying the nature of memory problems that users perceive themselves to be experiencing. The methodology of this study may have resulted in the recruitment of a more highly educated sample, but this may have served to provide greater insight and better self-evaluation of memory problems. The interesting findings are worthy of further exploration.

Comparing groups of non-user controls, cannabis only and cannabis/MDMA users, Croft *et al*. [62] found few differences in memory function between cannabis only and cannabis/MDMA users, but moderate memory and processing speed impairment was evident when comparing cannabis/MDMA users with non-user controls. This was across a battery of memory assessment instruments, including a VLT (Coughlan list and design learning), digit span, Warrington recognition memory, associative learning, as well as tests of other cognitive domains. While cannabis only and non-user control groups were not examined separately, (not being the primary groups of interest), the authors argued that the lack of difference between the two drug-using groups implied deficits to be cannabis-related and not due to MDMA, since cannabis use was common to both groups. Where minimal differences were found on memory tests between these groups (e.g., working memory for design learning), these were, however, in the direction of better performance by the combined cannabis/MDMA group. It is noteworthy that this group had a more extensive history of cannabis use (estimated mean lifetime joints 10964.9) compared to the cannabis-only using group (7762.4), and the authors posited a complex interaction between these substances whereby cannabis use may have attenuated MDMA-specific deficits.

Simon and Mattick [67] recruited cannabis-only and MDMA users with similar exposure to cannabis (around 65 joints per month) and equivalent IQ to examine the effects of MDMA on memory. The WMS-III was used to assess memory deficits. No significant group differences were detected, although frequency of cannabis use showed a trend toward predicting performance on visual immediate memory. The lack of a non-drug using control group in this study and limited variability within the cohorts to examine dose-response relationships may have limited the potential to detect specific substance-related memory effects [68].

In a study of verbal memory using a German version of the RAVLT, MDMA users with concomitant cannabis use, but not cannabis-only users, differed on most performance measures from non-user controls [69]. In contrast to the Croft *et al.* [62] study, cannabis use was lower among MDMA users than cannabis-only users (estimated mean lifetime episodes of use 547.1 *vs* 1033.4 respectively). The cannabis-only users of this study were relatively young (mean age 23.42) and were not heavy users: they had used cannabis for a mean 6.55 years, thus averaging about 13 joints per month (or less than 4 times per week as reported by the authors). This small sample also had a relatively higher IQ than the comparison groups of this study. These factors may explain the lack of significant impairment in RAVLT performance.

STUDIES OF PRENATAL/PERINATAL EXPOSURE

A long-standing concern that potential neurotoxic effects of drugs may affect critical periods of neurodevelopment has prompted investigation of the effects of substance use during pregnancy on outcomes in offspring. To date, there have been a limited number of investigations of prenatal exposure to cannabis, with memory-specific findings even more sparse. Two large cohort investigations have been following the cognitive and psychosocial development of offspring of cannabis-using and non-using women over many years: the Ottawa Prenatal Prospective Study (OPPS; [70]) and the Maternal Health Practices and Child Development Study (MHPCD; [71]). Both of these studies assessed mothers on a range of demographic variables and have sought to account for numerous potential confounds to determine any effect of prenatal exposure to cannabis.

Since 1978 the OPPS has assessed their low-risk – Caucasian and predominantly middle-class – cohort every few years [72], with the most recent published findings examining offspring at ages 18 to 22 [73]. During pregnancy, mothers were reported to have used either: no cannabis; less than six joints per week; or greater than or equal to six joints per week. The MHPCD, commenced in 1982, contrasts with the OPPS in that the cohort comprises high-risk individuals – of both Caucasian and African American parentage (47% and 53%, respectively), of a low socio-economic background and raised mostly by single mothers – who are thus less protected by potentially ameliorating demographic variables [74]. Multiple longitudinal observations have been made with the most recent published from the MHPCD examining offspring at the age of 10 [75]. Level of cannabis use during pregnancy was assessed in the MHPCD during each trimester with mothers classified into three categories: no use; less than one joint per day; or greater than or equal to one joint per day. These levels of use are comparable to the OPPS with children in both studies being classified as having been exposed prenatally, to potentially no, light-to-moderate, or high levels of cannabis.

Evidence of memory impairment across both samples has been minimal with a review of both these cohorts describing prenatal cannabis exposure as impacting upon memory inconsistently over repeated measurements of the same individuals [76]. At age 4, decreasing memory performance on memory subscales of the McCarthy Scales of Children's Ability was observed with increased prenatal marijuana exposure in the OPPS cohort [77]. This effect was not maintained among 9 to 12-year-olds, with increasing impairment with increased prenatal exposure holding true solely for aspects of executive functioning related to visual analysis, visual hypothesis testing and impulse control. Memory performance, as assessed by subtests of the WISC-III, the Auditory Working Memory Test, and the Gordon Diagnostic Delay and Vigilance Tasks, was not impaired [78]. Lack of impairment could be accounted for by the fact that some memory-related executive processes do not develop until several years later. At ages 13 to 16 memory impairment became evident when memory-related processing speed was taken into account, something not considered in previous analyses [79]. Performance on both Abstract Designs and Peabody

Spelling tests were poorer for children of heavy-cannabis-using mothers. These tests, rely on visual memory, analysis and integration and are sensitive to poorer processing speed capabilities. The authors cited evidence for this argument from unpublished data from the cohort on a motor tracing task where significantly slower latencies, but not fewer errors, were present. This suggests that compensatory processes may augment accuracy at the cost of speed.

By the ages of 17-18, some of the OPPS cohort had themselves commenced cannabis use and Fried, Watkinson and Gray [55] compared non-user controls (those with little to no personal use), to regular light (current use of less than 5 joints per week) and heavy users (five or more joints per week) and to a group of former regular users (no regular use for three or more months and less than two joints per week within the past two months). Greater prenatal exposure had occurred in the heavy user group. The authors were able to compare individual results with those from an earlier age, allowing adjustments for pre-drug performance. Assessments included the use of the WAIS-III, as well as multiple memory measures from the WMS-III: immediate memory index; general memory index; and working memory index. Immediate and delayed memory was found to be poorer for the heavy using group, as was visual processing speed, in comparison to controls. A lack of deficits in the former regular users (with a mean history of just over 2 ½ years and an estimated 4800 lifetime joints smoked, in contrast to current heavy users with also 2 ½ years experience and 1900 lifetime joints) was posited as evidence for neurocognitive recovery. An fMRI investigation of a sample of this cohort at ages 18-22 [73] found differential brain activation patterns, particularly within the PFC, evident for prenatally exposed individuals in the absence of overt performance differences during a response inhibition task. These differences between the prenatally exposed and non-exposed groups were maintained after controlling for prenatal nicotine, alcohol and caffeine exposure as well as current personal cannabis use in the sample, which was greater in the prenatally exposed group (6.36 *vs* 0.93 joints per week). The authors interpreted their findings as suggesting that prenatal exposure to cannabis is related to changes in neural activity that last into young adulthood.

Similar findings to the OPPS have been observed among the MHPCD cohort. Short-term memory impairment, as assessed by the Stanford-Binet Intelligence Scale, was observed for 3-year old MHPCD children, although moderated by pre-school educational experience for those of Caucasian parentage [80]. Limited impact was found upon memory at age 10 with first trimester heavy cannabis use by mothers found to weakly predict poorer performance on the Design Memory subtest of the Wide Range Assessment of Memory and Learning [71]. Determination of impact at older ages has not yet been published for the MHPCD cohort, so further changes during the adolescent years are as yet unknown. As with the OPPS study, findings have been suggestive of executive functioning deficits, with academic achievement related to such functioning at age 10 indicative of problems in this domain [75].

In contrast, prenatal (or neonatal) exposure to cannabinoids has unequivocally been shown to be harmful in animal studies, (e.g., [81-83]). Mereu *et al*. [83] found that in utero exposure to cannabinoids disrupted retention in a passive avoidance task in 40- and 80-day-old rats and this was accompanied by decreased hippocampal long-term potentiation and glutamate release, suggesting long-lasting, if not permanent, impairment of memory processes and their neural substrates. The authors surmised that these mechanisms may explain the observations of cognitive impairments in humans exposed to cannabis in utero, as have been discussed above. Given that there has been some evidence of cognitive dysfunction in the human cohorts, independent of their own cannabis use, enduring effects as a result of prenatal exposure, while possibly not severe, are likely. Whether these are specific to memory processes, or more closely tied with executive functioning and memory-related processing speed, remains unclear. It is possible that while younger individuals may be able to compensate for cognitive deficits at the cost of efficiency, the impact of prenatal exposure may become more evident later in life interacting with age-related cognitive decline.

PARAMETERS OF CANNABIS USE AFFECTING NEUROCOGNITION AND PERSISTENCE OF DEFICITS

As highlighted above in relation to verbal learning tasks (and here more broadly), neurocognitive deficits in adult cannabis users have variously been attributed to duration of cannabis use [4, 42, 43, 47], frequency of cannabis use [4, 44, 45] or cumulative dosage effects [46, 60, 84]. There is evidence that the effects of frequency and duration of use may be dissociable, as shorter lasting and potentially reversible effects on information processing, versus more enduring effects reflecting neural alterations that may be less amenable to recovery [4]. However, duration of use is necessarily confounded with increasing age and increasing cumulative dose of exposure. Frequency of use alone may not be a sufficiently good indicator without consideration of quantity used per occasion and cumulatively. Dose can usually only be estimated from self-report and, with significant variation in actual quantity of cannabis consumed in different sized smoking implements (e.g., joints, bongs, cones, blunts, etc) or estimated gram consumption, together with significant variation in the potency of cannabis consumed, only very imprecise estimates may be obtained. This is an impediment that continues to plague research in this field, which must continue to rely largely on self-report. Recommendations for future studies include obtaining as much detailed information as possible on each of these parameters, with corroborating evidence from sources such as hair analysis, which may be able to provide quantification of exposure over at least the few past months (e.g., [24]).

A significant source of variability in the studies reviewed above, and as evident from the summary information in Table **1**, is the duration of participant abstinence from cannabis use prior to testing. This has ranged from a minimum 3 (but mean 29) hours in one study [24] to a mean 20 years in another [58]. We have considered all of these diverse studies within our review as they met our definition of "unintoxicated" state and most studies attempted to ensure that participants were not acutely intoxicated at the time of testing. Clearly, the closer the assessment occurred to the last use of cannabis, the more likely any impairment found might potentially be attributed to cannabinoid residues that may still

be present within the brain, and might therefore be considered a subacute effect. Some studies have, however, used various statistical methods to aid interpretation of effects as being due to recent cannabis use versus longer-lasting deficits associated with other parameters of cannabis use, as mentioned above. That similar impairments have been found across studies with short abstention periods and in some of those with abstinence of over one month, suggests enduring residual effects that may last well beyond any period of acute intoxication. It may be, however, that following years of heavy cannabis use, the resultant effects of accumulated cannabinoids on altered neural functioning may induce a state of chronic intoxication that requires a significantly longer period to resolve, even beyond the elimination of cannabinoids from the body. Truly long-lasting deficits for months and years after cannabis use, if not accounted for by other confounds related to a propensity to use cannabis, and if shown to be dose-related, are likely to reflect long-term alterations to the functioning of the brain that may or may not be reversible. A close examination of the literature reviewed here failed to differentiate in any simplistic or clear manner specific memory deficits that are associated only with brief abstinence periods from cannabis (and hence subacute effects) from others that may be more apparent following prolonged abstinence. Further research, and ideally long-term prospective studies, are required to shed light on shorter-lasting versus longer-lasting effects and the persistence of deficits following abstinence from cannabis.

The prevailing investigations of recovery of cognitive function with prolonged abstinence from cannabis have produced conflicting results with some studies suggesting full recovery after 28 days abstinence [44], others showing partial early recovery and after a mean 2 years abstinence [4] and others still finding no recovery after 25-28 days abstinence [46, 60, 61]. Some evidence of impaired memory was apparent even 20 years after last regular cannabis use in the twin study of Lyons *et al*. [58]. The reasons for these differences are unclear but may be due in part to varying tasks and methodologies and differing characteristic populations. Few studies have assessed very long term users with histories of 20 – 30+ years of use as in some of our previous studies, or users with extreme heavy use.

Enduring deficits have been shown to be more likely to persist beyond cessation of cannabis use when use commenced prior to the age of 17 [48]. These findings suggest that age of onset may be a critical factor in the development and persistence of neurocognitive deficits and that the adolescent brain may be more vulnerable to the insult of even low-level cannabis use. Indeed, there is growing evidence for greater adverse cognitive outcomes when use is commenced during adolescence (e.g., prior to age 16 or 17) as opposed to young adulthood [21, 48, 49]. Early-onset cannabis use confers the greatest risk of developing psychosis, either in its own right (e.g., [85]), or as a gene by environment interaction [86]. Thus, individuals who begin to use cannabis when the brain is still developing may be most vulnerable to its deleterious effects. There is a growing recognition that substances affect the brain in different ways during adolescence versus adulthood (e.g., [87]) and insufficient research has investigated the unique effects of cannabis during this neurodevelopmentally vulnerable period. Animal studies have also demonstrated greater adverse consequences when cannabinoids are administered to adolescent rats (e.g., [88-91]) and effects on other critical neurodevelopmental periods (prenatal or perinatal) have been discussed above. Since adolescence is a critical period of structural and functional brain maturation [92], further investigation of the neurocognitive impact of cannabis use during this unique neurodevelopmental period is clearly warranted.

MEMORY DYSFUNCTION, VULNERABILITIES AND NEURAL INEFFICIENCY

The cumulative evidence from the above-reviewed research suggests that cannabis use does, in some fashion, impact negatively upon memory function. Greater memory deficits may be apparent in more complex tasks and among heavier cannabis users. The nature of memory deficits in chronic cannabis users is not dissimilar to that observed under acute intoxication. Chronic cannabis users in the unintoxicated state also show impaired immediate, but moreso delayed free recall of verbal information, poor retrieval of information from memory, and difficulties manipulating the contents of working memory. Recognition memory is inconsistently reported to be impaired. Organisational strategies within memory have not been sufficiently well researched. There is limited evidence for poor strategy use in spatial working memory. Several studies employed the CVLT and found similar impairment in cannabis users in learning, on measures of immediate and delayed recall, and sometimes in cued recall and recognition, to studies where other verbal learning tests have been administered to cannabis users. This suggests that providing word lists that were amenable to better organisation to facilitate encoding and recall, did not improve memory performance in cannabis users; either they failed to employ efficient organisational strategies or did not benefit from attempts to do so. Specific encoding manipulation studies, for example that systematically vary depth of encoding or the organisation of stimulus material, have yet to be conducted in chronic cannabis users. In the few studies where primacy/recency effects have been reported, cannabis users have tended to recall fewer words from the beginning of a word list and more words from the end, suggesting a greater reliance on short-term or working memory and poorer encoding. Cumulatively, there is evidence in support of encoding, storage and retrieval deficits in chronic cannabis users. The extent to which attentional and motivational factors may influence memory function has not been well established.

The overall similarity between the acute and chronic effects of cannabis on memory function speaks to potential residual effects associated with a state of chronic intoxication. Dose-, frequency- and recency-related impairment may reflect such a state due to the accumulation of cannabinoids. Where effects have been shown to be related to duration of cannabis use, or to persist beyond a period during which most cannabinoid residues would be eliminated, it is more difficult to ascribe these to a chronically intoxicated state but may reflect alterations to the functioning of the brain that require substantial time to revert to normality. A common theme that has emerged in the literature is a distinct lack of commonality in cataloguing the parameters of cannabis use among participants to obtain adequate estimates of the extent of exposure. A goal of future studies should be to document as much detailed information as possible regarding recent

and historical use of cannabis, quantifying the frequency of episodes of smoking and quantifying dose in terms of a more standardised measure such as cigarette sized joints. Large variation in the potency of cannabis smoked precludes any more precise estimation of actual dose of THC delivered.

There is likely to be a wide range of individual differences in the propensity to develop memory dysfunction associated with long-term heavy cannabis use. The influence of multiple interpersonal factors on resilience to and susceptibility to cognitive impairment deserves greater attention. Such factors may include personality and differing genotypes (e.g., [5, 93, 94]). A predisposition to substance use in general may also confer greater vulnerability to cannabis-related cognitive sequelae [95, 96] and requires further attention in prospective studies. While most recent studies have sought to match groups or otherwise covary potential confounds, and have done so in far better controlled ways than earlier research in this field, greater attention may need to be devoted to factors such as nicotine use and age of onset of cannabis and other substance use. One study has suggested that the use of nicotine may mask cannabis-related impairment [35], but interactions between cannabis use and tobacco, or indeed alcohol, have not been well studied and may be additive, synergistic or interact *via* potential neuroprotective mechanisms (e.g., [56, 97]). While determining the extent of neurocognitive dysfunction that may be attributed to cannabis alone is necessary to inform the mechanism of cannabis effects, this requires exclusion as much as possible of other substance use and the results of such studies may therefore not inform the nature of potential interactions in the general population where use of other substances is common among cannabis users. A similar argument may extend to investigations of very heavy cannabis users, who represent only a proportion of the wider cannabis-using population. As such, continued studies at both the extreme end of the cannabis-use spectrum together with studies of more moderate users and polydrug users are equally worthy, as long as the study designs enable investigation of appropriate questions and precision in hypotheses postulated. The interactive effects of various substances are also well placed for testing in preclinical studies, albeit extrapolation from animal studies to long-term use in humans is problematic.

Most studies have sought to match cannabis users and controls on IQ or else have used IQ as a covariate to determine cannabis-related memory-specific effects by accounting for confounding that may be due to differing cognitive reserves. Where possible, true measures of premorbid IQ obtained prior to the commencement of any cannabis use enable a more direct means of ensuring that later observed memory deficits are not due to poor intellectual functioning independent of subsequent substance use. In the absence of similar memory tests having been also administered premorbidly, memory deficits that are shown to be dose-related (or otherwise associated with cannabis use parameters) may then be interpreted as cannabis-specific sequelae. Few studies have been able to obtain such premorbid measures, however estimates of premorbid IQ and measures of current IQ require further examination in light of evidence suggesting potential interactions between cannabis effects and IQ. For example, cognitive impairments have been found to be greater in cannabis users of lower IQ than in higher IQ users in several studies (e.g., [4, 45]) and where differences between cannabis users and controls have tended to be of lower magnitude these have tended to be in cohorts of higher IQ (literature reviewed above and in [4]). Suggestions that individuals with borderline or low IQ might be even more susceptible to cannabis-induced deficits, particularly of short-term or recent memory have been posited for some time (e.g., [53]), as have suggestions that individuals of higher IQ may be able to compensate for detrimental effects of cannabis use (e.g., [4]), but these factors continue to be under-investigated. Differences between the 28 day abstinence studies of Pope *et al*. [44] and Bolla *et al*. [46] were highlighted above with regard to IQ differences: it is possible that neurocognitive deficits in cannabis users with lower IQ may also be less amenable to recovery following prolonged abstinence.

A general tendency across most studies of cannabis users to recruit participants with above average IQ, possibly due to ease of access to such individuals, in some instances may result in near ceiling performance in both cannabis users and controls, preventing the separation of groups on performance measures. Utilising tasks of sufficient complexity to discriminate between higher-IQ users and controls may be required for a more thorough examination of the impact of cannabis at this top end of intellectual capacity. Higher IQ individuals may be more capable of adopting alternate strategies or of engaging neural circuitry more efficiently during cognitive task performance, and this may either explain or confound some of the neuroimaging findings in cannabis users.

In general, findings of altered brain activation from imaging studies of cannabis users suggest compensatory processes activated to ameliorate cognitive deficits (e.g., [32, 33, 35, 57, 59, 61, 98]). More effortful processing appears to be engaged in an attempt to produce equivalent behavioural outcomes to normal cognitive functioning, sometimes successfully, other times not. Cannabis users may recruit additional brain regions or increase the activation of the same brain regions as controls, thus "working harder" [32], at a "higher neurophysiological cost" [33] to meet the demands of the task, until the demands of this cost or of the task exceed their available resources, at which point, performance deficits would likely become apparent.

Where decreased regional brain activation has also been observed in cannabis users (e.g., [19, 60, 61]), this is generally accompanied by increased activity in other regions, and the hypoactivity is interpreted not as reflecting greater neural efficiency, but as impaired activation of regions known to be involved in performing the task, regions that may include areas of high density cannabinoid receptors. Our knowledge regarding the complex effects of cannabis on resting state brain physiology, perfusion and chemistry is still far from complete, as is the knowledge required for accurate interpretation of brain activation in neuroimaging studies, both normative and of multiple other clinical populations. As such, any simplistic or mechanistic interpretation of increased versus decreased brain activation in neuroimaging studies is not appropriate and further deciphering or speculation is beyond the scope of this review. Further examination of the efficiency of neural connectivity in cannabis users is warranted, with particular attention to interactions between under-

activated and over-activated regions involved in specific tasks.

The engagement of compensatory mechanisms involving increased brain activation and recruitment of additional regions may be at the cost of neural and task-related efficiency. Lower efficiency may manifest in terms of longer latency measures and slower processing speed, which are evident in some of the studies of cannabis users reviewed above (e.g., [36, 37, 42, 46, 54, 55, 79]), but have perhaps not always been sufficiently considered within memory tasks. Cannabis users tend to produce longer latencies during tasks that they may nevertheless complete just as successfully as controls. Individuals with slower processing speed have been shown to activate PFC regions more than those with faster processing speeds, with a greater need for PFC executive control mechanisms to enable successful task performance, reflecting neural inefficiency [99]. Slowed processing speed is thought to underlie age-related cognitive decline, with individuals taking progressively longer to perform most cognitive operations as they age [100]. Some suggest that the nature of impairments associated with cannabis may reflect premature age-related cognitive decline (e.g., [4, 46]). It is also possible that greater cannabis-related memory deficits could manifest with the onset of age-related cognitive decline. The evidence with regard to age-effects interacting with cannabis-effects is convoluted. Some studies find greater impairment in older cannabis users, suggesting that young adults may draw upon greater cognitive reserve to overcome cannabis-related impairment, while other work suggests greater adverse consequences during adolescence. There may be a U-shaped relationship between age and cognitive-effects of cannabis, which would interact with the age of onset of cannabis use.

A recent study [101] found that an increase in the volume of white matter hyperintensities as individuals age correlated strongly with decreases in processing speed. Slower processing speed was considered to be due to a loss of neural efficiency in long association fibres as a result of the progression of periventricular white matter hyperintensities. These fibres connect distal cortical regions in the recruitment of cognitive function. Cognitive decline in other areas, such as memory, is not typically observed until shorter-association fibres (operating within cortical regions) are disrupted [102]. Evidence of white and grey matter changes in cannabis users has been reported in adult and adolescent cannabis users [21, 22] including greater regional density of white matter which could reflect early cognitive decline. Findings in older populations of cannabis users have attributed deficits to the greater years of cannabis exposure (e.g., [43]) but aging may well interact with the cumulative dose of exposure to cannabis.

Insufficient attention has been given to investigating gender differences in the neurocognitive sequelae of cannabis use. Pope and colleagues [45, 103] found some evidence of gender-specific cognitive effects of heavy cannabis use in their generally high-IQ sample: female heavy users remembered fewer items and made more errors than female light users in a visuospatial memory task, whereas male heavy users were more impaired in attentional/interference tasks and in delayed recall. Neubauer *et al.* [104] found task- and sex-specific lower regional brain activation among higher-IQ individuals; for males in a test of spatial ability and for females in a test of verbal ability. Females continue to be greatly under-represented in studies of cannabis users.

The involvement of the cannabinoid system in processes of critical importance to memory function and the effects of acute and chronic administration of cannabinoids on memory-relevant neural substrates are beyond the scope of this paper but have been described elsewhere [1, 5]. That long-term and heavy cannabis use may impact deleteriously upon the neural substrates of efficient memory processing is certainly conceivable, as is a potentially greater impact during critical neurodevelopmental periods. Even transient changes to neurotransmitter systems during such periods have been shown to cause lasting effects in the adult brain that can translate to neurological and psychiatric disorders (e.g., [105]). It is up to future research to continue to isolate more specifically precisely which components of the memory system are most affected, when and how.

CONCLUSION

Sufficient evidence has accumulated from recent studies of cannabis users in the unintoxicated state to conclude that long-term heavy cannabis use is associated with impaired memory function, *associated* being the key operative, given the wide range of studies reviewed in this paper. Our central tenet is that impaired memory function persists beyond the period of acute intoxication and is related to a variety of cannabis use parameters. Deficits have been shown to increase as a function of frequency, duration, dose and age of onset of cannabis use, but the precise parameters of cannabis use that result in memory deficits remain to determined. A number of studies of cannabis users abstinent for reasonably long periods suggest that dysfunctional memory may persist for some time after the acute intoxication, but whether this reflects the action of drug residues causing a state of chronic intoxication or whether a potential alteration of neural function requires a longer period of time to normalise, also remains to be determined. We have discussed a need to better characterise the nature of memory impairment, the specific parameters of cannabis use that are critical in its manifestation, and the propensity for memory deficits to persist. If memory function is impaired for hours or weeks following last use of cannabis, this is important public health information for the millions of cannabis users who operate in such "unintoxicated states" for substantial periods of their daily lives. As such, this impairment of memory function is just as critical to understand as is the very important question of whether recovery of function occurs following prolonged abstinence.

Recent research has made a number of advances in methodology and is beginning to ask pertinent questions but the field is still wide open for further, more detailed investigation. The precise nature of memory deficits in cannabis users has not been fully elucidated: there is evidence for impaired encoding, storage and retrieval. Much can be borrowed from cognitive neuroscience approaches to manipulating memory paradigms to understand more about each of these stages of memory function and how these may be impacted by cannabis use. Further functional neuroimaging studies could be greatly informative in determining the neural substrates underlying memory impairment and the efficiency of neural connections in cannabis users performing memory tasks, and

ERP studies of memory and other cognitive functions may provide fine temporal resolution to examine the specific cognitive processes that are impacted by cannabis use and may manifest in terms of memory impairment. A closer consideration of the memory deficits associated with specific parameters of cannabis use and interactions with age, IQ, personality factors, genetics and neural substrates including the endogenous cannabinoid system, will better inform our understanding of the effects of cannabis on memory, general cognition and brain function and the potential for recovery with abstinence. Combined multidisciplinary research approaches, including cognitive, neuroimaging, neurochemical and genetic, hold much promise for future research in this field.

Key Learning Objectives:

- Critically examine and summarise the major recent findings related to chronic cannabis use and memory.
- Better clarify the nature of memory deficits in cannabis users.
- Identify those factors that may influence the manifestation of memory impairment.

Future Research Questions:

- What are the specific processes within encoding, storage, manipulation and retrieval that are affected by long-term cannabis use and how?
- What parameters of cannabis use are critical in the manifestation of memory impairment?
- What other factors moderate, mediate or otherwise contribute to the evolution of memory deficits in cannabis users?
- What predisposing factors confer a vulnerability to memory deficits that may result from cannabis use?
- Does native cognitive ability (premorbid IQ) contribute to the successful use of compensatory mechanisms by chronic cannabis users?
- Are alternate neural structures recruited in this process at the cost of efficiency and, consequently, processing speed?
- How does memory impairment in cannabis users interact with the neurodevelopmental stage at which heavy cannabis use is commenced and with normal age-related cognitive decline?
- What is the time course (and neural substrates) of potential recovery of function?

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REFERENCES

[1] Ranganathan M, D'Souza DC. The acute effects of cannabinoids on memory in humans: a review. Psychopharmacology (Berl) 2006; 188: 425-44.

[2] Fletcher PC, Honey GD. Schizophrenia, ketamine and cannabis: Evidence of overlapping memory deficits. Trends Cogn Sci 2006; 10: 167-74.

[3] Iversen L. Cannabis and the brain. Brain 2003; 126: 1252-70.

[4] Solowij N. Cannabis and Cognitive Functioning. Cambridge, Cambridge University Press. 1998.

[5] Solowij N, Michie PT. Cannabis and cognitive dysfunction: Parallels with endophenotypes of schizophrenia? J Psychiatry Neurosci 2007; 32: 30-52.

[6] Grant I, Gonzalez R, Carey CL, Natarajan L, Wolfson T. Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study. J Int Neuropsychol Soc 2003; 9: 679-89.

[7] Egerton A, Allison C, Brett RR, Pratt JA. Cannabinoids and prefrontal cortical function: Insights from preclinical studies. Neurosci Biobehav Rev 2006; 30: 680-95.

[8] Alger BE. Endocannabinoid identification in the brain: Studies of breakdown lead to breakthrough, and there may be NO hope. Sci. STKE 2005; 309: pe51.

[9] Chevaleyre V, Takahashi KA, Castillo PE. Endocannabinoid-mediated synaptic plasticity in the CNS. Annu Rev Neurosci 2006; 29: 37-76.

[10] Hampson RE, Deadwyler SA. Cannabinoids reveal the necessity of hippocampal neural encoding for short-term memory in rats. J Neurosci 2000; 20: 8932-42.

[11] Hoffman AF, Oz M, Caulder T, Lupica CR. Functional tolerance and blockade of long-term depression at synapses in the nucleus accumbens after chronic cannabinoid exposure. J Neurosci 2003; 23: 4815-20.

[12] Mato S, Chevaleyre V, Robbe D, Pazos A, Castillo PE, Manzoni OJ. A single in-vivo exposure to Delta 9THC blocks endocannabinoid-mediated synaptic plasticity. Nat Neurosci 2004; 7: 585-6.

[13] Tselnicker I, Keren O, Hefetz A, Pick CG, Sarne Y. A single low dose of tetrahydrocannabinol induces long-term cognitive deficits. Neurosci Lett 2007; 411: 108-11.

[14] Wilson RI, Nicoll RA. Neuroscience - Endocannabinoid signaling in the brain. Science 2002; 296: 678-82.

[15] Howlett AC, Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Porrino LJ. Cannabinoid physiology and pharmacology: 30 years of progress. Neuropharmacology 2004; 47: 345-58.

[16] Piomelli D. The molecular logic of endocannabinoid signalling. Nat Rev Neurosci 2003; 4: 873-84.

[17] Sim-Selley LJ. Regulation of cannabinoid CB1 receptors in the central nervous system by chronic cannabinoids. Crit Rev Neurobiol 2003; 15: 91-118.

[18] Block RI, O'Leary DS, Ehrhardt JC, *et al.* Effects of frequent marijuana use on brain tissue volume and composition. Neuroreport 2000; 11: 491-6.

[19] Jager G, Van Hell HH, De Win MML, *et al.* Effects of frequent cannabis use on hippocampal activity during an associative memory task. Eur Neuropsychopharmacol 2007; 17: 289-97.

[20] Tzilos GK, Cintron CB, Wood JBR, *et al.* Lack of hippocampal volume change in long-term heavy cannabis users. Am J Addict 2005; 14: 64-72.

[21] Wilson W, Mathew R, Turkington T, Hawk T, Coleman RE, Provenzale J. Brain morphological changes and early marijuana use: A magnetic resonance and positron emission tomography study. J Addict Dis 2000; 19: 1-22.

[22] Matochik JA, Eldreth DA, Cadet JL, Bolla KI. Altered brain tissue composition in heavy marijuana users. Drug Alcohol Depend 2005; 77: 23-30.

[23] Yücel M, Solowij N, Respondek C, *et al.* Regional brain abnormalities associated with heavy long-term cannabis use. in revision.

[24] Hermann D, Sartorius A, Welzel H, *et al.* Dorsolateral prefrontal cortex N-acetylaspartate/total creatine (NAA/tCr) loss in male recreational cannabis users. Biol Psychiatry 2007; 61: 1281-9.

[25] Chan GCK, Hinds TR, Impey S, Storm DR. Hippocampal neurotoxicity of Delta(9)-tetrahydrocannabinol. J Neurosci 1998; 18: 5322-32.

[26] Landfield PW, Cadwallader LB, Vinsant S. Quantitative changes in hippocampal structure following long term exposure to delta-9-tetrahydrocannabinol - Possible mediation by glucocorticoid systems. Brain Res 1988; 443: 47-62.

[27] Lawston J, Borella A, Robinson JK, Whitaker-Azmitia PM. Changes in hippocampal morphology following chronic treatment with the synthetic cannabinoid WIN 55,212-2. Brain Res 2000; 877: 407-10.

[28] Scallet AC, Uemura E, Andrews A, *et al.* Morphometric studies of the rat hippocampus following chronic delta-9-tetrahydrocannabinol (THC). Brain Res 1987; 436: 193-8.

[29] D'Souza DC, Perry E, MacDougall L, *et al.* The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. Neuropsychopharmacology 2004; 29: 1558-72.

[30] Ilan AB, Smith ME, Gevins A. Effects of marijuana on neurophysiological signals of working and episodic memory. Psychopharmacology (Berl) 2004; 176: 214-22.

[31] Lane SD, Cherek DR, Lieving LM, Tcheremissine OV. Marijuana effects on human forgetting functions. J Exp Anal Behav 2005; 83: 67-83.

[32] Kanayama G, Rogowska J, Pope HG, Gruber SA, Yurgelun-Todd DA. Spatial working memory in heavy cannabis users: a functional magnetic resonance imaging study. Psychopharmacology (Berl) 2004; 176: 239-47.

[33] Jager G, Kahn RS, Van den Brink W, Van Ree JM, Ramsey NF. Long-term effects of frequent cannabis use on working memory and attention: an fMRI study. Psychopharmacology (Berl) 2006; 185: 358-68.

[34] Jacobsen LK, Mencl WE, Westerveld M, *et al*. Impact of cannabis use on brain function in adolescents. Ann NY Acad Sci 2004;1021:384-90.

[35] Jacobsen LK, Pugh KR, Constable RT, Westerveld M, Mencl WE. Functional correlates of verbal memory deficits emerging during nicotine withdrawal in abstinent adolescent cannabis users. Biol Psychiatry 2007; 61: 31-40.

[36] Wadsworth EJK, Moss SC, Simpson SA, Smith AP. Cannabis use, cognitive performance and mood in a sample of workers. J Psychopharmacol (Oxf) 2006; 20: 14-23.

[37] Harvey MA, Sellman JD, Porter RJ, Frampton CM. The relationship between non-acute adolescent cannabis use and cognition. Drug Alcohol Rev 2007; 26: 309-19.

[38] Respondek C, Solowij N, Ward PB. An investigation of neurocognitive performance, verbal learning ability and fMRI indices of cognitive functioning in long-term cannabis users. Aust J Psychol 2004; 56: 219.

[39] Curran HV, Brignell C, Fletcher S, Middleton P, Henry J. Cognitive and subjective dose-response effects of acute oral Delta(9)-tetrahydrocannabinol (THC) in infrequent cannabis users. Psychopharmacology (Berl) 2002; 164: 61-70.

[40] Lezak MD, Howieson DB, Loring DW, Hannay HJ, Fischer JS. Neuropsychological assessment (4th ed.). New York, NY, Oxford University Press. 2004.

[41] Schmidt M. Rey Auditory and Verbal Learning Test: A handbook. Los Angeles, CA, Western Psychological Services. 1996.

[42] Messinis L, Kyprianidou A, Malefaki S, Papathanasopoulos P. Neuropsychological deficits in long-term frequent cannabis users. Neurology 2006; 66: 737-9.

[43] Solowij N, Stephens RS, Roffman RA, *et al*. Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA 2002; 287: 1123-31.

[44] Pope HG, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D. Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry 2001; 58: 909-15.

[45] Pope HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. JAMA 1996; 275: 521-7.

[46] Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL. Dose-related neurocognitive effects of marijuana use. Neurology 2002; 59: 1337-43.

[47] Fletcher JM, Page J, Francis DJ, *et al*. Cognitive correlates of long-term cannabis use in Costa Rican men. Arch Gen Psychiatry 1996; 53: 1051-7.

[48] Pope HG, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D. Early-onset cannabis use and cognitive deficits: what is the nature of the association? Drug Alcohol Depend 2003; 69: 303-10.

[49] Ehrenreich H, Rinn T, Kunert HJ, *et al*. Specific attentional dysfunction in adults following early start of cannabis use. Psychopharmacology (Berl) 1999; 142: 295-301.

[50] Huestegge L, Radach R, Kunert HJ. Effects of long-term cannabis consumption with early age of onset on oculomotor control and visual information processing. 2004 Symposium on the Cannabinoids; 2004 Burlington, VT, International Cannabinoid Research Society. 2004; 88.

[51] Huestegge L, Radach R, Kunert HJ, Heller D. Visual search in long-term cannabis users with early age of onset. Prog Brain Res 2002;140:377-94.

[52] Kempel P, Lampe K, Parnefjord R, Hennig J, Kunert HJ. Auditory-evoked potentials and selective attention: Different ways of information processing in cannabis users and controls. Neuropsychobiology 2003; 48: 95-101.

[53] Schwartz RH, Gruenewald PJ, Klitzner M, Fedio P. Short-term memory impairment in cannabis-dependent adolescents. Am J Dis Child 1989; 143: 1214-9.

[54] Medina KL, Hanson KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF. Neuropsychological functioning in adolescent marijuana users: Subtle deficits detectable after a month of abstinence. J Int Neuropsychol Soc 2007; 13: 807-20.

[55] Fried PA, Watkinson B, Gray R. Neurocognitive consequences of marihuana - a comparison with pre-drug performance. Neurotoxicol Teratol 2005; 27: 231-9.

[56] Medina KL, Schweinsburg AD, Cohen-Zion M, Nagel BJ, Tapert SF. Effects of alcohol and combined marijuana and alcohol use during adolescence on hippocampal volume and asymmetry. Neurotoxicol Teratol 2007; 29: 141-52.

[57] Schweinsburg AD, Schweinsburg BC, Cheung EH, Brown GG, Brown SA, Tapert SF. fMRI response to spatial working memory in adolescents with comorbid marijuana and alcohol use disorders. Drug Alcohol Depend 2005; 79: 201-10.

[58] Lyons MJ, Bar JL, Panizzon MS, *et al*. Neuropsychological consequences of regular marijuana use: a twin study. Psychol Med 2004; 34: 1239-50.

[59] Block RI, O'Leary DS, Hichwa RD, *et al*. Effects of frequent marijuana use on memory-related regional cerebral blood flow. Pharmacol Biochem Behav 2002; 72: 237-50.

[60] Bolla KI, Eldreth DA, Matochik JA, Cadet JL. Neural substrates of faulty decision-making in abstinent marijuana users. Neuroimage 2005; 26: 480-92.

[61] Eldreth DA, Matochik JA, Cadet JL, Bolla KI. Abnormal brain activity in prefrontal brain regions in abstinent marijuana users. Neuroimage 2004; 23: 914-20.

[62] Croft RJ, Mackay AJ, Mills ATD, Gruzelier JGH. The relative contributions of ecstasy and cannabis to cognitive impairment. Psychopharmacology (Berl) 2001; 153: 373-9.

[63] Parrott AC, Milani RM, Parmar R, Turner JJD. Recreational ecstasy/MDMA and other drug users from the UK and Italy: Psychiatric symptoms and psychobiological problems. Psychopharmacology (Berl) 2001; 159: 77-82.

[64] Rodgers J. Cognitive performance amongst recreational users of "ecstasy". Psychopharmacology (Berl) 2000; 151: 19-24.

[65] Gouzoulis-Mayfrank E, Daumann J. The confounding problem of polydrug use in recreational ecstasy/MDMA users: a brief overview. J Psychopharmacol 2006; 20: 188-93.

[66] Rodgers J, Buchanan T, Scholey AB, Heffernan TM, Ling J, Parrott A. Differential effects of Ecstasy and cannabis on self-reports of memory ability: a web-based study. Hum Psychopharmacol Clin Exp 2001; 16: 619-25.

[67] Simon NG, Mattick RP. The impact of regular ecstasy use on memory function. Addiction 2002; 97: 1523-9.

[68] Parrott AC, Milani RM. Cannabis, ecstasy/MDMA and memory: A commentary on Simon & Mattick's recent study. Addiction 2003; 98: 1003-4.

[69] Quednow BB, Jessen F, Kuhn KU, Maier W, Daum I, Wagner M. Memory deficits in abstinent MDMA (ecstasy) users: neuropsychological evidence of frontal dysfunction. J Psychopharmacol 2006; 20: 373-84.

[70] Fried P, Watkinson B, James D, Gray F. Current and former marijuana use: preliminary findings of a longitudinal study of effects on IQ in young adults. Can Med Assoc J 2002; 166: 887-91.

[71] Richardson GA, Ryan C, Willford J, Day NL, Goldschmidt L. Prenatal alcohol and marijuana exposure: Effects on neuropsychological outcomes at 10 years. Neurotoxicol Teratol 2002; 24: 309-20.

[72] Fried PA, Watkinson B. Differential effects on facets of attention in adolescents prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 2001; 23: 421-30.

[73] Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on visuospatial working memory: An fMRI study in young adults. Neurotoxicol Teratol 2006; 28: 286-95.

[74] Leech SL, Richardson GA, Goldschmidt L, Day NL. Prenatal substance exposure: Effects on attention and impulsivity of 6-year-olds. Neurotoxicol Teratol 1999; 21: 109-18.

[75] Goldschmidt L, Richardson GA, Cornelius MD, Day NL. Prenatal marijuana and alcohol exposure and academic achievement at age 10. Neurotoxicol Teratol 2004; 26: 521-32.

[76] Huizink AC, Mulder EJH. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. Neurosci Biobehav Rev 2006; 30: 24-41.

[77] Fried PA, Watkinson B. 36-month and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. J Dev Behav Pediatr 1990; 11: 49-58.
[78] Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 1998; 20: 293-306.
[79] Fried PA, Watkinson B, Gray R. Differential effects on cognitive functioning in 13-to 16-year-olds prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 2003; 25: 427-36.
[80] Day NL, Richardson GA, Goldschmidt L, *et al.* Effect of prenatal marijuana exposure on the cognitive-development of offspring at age-3. Neurotoxicol Teratol 1994; 16: 169-75.
[81] Fride E. The endocannabinoid-CB1 receptor system in pre- and postnatal life. Eur J Pharmacol 2004; 500: 289-97.
[82] Fride E. The endocannabinoid-CB receptor system: Importance for development and in pediatric disease. Neuroendocrinol Lett 2004; 25: 24-30.
[83] Mereu G, Fa M, Ferraro L, *et al*. Prenatal exposure to a cannabinoid agonist produces memory deficits linked to dysfunction in hippocampal long-term potentiation and glutamate release. Proc Natl Acad Sci USA 2003; 100: 4915-20.
[84] Chang L, Yakupov R, Cloak C, Ernst T. Marijuana use is associated with a reorganized visual-attention network and cerebellar hypoactivation. Brain 2006; 129: 1096-112.
[85] Stefanis NC, Delespaul P, Henquet C, Bakoula C, Stefanis CN, Van Os J. Early adolescent cannabis exposure and positive and negative dimensions of psychosis. Addiction 2004; 99: 1333-41.
[86] Caspi A, Moffitt TE, Cannon M, *et al.* Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene X environment interaction. Biol Psychiatry 2005; 57: 1117-27.
[87] White AM, Swartzwelder HS. Hippocampal function during adolescence - A unique target of ethanol effects. Ann N Y Acad Sci 2004; 1021: 206-20.
[88] O'Shea M, Singh ME, McGregor IS, Mallet PE. Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats. J Psychopharmacol 2004; 18: 502-8.
[89] Pistis M, Perra S, Pillolla G, Melis M, Muntoni AL, Gessa GL. Adolescent exposure to cannabinoids induces long-lasting changes in the response to drugs of abuse of rat midbrain dopamine neurons. Biol Psychiatry 2004; 56: 86-94.
[90] Schneider M, Koch M. Chronic pubertal, but not adult chronic cannabinoid treatment impairs sensorimotor gating, recognition memory, and the performance in a progressive ratio task in adult rats. Neuropsychopharmacology 2003; 28: 1760-9.
[91] Schneider M, Koch M. Deficient social and play behavior in juvenile and adult rats after neonatal cortical lesion: Effects of chronic pubertal cannabinoid treatment. Neuropsychopharmacology 2005; 30: 944-57.
[92] Paus T. Mapping brain maturation and cognitive development during adolescence. Trends Cogn Sci 2005; 9: 60-8.
[93] Agrawal A, Lynskey MT. The genetic epidemiology of cannabis use, abuse and dependence. Addiction 2006; 101: 801-12.
[94] Lynskey MI, Grant JD, Nelson EC, *et al*. Duration of cannabis use - a novel phenotype? Addict Behav 2006; 31: 984-94.
[95] Yücel M, Lubman DI, Solowij N, Brewer WJ. Neurobiological and neuropsychological pathways into substance use and addictive behaviour. In Wood SJ, Allen NB, Pantelis C Eds, The Neuropsychology of Mental Illness. Cambridge, Cambridge University Press in press.
[96] Yücel M, Lubman DI, Solowij N, Brewer W. Understanding drug addiction: A neuropsychological perspective. Aust N Z J Psychiatry in press.
[97] Parrott A, Gouzoulis-Mayfrank E, Rodgers J, Solowij N. Ecstasy/MDMA and cannabis: the complexities of their interactive neuropsychobiological effects. J Psychopharmacol 2004; 18: 579-80.
[98] Jager G, Van Hell HH, De Win MM, *et al.* Altered brain activity in cannabis users during associative memory: an fMRI study. Eur Neuropsychopharmacol 2005; 15: S585-S6.
[99] Rypma B, Berger JS, Prabhakaran V, *et al.* Neural correlates of cognitive efficiency. Neuroimage 2006; 33: 969-79.
[100] Sliwinski M, Buschke H, Kuslansky G, Senior G, Scarisbrick D. Proportional slowing and addition speed in old and young-adults. Psychol Aging 1994; 9: 72-80.
[101] van den Heuvel DMJ, ten Dam VH, de Craen AJM, *et al*. Increase in periventricular white matter hyperintensities parallels decline in mental processing speed in a non-demented elderly population. J Neurol Neurosurg Psychiatry 2006; 77: 149-53.
[102] Tisserand DJ, Jolles J. On the involvement of prefrontal networks in cognitive ageing. Cortex 2003; 39: 1107-28.
[103] Pope HG, Jacobs A, Mialet JP, YurgelunTodd D, Gruber S. Evidence for a sex-specific residual effect of cannabis on visuospatial memory. Psychother Psychosom 1997; 66: 179-84.
[104] Neubauer AC, Grabner RH, Fink A, Neuper C. Intelligence and neural efficiency: Further evidence of the influence of task content and sex on the brain - IQ relationship. Cogn Brain Res 2005; 25: 217-25.
[105] Ansorge MS, Zhou MM, Lira A, Hen R, Gingrich JA. Early-life blockade of the 5-HT transporter alters emotional behavior in adult mice. Science 2004; 306: 879-81.

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