Cognitive abnormalities and *cannabis* use

Anormalidades cognitivas no uso da cannabis

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Abstract

Objective: Evidence that *cannabis* use impairs cognitive function in humans has been accumulating in recent decades. The purpose of this overview is to update knowledge in this area with new findings from the most recent literature. **Method:** Literature searches were conducted using the Web of Science database up to February 2010. The terms searched were: "cannabi*" or "marijuana", and "cogniti*" or "memory" or "attention" or "executive function", and human studies were reviewed preferentially over the animal literature. **Discussion:** *Cannabis* use impairs memory, attention, inhibitory control, executive functions and decision making, both during the period of acute intoxication and beyond, persisting for hours, days, weeks or more after the last use of *cannabis*. Pharmacological challenge studies in humans are elucidating the nature and neural substrates of cognitive changes associated with various cannabinoids. Long-term or heavy *cannabis* use appears to result in longer-lasting cognitive abnormalities and possibly structural brain alterations. Greater adverse cognitive effects are associated with *cannabis* use commencing in early adolescence. **Conclusion:** The endogenous cannabinoid system is involved in regulatory neural mechanisms that modulate processes underlying a range of cognitive functions that are impaired by *cannabis*. Deficits in human users most likely therefore reflect neuroadaptations and altered functioning of the endogenous cannabinoid system.

Descriptors: *Cannabis*; Cannabinoids; Cognition; Physiological processes/drug effects; Neurobehavioral manifestations

Resumo

Objetivo*: Evidências de que o uso de* cannabis *prejudica funções cognitivas em humanos têm-se acumulado nas décadas recentes. O propósito desta revisão é o de atualizar o conhecimento nesta área com novos achados a partir da literatura mais recente.* ***Método:*** *As buscas na literatura foram realizadas utilizando-se o banco de dados Web of Science até fevereiro de 2010. Foram buscados os termos "*cannabi**"* ou "*marijuana*" e "*cogniti**"* ou "*memory*" ou "*attention*" ou "*executive function*", e os estudos em humanos foram revisados preferencialmente em relação aos estudos em animais.* ***Discussão:*** *O uso de* cannabis *prejudica a memória, a atenção, o controle inibitório, as funções executivas e a tomada de decisões, tanto durante como após o período de intoxicação aguda, persistindo por horas, dias, semanas ou mais após o último uso. Os estudos de desafio farmacológico em humanos estão elucidando a natureza e os substratos neurais das alterações cognitivas associadas a vários canabinoides. O uso pesado ou de longo prazo de* cannabis *parece resultar em anormalidades cognitivas mais duradouras e possivelmente em alterações cerebrais estruturais. Efeitos cognitivos adversos maiores estão associados ao uso de* cannabis *quando este começa no início da adolescência.* ***Conclusão****: O sistema canabinoide endógeno está envolvido nos mecanismos de regulação neural que modulam os processos subjacentes a uma gama de funções cognitivas que estão prejudicadas pela* cannabis*. Os déficits em usuários humanos muito provavelmente refletem, portanto, neuroadaptações e o funcionamento alterado do sistema canabinoide endógeno.*

Descritores*: Cannabis; Canabinoides; Cognição; Processos fisiológicos/efeitos de drogas; Manifestações neurocomportamentais*

Introduction

Concerns regarding the adverse consequences of *cannabis* use continue to grow. This is well founded given that *cannabis* is the most widely used illicit substance in the world, with use often beginning in adolescence, a key period for neural and psychosocial development.

While the cognitively impairing effects of *cannabis* during acute intoxication have been acknowledged for some time, an accumulating body of evidence indicates that long-term or heavy *cannabis* use results in definite but subtle cognitive impairments that persist beyond the period of acute intoxication. The extent to which such deficits persist in the longer-term remains a controversial area for debate within the field of human *cannabis* research. Some studies demonstrate cognitive dysfunction in *cannabis* users during intoxication and for several hours following smoking,[1,2] others show impairment for a few days,[3,4] and yet others have shown lasting impairments for more than a month

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following cessation of use.[5] Understanding the persistence of cognitive deficits associated with *cannabis* use is not a simple matter of organising the literature by cognitive domains to determine which kinds of tasks may elicit shorter- or longer-lasting effects of *cannabis*, because comparisons across studies are very much confounded by varying levels of exposure to *cannabis* (if not other substances as well). Elucidating the nature and extent of cognitive dysfunction resulting from *cannabis* use will require significant further research to determine the parameters of use that result in cognitive deficits across a range of tasks and cognitive domains.

Various parameters of *cannabis* use and their relationship to cognitive impairment can be examined when looking at deficits that persist for a period of 24 hours or longer. Relationships between cognitive performance and frequency of *cannabis* use may indicate a residual effect of acute or chronic intoxication that would likely dissipate with the reduction or cessation of use. Associations with the dose of *cannabis* used might similarly reflect a residual effect, or in the case of cumulative dose of exposure, may indicate more enduring dose-related brain changes. Associations with duration of use imply a more enduring impairment, rather than one resulting from cannabinoid residues, and one which likely reflects actual alterations to brain function over the long term and gradual neuroadaptation. The age of onset of *cannabis* use has received much attention in recent years. This is in light of evidence that the age of initiation of *cannabis* use is decreasing,[6-9] with concerns regarding exposure during the critical neurodevelopmental period of early adolescence and a recognition that the adolescent brain is more susceptible to drug insult.[10]

The extent to which cognitive deficits resulting from *cannabis* may be reversible upon cessation of use is inconclusive. One study suggests function is recovered within one month of abstinence,[3] another study indicates that recovery does not occur after 28 days of monitored abstinence,[5] and others suggest that partial recovery may occur.[11,12] With the recent reporting of regional structural brain changes in long-term heavy *cannabis* users (reduction in hippocampal and amygdala volumes),[13] research has yet to examine the extent to which such alterations may be reversible with abstinence.

Cognitive impairment in *cannabis* users is most often detected in memory, attention and inhibitory control and executive functions. There is no doubt that the endogenous cannabinoid system plays a critical role in these functions and that their disruption by acute *cannabis* administration is cannabinoid receptor (CB_1) mediated. Novel and specific roles of different cannabinoids in *cannabis* plant matter [eg. THC versus cannabidiol (CBD)] are increasingly being elucidated. We have previously reviewed the literature to 2007 in the context of the similarity between cognitive deficits in *cannabis* users and those observed in schizophrenia[14] and as specific to memory function.[15] This paper will update our knowledge with evidence from the most recent studies of cognitive function in human users with a focus on the long-term effects of *cannabis* use. We also consider recent research elucidating the effects of acute *cannabis* administration in humans, studies of brain structure and function, and in brief, evidence from animal studies of acute and chronic administration of cannabinoids. We group the studies reviewed according to the primary cognitive domains identified as being affected by *cannabis*: attention, inhibition, working memory/executive functions and verbal memory.

Method

Literature searches were conducted using the Web of Science database from January 2007 through February 2010 to update previous reviews performed by the authors with select literature to incorporate in this specific overview of the area. The terms searched were: "*cannabi**" or "marijuana" and "cogniti*" or "memory" or "attention" or "executive function" and human literature was reviewed preferentially over animal literature.

Discussion

1. Acute effects on human cognition

During the acute intoxication, *cannabis* induces perceptual distortions, and impairs memory and concentration. Recent years have seen a revival of interest in examining the acute effects of cannabinoids on cognition in humans, with greater application of prospective, double-blind, placebo-controlled cross-over designs, and with particular interest in relation to understanding the psychotomimetic effects of *cannabis*.

A range of attentional processes are impaired by *cannabis* acutely. Impaired performance on sustained attention (eg. on continuous performance tasks), selective, focused and divided attention tasks, as well as in preattentive sensory memory have been demonstrated following acute doses of *cannabis* (THC or *cannabis* extract) to humans.[16-19] Impaired performance, in terms of accuracy, increased error rates and slowed reaction times, has been shown to be dose-related in some studies.[18] Tolerance may develop to some of the acute effects of *cannabis* in regular users. For example, Ramaekers et al. found impaired performance on a divided attention task following high dose 500µg/kg THC only in occasional but not heavy users, whereas both occasional and heavy users exhibited inhibitory control deficits in a Stop Signal task.[19] Altered inhibitory processing is evident following acute intoxication, in particular through impulsive responding.[20] Hart et al. found evidence of a greater incidence of premature responding during acute intoxication in a range of tasks, discussing this in terms of failures of inhibitory control over inappropriate responses.[21] Acute administration of THC increased impulsive responding on a Stop Signal Task, but did not affect Go/NoGo task performance in one study,[20] although McGuire et al. showed in an imaging study that THC attenuated activation in the right inferior frontal cortex during a Go/NoGo task.[22]

O'Leary et al. showed that 20mg of THC had dramatic effects in occasional *cannabis* users on regional cerebral blood flow during the performance of a dichotic auditory selective attention task, but that these changes were not task-related.[17] Acute effects of cannabinoids on electrophysiology have been demonstrated in infrequent *cannabis* users for the mismatch negativity (MMN) component of the event-related potential (ERP) (MMN being

an index of preattentive sensory memory)[23] and the P300 component (an index of the allocation of attentional resources and updating of memory traces).[24] Interestingly, Juckel et al.[23] found no effect of a relatively low dose of THC alone (10mg) on the mismatch negativity but an enhancement of the component when THC was co-administered with 5.4mg CBD, pertinent to the proposed antipsychotic properties of CBD. Mismatch negativity is diminished in people with schizophrenia.[25,26] On the other hand, Roser et al.[24] showed with the same doses that both THC alone and THC with CBD reduced the auditory P300 amplitude, which is also known to be reduced in schizophrenia and other clinical populations.

D'Souza et al. conducted a rigorous investigation of the effects of intravenous THC administered to healthy volunteers who had experience with *cannabis* use but who were not heavy users.[27] THC induced transient positive and negative schizophrenia-like symptoms and impaired working memory, verbal memory, distractibility and verbal fluency. Similarly, Morrison et al. report induction of positive psychotic symptoms and deficits in verbal episodic memory and executive function following administration of intravenous THC.[28] 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. Deficits in verbal learning and memory are perhaps the most robust impairments associated with acute *cannabis* use[2,16,27-29] and impaired immediate and delayed free recall of information was emphasised in one recent review of the acute effects of *cannabis* on memory function,[29] while another described 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.[30]

Ilan et al. found that acute intoxication resulted in greater intrusion errors during recognition memory, and those subjects who were most affected by *cannabis* showed a reduced ERP difference between previously studied words and new distractor words, suggesting a disruption of neural mechanisms underlying memory for recent study episodes.[16] Curran et al.[2] found that a high dose of THC (15mg) resulted in no learning occurring over a 3-trial selective reminding task, while Bhattacharyya and McGuire et al. reported a series of neuroimaging studies of the effects of orally administered 10mg THC or 600mg CBD on the neural bases of verbal learning.[22,31,32] They found that the effects of *cannabis* on verbal learning were mediated through its influence on left temporal activity (particularly parahippocampal), with modulation also of medial prefrontal and anterior cingulate activity, during encoding or retrieval of information. These studies also elucidated the neural basis of the anxiogenic or anxiolytic effects of THC and CBD, respectively, as pertinent to understanding the propensity for *cannabis* to induce psychotic symptoms. Other recent neuroimaging studies of acute administration effects of cannabioids have been reviewed by Martin-Santos et al.[33]

Working memory is disrupted by acute *cannabis* use.[16,27,34] Performance, electroencephalogram (EEG), and ERP measures were impaired on a spatial *n-back* task after smoked *cannabis*,[16] and acute administration of THC impaired delay-dependent discrimination within working memory in a delayed matching to sample task.[34] Conversely, in another study, acute THC administration was found to spare working memory but impair episodic memory in infrequent *cannabis* users, with no residual effects 24 or 48 hours later.[21] Regular but infrequent *cannabis* users showed dose-dependently impaired performance (greater errors) on a Sternberg memory task following acute administration of THC[17] and these have been associated with reduced frontal-midline EEG theta power.[35]

Thus, further evidence has accumulated for a disruption of attention, memory, and inhibitory control following acute administration of *cannabis* to humans, with some elucidation of the neural substrates of these effects, including evidence of differential effects of different cannabinoids (such as THC and CBD). It appears also that the response to acute cannabinoid administration is mediated by *cannabis* use history and the development of tolerance to the acute effects in some cognitive tasks, but insufficient research has determined in any systematic way the parameters of *cannabis* use that lead to the development of tolerance, the doses that may or may not elicit impaired performance in regular users, or the cognitive tasks that are amenable to tolerance. For example, Boucher et al. showed that impairments in spatial working memory in rats are resistant to tolerance after extended administration of THC.[36] Nor has research determined whether or how regular users may develop compensatory strategies during the acute intoxication to facilitate performance that might otherwise be impaired. For example, in a risky decision-making task, Rogers et al. showed a reduction of risky behaviour following low dose sublingual administration of THC to healthy young adults (not regular *cannabis* users), with an adoption of more cautious cognitive strategies to compensate for the perceived disruption of effective decision making by *cannabis*.[37] Regular users, due to their greater experience with *cannabis*, might be more likely to develop alternate compensatory strategies, but this hypothesis remains to be tested. Another study of decision making as assessed by the Iowa Gambling Task found no disruption to risky behaviour, only a slowing of performance, in daily *cannabis* users during acute intoxication.[38]

2. Long-term effects on human cognition

Studies of long-term and heavy *cannabis* users, tested in the unintoxicated state, have continued to investigate residual or persistent effects of *cannabis* on cognitive function, with gradually greater control over confounds, and more attention to the parameters of *cannabis* use.

1) Attention

Sustained attention, most often measured by continuous performance tasks (CPTs), is inconsistently impaired. Pope et al. found performance on CPTs to be insensitive to chronic *cannabis* use in adults,[3] but Jacobsen et al. found that adolescent *cannabis* users made significantly more errors than non-using controls and increased errors trended toward an association

with greater exposure to *cannabis*.[39] A recent study examined sustained attention in 132 long-term *cannabis* users divided into an early onset group (those who had commenced *cannabis* use prior to the age of 15 years) and a late onset group (≥ 15 years).[40] Early onset users performed significantly worse on the sustained attention task, with no performance differences between the late onset group and controls. However, even in the absence of overt performance deficits, lower glucose metabolism in orbitofrontal, temporal, hippocampal and parahippocampal regions was observed during CPT performance in regular *cannabis* users.[41] A study of preattentive pre-pulse inhibition (PPI) attributed poor performance by chronic *cannabis* users to deficits in sustained attention, which were also associated with greater frequency of *cannabis* use.[42]

Selective and divided attention deficits in chronic *cannabis* users have been shown to be related to duration, frequency, and age of onset of use.[11,12,43-48] Long-term users have difficulty filtering out irrelevant information, a deficit that became more pronounced the longer that *cannabis* had been used.[11,12,43,44,46] Further, only partial recovery was evident after a mean abstinence period of two years and no improvement with increasing months of abstinence, suggesting partial recovery may occur relatively soon after cessation of use and enduring impairment may reflect longer-lasting neuroadaptations.[11,12] Early onset of *cannabis* use (i.e. prior to 16 years) was a strong predictor of attentional deficits during adulthood,[47] and even relatively light use of once a week was related to some attentional dysfunction in young adults.[48] Heavy users also showed a slowing of information processing during selective attention, as indexed by the P300 component which became increasingly delayed the more frequently that *cannabis* was used.[44,46] This research provided evidence of differential deficits associated with frequency versus duration of *cannabis* use, reflecting shorter- versus longer-lasting effects.[44,46] P300 amplitude, thought to reflect the allocation of attentional resources and reflect inhibitory processes, has also been found to be reduced in early onset users,[49] as well as in adult *cannabis* users.[43,46]

2) Inhibition

As cited above under acute effects, impaired inhibitory processing can be assessed through behavioural tasks such as the Stroop, Go/NoGo and a variety of decision-making and gambling tasks, and is also impaired in long-term *cannabis* users.[4,5,50-55] Such tasks require the selection of an appropriate response whilst simultaneously inhibiting the inappropriate response. It has been suggested that the endocannabinoid system may modulate dopaminergic prefrontal cortical and accumbal activity and contribute to inappropriate incentive salience to irrelevant stimuli, which may underlie attentional and inhibitory processing and decision-making deficits.[14,56,57] Imaging studies show altered dorsolateral prefrontal cortical (DLPFC) and anterior cingulate (ACC) activation during the interference condition of the Stroop Task, despite reasonable task performance in *cannabis* users[54] and 1-month abstinent *cannabis* users.[50] Performance on the Stroop task is inconsistently impaired in chronic *cannabis* users,[3-5,40,46] but poorer performance has been associated with various parameters of use (duration, dose, early onset)[4,5,40,58] that may interact with low IQ,[5] and with altered electrophysiology.[58] Similarly, in a Go/NoGo task, adolescent *cannabis* users' task performance was adequate following one month abstinence, however altered activation was observed in frontal and parietal brain regions, with users requiring increased neural effort during the inhibition condition to maintain performance levels.[59] In chronic adult users also with adequate inhibitory control performance, commission errors increased and a diminished capacity for behaviour monitoring and error-awareness was associated with hypoactivity in the ACC and right insula.[55]

3) Working memory and other executive functions

Working memory is the temporary encoding and manipulation of information that is a core component of executive functions of cognition; the involvement of the cannabinoid system in working memory has been well documented.[14,57] Executive function tasks have been found to be impaired in both acute and chronic *cannabis* use (e.g. verbal fluency, Wisconsin Card Sorting Task, Ravens Progressive Matrices, Tower of London),[3-5,60-62] but few studies have addressed working memory directly in *cannabis* users and this is an area that is receiving increasing interest. Both adolescent and adult chronic *cannabis* users have shown impaired working memory on several measures from the Cambridge Neuropsychological Test Automated Battery (CANTAB) including Rapid Visual Information Processing, Pattern Recognition Memory, Spatial Recognition Memory, Spatial Span, Spatial Working Memory and Visuospatial Paired Associate Learning.[63,64] Impairments in visuospatial working memory may in part be due to deficits in basic temporal processing of saccades during oculomotor function.[65] Performance on an *n-back* auditory working memory task was shown to be impaired as memory load increased in abstinent adolescent *cannabis* users, with some evidence of altered regional brain activation emerging during nicotine withdrawal.[66] Other tasks such as the Sternberg working memory task have shown no performance deficits in abstinent adolescents or young adults, but altered regional brain activation (prefrontal and parietal) that was related to task novelty, as opposed to practice, was reflective of greater effort being required to achieve the task.[67,68] Further neuroimaging studies indicate that *cannabis* users recruit additional brain regions in a compensatory manner in order to achieve adequate performance on working memory tasks.[33,69,70]

In a recent study of verbal fluency, a task that relies heavily on executive functions, McHale et al. found that young adult *cannabis* users with recent use in the past week generated fewer words than those abstinent for at least one week, and both generated fewer words than non-user controls.[62] The authors suggested some recovery of cognitive ability with abstinence, but this may have been confounded by frequency of use as the abstinent group comprised twice/weekly users, whereas users in the recent use group smoked 5-6 times/week.

4) Verbal memory and other memory processes

Verbal memory is consistently impaired in chronic *cannabis* users, with significantly impaired performance on word list

learning tasks (e.g. Rey Auditory Verbal Learning Task (RAVLT), the California Verbal Learning Task (CVLT), and Buschke's Selective Reminding Task).[4,5,46,60,71-73] These studies have been extensively reviewed elsewhere, together with some early neuroimaging studies of verbal memory in *cannabis* users.[14,15,46,73,74] Overall, the evidence suggests that long-term or heavy *cannabis* users show impaired encoding, storage, manipulation and retrieval mechanisms.[15] Users learn fewer words across trials and recall fewer words particularly after interference or delay. Several studies have shown that these deficits are variously attributed to duration of *cannabis* use,[4] frequency of use,[3] or cumulative dosage effects.[5] Some studies have shown recovery of memory function following a period of 28 days abstinence,[3] others have shown that such deficits persist after this period,[5] while others suggest at least partial recovery (Solowij, unpublished data). In the study that showed recovery, this was less apparent when *cannabis* use was commenced at an early age.[61] Verbal memory was found to be impaired in adolescent *cannabis* users[63] and minimum 23 day-abstinent adolescents and associated with lifetime episodes of use.[75] Prospective memory has been demonstrated to be impaired in adolescent[76] and young adult users,[62,76] particularly time-based prospective memory.[62]

Recent neuroimaging studies have sought to elucidate the acute effects of THC and other cannabinoids (eg. CBD) on neural substrates subserving verbal memory, as discussed above,[32,33] or attempted to relate brain structural changes in *cannabis* users to verbal memory deficits. For example, Yücel et al. found significantly reduced hippocampal volumes in long-term heavy *cannabis* users, who were also significantly impaired on the RAVLT, but memory performance was unrelated to hippocampal volumes.[13] Such complex verbal learning tasks likely involve functional connectivity across a wide range of brain regions, and impaired performance is likely to be associated more with the functional activation of those regions, rather than their structure. A recent electrophysiological study in chronic users found poor word recall and alteration of the ERP subsequent memory effect during encoding, a component thought to originate in the hippocampal region, and this alteration was associated with a longer duration of *cannabis* use and an earlier onset of use.[77]

More specific hippocampal-dependent tasks, such as pictorial associative memory tasks, have also been investigated in one week abstinent *cannabis* users.[78,79] Task performance did not differ between moderately-using young adults and non-user controls but recall accuracy decreased as a function of exposure to *cannabis*, and decreased activation was observed in users in bilateral parahippocampal regions and in the right DLPFC during learning.[78] However, a study of adolescents found increased activation in the fusiform/parahippocampal area, inferior frontal gyrus, DLPFC, superior parietal cortex and the ACC,[79] suggestive of increased neural effort. A study of hippocampal-dependent face-name learning in young adult frequent users found impaired learning, short- and long-term memory, and hypoactivation of frontal and temporal regions with concomitant hyperactivation of parahippocampal regions during learning, reflective of both functional deficits and compensatory processes.[80] When different studies have shown hypoactivation or hyperactivation in the same regions during performance of similar tasks (eg. Stroop),[50,54] this may be due to variable parameters of *cannabis* use, such as the extent of exposure or age of onset, but further research is required to understand when and under what conditions increased or decreased activation is likely to manifest as well as the extent to which other brain regions are recruited to compensate for inefficiency.

5) Other cognitive functions

Cannabis alters the perception of time, both during the acute intoxication and in some studies of chronic users.[4,21,46,57] Typically, time is underestimated – the subjective experience is of time passing more slowly. Time estimation involves the ability to judge and plan the temporal order of behavioural events in order to allow the successful adaptation of behaviour.[57] These processes may be underpinned by cannabinoid modulation of cortical glutamatergic and striatal dopaminergic transmission, and the neural substrates implicated include the cerebellum, basal ganglia, prefrontal cortex, and parietal cortex.[57] Chronic *cannabis* users have been shown to be impaired in a classical delayed eye-blink conditioning task that reflects cerebellar functional integrity (cerebellar-dependent associative learning),[81] and recent data suggest cerebellar structural alterations in chronic *cannabis* users.[82]

Since *cannabis* alters mood during the acute intoxication, interest has grown in examining emotion and affect processing in chronic *cannabis* users. Gruber et al. examined regional brain activation to masked affective stimuli in heavy *cannabis* users and found altered frontal and limbic activity, with decreased activation of anterior cingulate and amygdala regions compared to controls, and differential effects for masked happy versus angry faces.[83] Two studies of acute *cannabis* administration also found modulation of amygdala activity during processing of fearful faces.[84,85] We reported significantly reduced amygdala volumes in long-term heavy *cannabis* users[13] but it is not yet known whether this is associated with emotional or affect processing deficits. Altered affective processing may pose difficulties for effective communication and decision making, particularly if cingulate driven inhibition of inappropriate emotional responses became problematic. Other recent neuroimaging research has examined reward processing mechanisms in chronic users, showing increased cerebellar and ventrostriatal activation during reward anticipation, of which the latter was correlated with the duration of *cannabis* use and lifetime dose of exposure.[86] In a study of neural activation underlying motor function, chronic *cannabis* users showed diminished activity of the supplementary motor cortex and area BA32, persisting after 28 days of abstinence, despite adequate response execution,[87] indicating incomplete recovery of optimal motor planning and execution.

3. Brain structure and function

Evidence for structural brain changes in *cannabis* users has been lacking: a number of studies have found no or few global

or regional changes in brain tissue volume or composition,[78,88,89] but some found grey and white matter density changes globally[90] or in parahippocampal areas.[91] In a recent review[92] we examined the evidence for structural brain alterations in *cannabis* users and found that of 13 studies, the majority using MRI, the evidence was inconsistent. Where differences were found between users and non-users, they were most apparent in association with greater dose of exposure to *cannabis* and were most often localised to the hippocampal region.

Using more sensitive measures and assessing *cannabis* users with far greater exposure to *cannabis* than previous studies, a recent study from our own group[13] found significant reduction of bilateral hippocampal (12%) and amygdala (7%) volumes in adults with a mean 20 years of near daily use compared to age, gender, and IQ matched non-user controls. The reduction of left hippocampus was dose-related, correlating with the cumulative dose of exposure to *cannabis* over the past 10 years, suggesting a causal effect. These results accord with evidence of hippocampal toxicity from the animal literature where animals were exposed to similar large doses over comparable proportions of their lifespan and showed decreases in neuronal volume, neuronal and synaptic density, and dendritic length of CA3 pyramidal neurons.[93-96] That the *cannabis* users of our study had used three times more *cannabis* over their lifespan than those of a study of users with a similar duration of use but no hippocampal alteration observed,[97] suggests that there may a threshold of cumulative exposure beyond which these changes in the brain may manifest.

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 cerebral blood flow compared to later onset users.[90] A recent study has reported altered cortical gyrification in the frontal lobe and abnormal age-related changes to gyrification and cortical thickness in adolescent and young adult users.[98]

Several studies have now reported on diffusion tensor imaging (DTI) measures of white matter structural integrity in *cannabis* users. Two studies found few differences between *cannabis* users and controls,[54,99] whereas increasing evidence for pathology has come from more recent studies of young adult[100,101] and adolescent[102,103] *cannabis* users, in the corpus callosum and various fronto-temporal, occipito-frontal and posterior connections that develop during adolescence. It is suggested that *cannabis* use, particularly during adolescence, may affect the trajectory of normal brain maturation resulting in white matter aberrations, which may underlie compromised cognitive processing. We have also reported cerebellar white matter reduction in adult long-term heavy users.[82]

Further evidence of diminished neuronal and axonal integrity comes from a magnetic resonance spectroscopic study showing dose-related changes in DLPFC, ACC and putamen/globus pallidum, but not hippocampus.[104] Changes in regional cerebral blood volume during 28 days of supervised abstinence have been reported, with some evidence for frontal normalisation with continued abstinence, but persistence of alterations in temporal and cerebellar regions.[105] Acute and chronic effects of *cannabis* have also been examined on levels of nerve growth factor and brain-derived neurotrophic factor (BDNF) in serum, showing some evidence of lowered resting levels in *cannabis* users,[106,107] and cannabinoid modulation of these proteins is evident from a growing number of preclinical studies.

4. Animal research

A wealth of preclinical research now shows an unequivocal role for the endogenous cannabinoid system in attention, memory, executive functions, inhibitory control, and multiple other cognitive processes, and that these are impaired following both acute and chronic cannabinoid administration.[14,57,108,109] Even a single administration of an ultra-low dose of THC (0.001-0.002mg/kg) has been shown to result in long-term cognitive impairments in mice (3 weeks to 4 months post-injection).[110,111]

Animal studies support the notion that the developing brain is more susceptible to the acute and chronic effects of exogenous cannabinoids, particularly the hippocampus.[112-114] Evidence is building from studies in which animals have been exposed prenatally or during the pubertal/adolescent period, with greater immediate adverse effects on cognition and behaviour observed in comparison to animals exposed during adulthood, as well as such effects persisting into adulthood with no further cannabinoid exposure.[10,112-117]

Cannabinoid effects are prominent in the hippocampus[118,119] and depend on interactions with GABA(A) receptors.[120] Further, modulatory mechanisms of the endocannabinoid system on prefrontal cortical and striatal dopamine and glutamate transmission are strongly supported by preclinical evidence.[57] In line with human studies, potentiation and antagonism of cannabinoid-induced spatial working memory deficits in rats have also been shown to be dependent on the ratio between THC and CBD.[121]

Conclusion

There is good evidence now that long-term heavy *cannabis* use results in cognitive deficits that have been shown to increase as a function of frequency, duration, dose, and age of onset of *cannabis* use. There is growing recognition that *cannabis* users are impaired on many of the same types of cognitive tests on which people with schizophrenia are also impaired,[14] and recent research has sought to elucidate the neural substrates of impaired cognition during acute intoxication. These research directions will inform the mechanisms by which *cannabis* may trigger psychotic symptoms or episodes, as the association between *cannabis* use and schizophrenia is compelling[122,123] and considered a significant public health concern. The endogenous cannabinoid system is altered in schizophrenia[124,125] but insufficient research has addressed the nature of alterations to this system following chronic *cannabis* use in otherwise healthy humans.

The endocannabinoid system appears to be unequivocally involved, either directly or indirectly (through interactions with other neuromodulators), in the cognitive deficits resulting from *cannabis* exposure.[57,113] Its dysfunction may be inferred from cannabinoid challenge studies and research with chronic *cannabis* users. Future research utilising CB_1 receptor probes and improved analytic techniques for assessing endocannabinoids in humans[125] should enhance our understanding of the role of this system in cognitive impairment. There are individual differences in response to *cannabis* in the short- and long-term, and understanding what constitutes a susceptibility to greater adverse effects[126] must be a priority for further research. Genetic research will inform specific vulnerabilities toward the development of cognitive deficits following exposure to *cannabis*, as have been identified already in relation to variations in the catechol-O-methyltransferase (COMT Val158Met) gene, involved in regulating dopaminergic transmission and metabolism.[127] There is some evidence for structural brain changes in long-term heavy *cannabis* users and animal research continues to explicate the mechanisms of action of cannabinoids on cognition and brain function. Together, the knowledge gleaned from these studies will inform not only a greater understanding of adverse effects of cannabinoids, but the potential for therapeutic applications of cannabinoids.[128] A wealth of integrative data from multimodal neuroimaging studies of humans is expected to provide significant advances in this field in coming years.

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Nadia Solowij	University of Wollongong	-	-	-	-	-	-
Nicole Pesa	Student University of Wollongong	-	-	-	-	-	-

** Modest*
*** Significant*
**** Significant: Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
For more information, see Instructions for authors.

References

1. Fant RV, Heishman SJ, Bunker EB, Pickworth WB. Acute and residual effects of marijuana in humans. *Pharmacol Biochem Behav.* 1998;60(4):777-84.
2. Curran HV, Brignell C, Fletcher S, Middleton P, Henry J. Cognitive and subjective dose-response effects of acute oral Δ9-tetrahydrocannabinol (THC) in infrequent *cannabis* users. *Psychopharmacology* (Berl). 2002;164(1):61-70.
3. Pope HG, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd. Neuropsychological performance in long-term *cannabis* users. *Arch Gen Psychiatry*. 2001;58(10):909-15.
4. Solowij N, Stephens RS, Roffman RA, Babor T, Kadden R, Miller M, Christiansen K, McRee B, Vendetti J, for the Marijuana Treatment Project Research Group. Cognitive functioning of long-term heavy *cannabis* users seeking treatment. *JAMA*. 2002;287(9):1123-31.
5. Bolla KI, Brown K, Eldreth D, Tate K, Cadet JL. Dose-related neurocognitive effects of marijuana use. *Neurology*. 2002;59(9):1337-43.
6. Degenhardt L, Lynskey M, Hall W. Cohort trends in the age of initiation of drug use in Australia. *Aust N Z J Public Health*. 2000;24(4):421–6.
7. Degenhardt L, Chiu WT, Sampson N, Kessler RC, Anthony JC, Angermeyer M, Bruffaerts R, de Girolamo G, Gureje O, Huang Y, Karam A, Kostyuchenko S, Lepine JP, Mora ME, Neumark Y, Ormel JH, Pinto-Meza A, Posada-Villa J, Stein DJ, Takeshima T, Wells JE. Toward a global view of alcohol, tobacco, *cannabis*, and cocaine use: Findings from the WHO World Mental Health Surveys. *PLoS Med.* 2008;5(7):e141.
8. Copeland J, Swift W. *Cannabis* use disorder: epidemiology and management. *Int Rev Psychiatry*. 2009;21(2):96-103.
9. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *The State of the Drugs Problem in Europe: Annual Report 2009*. Luxembourg: Publications Office of the European Union; 2009.
10. Schneider M. Puberty as a highly vulnerable developmental period. *Addict Biol*. 2008;13(2):253-63.
11. Solowij N. Do cognitive impairments recover following cessation of *cannabis* use? *Life Sci*. 1995;56(23-24):2119-26.
12. Solowij N, Grenyer BF, Chesher G, Lewis J. Biopsychosocial changes associated with cessation of *cannabis* use: a single-case study of acute and chronic cognitive effects, withdrawal and treatment. *Life Sci*. 1995;56(23-24):2127-34.
13. Yücel M, Solowij N, Respondek C, Whittle S, Fornito A, Pantelis C, Lubman DI. Regional brain abnormalities associated with long-term heavy *cannabis* use. *Arch Gen Psychiatry*. 2008;65(6):694-701.
14. Solowij N, Michie P. *Cannabis* and cognitive dysfunction: Parallels with endophenotypes of Schizophrenia? *J Psychiatry Neurosci*. 2007;32(1):30-52.
15. Solowij N, Battisti R. The chronic effects of *cannabis* on memory in humans: A review. *Curr Drug Abuse Rev*. 2008;1(1):81-98.
16. Ilan AB, Smith ME, Gevins A. Effects of marijuana on neuropsychological signals of working and episodic memory. *Psychopharmacology* (Berl). 2004;176(2):214-22.
17. O'Leary DS, Block RI, Koeppel JA, Schultz SK, Magnotta VA, Boles Ponto L, Watkins GL, Hichwa, RD. Effects of smoking marijuana on focal attention and brain blood flow. *Hum Psychopharmacol Clin Exp.* 2007;22(2):135-48.
18. Hunault CC, Mensinga TT, Böcker KBE, Schipper CMA, Kruidenier M, Leenders MEC, de Vries I, Meulenbelt J. Cognitive and psychomotor effects in males after smoking a combination of tobacco and *cannabis* containing up to 69 mg delta-9-tetrahydrocannabinol (THC). *Psychopharmacology* (Berl). 2009;204(1):85-94.
19. Ramaekers JG, Kauert G, Theunissen EL, Toennes SW, Moeller MR. Neurocognitive performance during acute THC intoxication in heavy and occasional *cannabis* users. *J Psychopharmacol*. 2009;23(3):266-77.
20. McDonald J, Schleifer L, Richards JB, de Wit, H. Effects of THC on behavioural measures of impulsivity in humans. *Neuropsychopharmacology*. 2003;28(7):1356-65.

21. Hart CL, van Gorp W, Haney M, Foltin RW, Fischman MW. Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology*. 2001;25(5)*:*757-65.

22. McGuire P, Crippa J, Martin-Santos R, O'Carroll C, Bhattacharyya S, Borgwardt S, Fusar-Poli P, Atakan Z. Effects of *cannabis* on memory and response inhibition. *Eur Psychiatry*. 2007;22(Suppl1):S20.

23. Juckel G, Roserb P, Nadulskic T, Stadelmann AM, Gallinat J. Acute effects of Delta9-tetrahydrocannabinol and standardized *cannabis* extract on the auditory evoked mismatch negativity. *Schizophr Res*. 2007;97(1-3):109-17.

24. Roser P, Juckel G, Rentzsch J, Nadulski T, Gallinat J, Stadelmann AM. Effects of acute oral Delta9-tetrahydrocannabinol and standardized *cannabis* extract on the auditory P300 event-related potential in healthy volunteers. *Eur Neuropsychopharmacol*. 2008;18(8):569-77.

25. Shelley AM, Ward PB, Catts SV, Michie PT, Andrews S, McConaghy N. Mismatch negativity – an index of a preattentive processing deficit in schizophrenia. *Biol Psychiatry*. 1991;30(10):1059-62.

26. Michie PT. What has MMN revealed about the auditory system in schizophrenia? *Int J Psychophysiol*. 2001;42(2):177-94.

27. D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: Implications for psychosis. *Neuropsychopharmacology*. 2004;29(8)*:*1558-72.

28. Morrison PD, Zois V, McKeown DA, Lee TD, Holt DW, Powell JF, Kapur S, Murray RM. The acute effects of synthetic intravenous Delta9-tetrahydrocannabinol on psychosis, mood and cognitive functioning. *Psychol Med*. 2009;39(10):1607-16.

29. Ranganathan M, D'Souza DC. The acute effects of cannabinoids on memory in humans: a review. *Psychopharmacology* (Berl). 2006;188(4):425-44.

30. Fletcher PC, Honey GD. Schizophrenia, ketamine and *cannabis*: Evidence of overlapping memory deficits. *Trends Cogn Sci*. 2006;10(4):167-74.

31. Bhattacharyya S, Fusar-Poli P, Borgwardt S, Allen P, Martin-Santos R, O'Carroll C, Seal M, Atakan Z, Nosarti C, McGuire PK. Delta-9-tetrahydrocannabinol modulates activity in temporal cortex during processing of verbal episodic memory. *Eur Neuropsychopharmacol*. 2007;17(Suppl4):S285.

32. Bhattacharyya S, Fusar-Poli P, Borgwardt S, Martin-Santos R, Nosarti C, O'Carroll C, Allen P, Seal ML, Fletcher PC, Crippa JA, Giampietro V, Mechelli A, Atakan Z, McGuire P. Modulation of mediotemporal and ventrostriatal function in humans by Delta9-Tetrahydrocannabinol: A neural basis for the effects of *cannabis* sativa on learning and psychosis. *Arch Gen Psychiatry.* 2009;66(4):442-51.

33. Martin-Santos R, Fagundo AB, Crippa JA, Atakan Z, Bhattacharyya S, Allen P, Fusar-Poli P, Borgwardt S, Seal M, Busatto GF, McGuire P. Neuroimaging in *cannabis* use: a systematic review of the literature. *Psychol Med*. 2010;40(3):383-98.

34. Lane SD, Cherek DR, Lieving LM, Tcheremissine OV. Marijuana effects on human forgetting functions. *J Exp Anal Behav*. 2005;83(1):67-83.

35. Bocker KB, Gerritsen J, Kruidenier M, Hunault CC, Mensinga TT, Kenemans JL. Smoking high potency marijuana: theta power correlates with memory search. *Eur Neuropsychopharmacol.* 2007;17(Suppl4):S553.

36. Boucher AA, Vivier L, Metna-Laurent M, Brayda-Bruno L, Mons N, Arnold JC, Micheau J. Chronic treatment with Delta(9)-tetrahydrocannabinol impairs spatial memory and reduces zif268 expression in the mouse forebrain. *Behav Pharmacol.* 2009;20(1)*:*45-55.

37. Rogers RD, Wakeley J, Robson PJ, Bhagwagar Z, Makela P. Reinforcement processing in the risky decision-making of young healthy adults. *Neuropsychopharmacology.* 2007;32(2):417-28.

38. Vadhan NP, Hart CL, van Gorp WG, Gunderson EW, Haney M, Foltin RW. Acute effects of smoked marijuana on decision making, as assessed by a modified gambling task, in experienced marijuana users. *J Clin Exp Neuropsychol.* 2007;29(4):357-64.

39. Jacobsen LK, Mencl WE, Westerveld M, Pugh KR. Impact of *cannabis* use on brain function in adolescents. *Ann N Y Acad Sci.* 2004;1021:384-90.

40. Novaes MA, Guindalini C, Almeida P, Jungerman F, Bolla K, Laranjeira R, Lacerda A, Bressan RA. *Cannabis* use before age 15 years is associated with poorer attention and executive function. *Biol Psychiatry.* 2008;63(Suppl55)*:*18S-9.

41. Voytek B, Berman SM, Hassid BD, Simon SL, Mandelkern MA, Brody AL, Monterosso J, Ling W, London ED. Differences in regional brain metabolism associated with marijuana abuse in methamphetamine abusers. *Synapse.* 2005;57(2):113-5.

42. Scholes KE, Martin-Iverson MT. Alterations to pre-pulse inhibition (PPI) in chronic *cannabis* users are secondary to sustained attention deficits. *Psychopharmacology.* 2009;207(3):469-84.

43. Solowij N, Michie P, Fox AM. Effects of long-term *cannabis* use on selective attention: an event-related potential study. *Pharmacol Biochem Behav.* 1991;40(3):683-8.

44. Solowij N, Michie P, Fox AM. Differential impairments of selective attention due to frequency and duration of *cannabis* use. *Biol Psychiatry.* 1995;37(10)*:*731-9.

45. Fletcher JM, Page JB, Francis DJ, Copeland K, Naus MJ, Davis CM, Morris R, Krauskopf D, Satz P. Cognitive correlates of long-term *cannabis* use in Costa Rica men. *Arch Gen Psychiatry.* 1996;53(11)*:*1051-7.

46. Solowij N. *Cannabis and cognitive functioning*. Cambridge: Cambridge University Press; 1998.

47. Ehrenreich H, Rinn T, Kunert HJ, Moeller MR, Poser W, Schilling L, Gigerenzer G, Hoehe MR. Specific attentional dysfunction in adults following early start of *cannabis* use. *Psychopharmacology* (Berl). 1999;142(3):295-301.

48. Skosnik PD, Spatz-Glenn L, Park S. *Cannabis* use s associated with schizotypy and attentional disinhibition. *Schizophr Res.* 2001;48(1)*:*83-92.

49. 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(2):95-101.

50. Eldreth DA, Matochik JA, Cadet JL, Bolla KI. Abnormal brain activity in prefrontal regions in abstinent marijuana users. *Neuroimage*. 2004;23(3):914-20.

51. Whitlow CT, Liguori A, Livengood LB, Hart SL, Mussat-Whitlow BJ, Lamborn CM, Laurienti PJ, Porrino LJ. Long-term heavy marijuana users make costly decisions on a gambling task. *Drug Alcohol Depend*. 2004;76(1):107-11.

52. Smith AM, Fried PA, Hogan MJ, Cameron I. Effects of prenatal marijuana on response inhibition: an fMRI study of young adults. *Neurotoxicol Teratol.* 2004;26(4):533-42.

53. Bolla KI, Eldreth DA, Matochik JA, Cadet JL. Neural substrates of faulty decision-making in abstinent marijuana users. *Neuroimage.* 2005;26(2)*:*480-92.

54. Gruber S, Yurgelun-Todd D. Neuroimaging of marijuana smokers during inhibitory processing: a pilot investigation. *Brain Res Cogn Brain Res.* 2005;23(1)*:*107-18.

55. Hester R, Nestor L, Garavan H. Impaired error awareness and anterior cingulate cortex hypoactivity in chronic *cannabis* users. *Neuropsychopharmacology.* 2009;34(11):2450-8.

56. Melis M, Perra S, Muntoni AL, Pillolla G, Lutz B, Marsicano G, Di Marzo V, Gessa GL, Pistis M. Prefrontal cortex stimulation induces 2-arachidonoyl-glycerol-mediated suppression of excitation in dopamine neurons. *J Neurosci.* 2004;24(47):10707-15.

57. Pattij T, Wiskerke J, Schoffelmeer AN. Cannabinoid modulation of executive functions. *Eur J Pharmacol.* 2008;585(2-3)*:*458-63.

58. Battisti RA, Roodenrys S, Johnstone S, Pesa N, Hermens D, Solowij N. Chronic *cannabis* users show altered neurophysiological functioning on Stroop task conflict resolution. *Clin EEG Neurosci.* In press 2010.

59. Tapert SF, Schweinsburg AD, Drummond SPA, Paulus MP, Brown SA, Yang TT, Frank LR. Functional MRI of inhibitory processing in abstinent adolescent marijuana users. *Psychopharmacology*. 2007;194(2)*:*173-83.

60. Pope HG, Yurgelun-Todd D. The residual cognitive effects of heavy marijuana use in college students. *JAMA.* 1996;275(7):521-7.

61. 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(3)303-10.

62. McHale S, Hunt N. Executive function deficits in short-term abstinent *cannabis* users. *Hum Psychopharmacol Clin Exp.* 2008;23(5):409-15.

63. Harvey MA, Sellman JD, Porter RJ, Frampton CM. The relationship between non-acute adolescent *cannabis* use and cognition. *Drug Alcohol Rev.* 2007;26(3):309-19.

64. Solowij N, Respondek C, Battisti R, Whittle S, Lubman D, Yücel M. Visuospatial memory deficits in long term heavy *cannabis* users: relation to psychotic symptoms and regional brain volumes, *Int J Neuropsychopharmacol.* 2008;11(Suppl1):242.

65. Huestegge L, Radach R, Kunert HJ. Long-term effects of *cannabis* on oculomotor function in humans. *J Psychopharmacol* 2009;23(6):714-22.

66. 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(1):31-40.

67. 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(3):358-68.

68. Jager G, Luijten M, Block RI, Ramsey NF. Effects of *cannabis* use on cognitive brain function in adolescents: short-term memory, long-term consequences? *Eur Neuropsychopharmacol.* 2008;18(Suppl4):S533.

69. 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(3-4):239-47.

70. Padula, CB, Schweinsburg AD, Tapert SF. Spatial working memory performance and fMRI activation interactions in abstinent adolescent marijuana users. *Psychol Addict Behav.* 2007;21(4):478-87.

71. Pope HG, Gruber AJ, Hudson JI, Yurgelun-Todd D. Cognitive measures in long-term *cannabis* users. *J Clin Pharmacol.* 2002;42(Suppl11):41S-7.

72. Messinis L, Kypriandou A, Malefaki S, Papathanasopoulos P. Neuropsychological deficits in long-term frequent *cannabis* users. *Neurology.* 2006;66(5):737-9.

73. Block RI, O'Leary DS, Hichwa RD, Augustinack JC, Boles Ponto LL, Ghoneim MM, Arndt S, Hurtig RR, Watkins GL, Hall JA, Nathan PE,. Andreasen NC. Effects of frequent marijuana use on memory-related regional cerebral blood flow. *Pharmacol Biochem Behav.* 2002;72(1-2):237-50.

74. Grant I, Gonzalez R, Carey CL, NataRrajan L, Wolfson T. Non-acute (residual) neurocognitive effects of *cannabis* use: A meta-analytic study. *J Int Neuropsychol Soc.* 2003;9(5):679-89.

75. 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(5):807-20.

76. Bartholomew J, Holroyd S, Heffernan TM. Does *Cannabis* use affect prospective memory in teenagers and young adults? *Eur Psychiatry.* 2008;23(Suppl2):S305.

77. Battisti RA, Roodenrys S, Johnstone SJ, Respondek C, Hermens DF, Solowij N. Chronic use of *cannabis* and poor neural efficiency in verbal memory ability. *Psychopharmacology.* In press 2010.

78. Jager G, Van Hell HH, De Win MM, Kahn RS, Van den Brink W, Van Ree JM, Ramsey NF. Effects of frequent *cannabis* use on hippocampal activity during an associative memory task. *Eur Neuropsychopharmacol.* 2007;17(4):289-97.

79. Luijten M, Jager G, Block RI, Zuccarelli JM, Becker MM, Ramsey NF. Effects of *cannabis* use on associative memory in adolescents, and the role of personality measures: an fMRI study. *Eur Neuropsychopharmacol* 2007;17(Suppl4):S552-3.

80. Nestor L, Roberts G, Garavan H, Hester R. Deficits in learning and memory: Parahippocampal hyperactivity and frontocortical hypoactivity in *cannabis* users. *Neuroimage.* 2008;40(3):1328-39.

81. Skosnik PD, Edwards CR, O'Donnell BF, Steffen A, Steinmetz JE, Hetrick WP. *Cannabis* use disrupts eyeblink conditioning: Evidence for cannabinoid modulation of cerebellar-dependent learning. *Neuropsychopharmacology.* 2008;33(6):1432-40.

82. Solowij N, Respondek C, Whittle S, Lindsay E, Lubman D, Yücel M. Cerebellar grey and white matter changes associated with *cannabis* use in schizophrenia and in healthy controls. *Neuroimage.* 2008;41(Suppl1):S83.

83. Gruber SA, Rogowska J, Yurgelun-Todd DA. Altered affective response in marijuana smokers: An fMRI study. *Drug Alcohol Depend.* 2009;105(1-2):139-53.

84. Phan KL, Angstadt M, Golden J, Onyewuenyi I, Popovska A, de Wit H. Cannabinoid modulation of amygdala reactivity to social signals of threat in humans. *J Neuroscience.* 2008;28(10):2313-9.

85. Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, Seal M, Surguladze SA, O'Carrol C, Atakan Z, Zuardi AW, McGuire PK. Distinct effects of (delta)9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Arch Gen Psychiatry.* 2009;66(1):95-105.

86. Nestor L, Hester R, Garavan H. Increased ventral striatal BOLD activity during non-drug reward anticipation in *cannabis* users. *Neuroimage*. .In press 2010.

87. Pillay SS, Rogowska J, Kanayama G, Gruber S, Simpson N, Pope HG, Yurgelun-Todd DA. *Cannabis* and motor function: fMRI changes following 28 days of discontinuation. *Exp Clin Psychopharmacol.* 2008;16(1):22-32.

88. Block RI, O'Leary DS, Ehrhardt JC, Augustinack JC, Ghoneim MM, Arndt S, Hall JA. Effects of frequent marijuana use on brain tissue volume and composition. *Neuroreport.* 2000;11(3):491-6.

89. Tzilos GK, Cintron CB, Wood JBR, Simpson NS, Young AD, Pope HG, Yirgelun-Todd DA. Lack of hippocampal volume change in long-term heavy *cannabis* users. *Am J Addict.* 2005;14(1):64-72.

90. Wilson W, Matthew 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):1-22.

91. Matochik JA, Eldreth DA, Cadet JL, Bolla KI. Altered brain tissue composition in heavy marijuana users. *Drug Alcohol Depend.* 2005;77(1):23-30.

92. Lorenzetti V, Lubman DI, Whittle S, Solowij N, Yücel M. Structural MRI findings in long-term *cannabis* users: What do we know? *Subst Use Misuse.* In press 2010.

93. Scallet AC, Uemura E, Andrews A, Ali SF, McMillan DE, Paule MG, Brown RM, Slikker W. Morphometric studies of the rat hippocampus following chronic delta-9-tetrahydrocannabinol (THC). *Brain Res.* 1987;436(1):193-8.

94. Landfield PW, Cadwallader LB, Vincent S. Quantitative changes in hippocampal structure following long-term exposure to delta-9-tetrahydrocannabinol: possible mediation by glutocorticoid systems. *Brain Res.* 1988;443(1-2):47-62.

95. Chan GC, Hinds TR, Impey S, Storm DR. Hippocampal neurotoxicity of delta(9)-tetrahydrocannabinol. *J Neurosci.* 1998;18(14):5322-32.

96. 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(2):407-10.

97. Tzilos GK, Cintron CB, Wood JB, Simpson NS, Young AD, Pope HG, Yurgelun-Todd DA. Lack of hippocampal volume change in long-term heavy *cannabis* users. *Am J Addict.* 2005;14(1):64-72.

98. Mata I, Perez-Iglesias R, Roiz-Santiañez R, Tordesillas-Gutierrez D, Pazos A, Gutierrez A, Vazquez-Barquero JL, Crespo-Facorro B. Gyrification brain abnormalities associated with adolescence and early-adulthood *cannabis* use. *Brain Res.* In press 2010.

99. DeLisi LE, Bertisch HC, Szulc KU, Majcher M, Brown K, Bappal A, Ardekani BA. A preliminary DTI study showing no brain structural change associated with adolescent *cannabis* use. *Harm Reduct J.* 2006;3(1):17.

100. Arnone D, Barrick TR, Chengappa S, Mackay CE, Clark CA, Abou-Saleh MT. Corpus callosum damage in heavy marijuana use: Preliminary evidence from diffusion tensor tractography and tract-based spatial statistics. *Neuroimage.* 2008;41(3):1067-74.

101. Allin M, Khan O, Walshe M, Kontis D, Nosarti C, Barker G, Rifkin L, Murray RM. *Cannabis* smoking and white matter in healthy volunteers. *Schizophr Bull.* 2009;35(Suppl 1):201.

102. Ashtari M, Cervellione K, Cottone J, Ardekani BA, Kumra S. Diffusion abnormalities in adolescents and young adults with a history of heavy *cannabis* use. *J Psychiatr Res.* 2009;43(3):189-204.

103. Bava S, Frank LR, McQueeny T, Schweinsburg BC, Schweinsburg AD, Tapert SF. Altered white matter microstructure in adolescent substance users. *Psychiatry Res Neuroimaging*. 2009;173(3):228-37.

104. Hermann D, Sartorius A, Welzel H, Walter S, Skopp G, Ende G, Mann K. Dorsolateral prefrontal cortex N-acetylaspartate/total creatine (NAA/tCr) loss in male recreational *cannabis* users. *Biol Psychiatry.* 2007;61(11):1281-9.

105. Sneider JT, Pope HG Jr, Silveri MM, Simpson NS, Gruber SA, Yurgelun-Todd DA. Differences in regional blood volume during a 28-day period of abstinence in chronic *cannabis* smokers. *Eur Neuropsychopharmacol.* 2008;18(8):612-9.

106. Angelucci F, Ricci V, Spalletta G, Pomponi M, Tonioni F, Caltagirone C, Bria P. Reduced serum concentrations of nerve growth factor, but not brain-derived neurotrophic factor, in chronic *cannabis* abusers. *Eur Neuropsychopharmacol*. 2008;18(12):882-7.

107. D'Souza DC, Pittman B, Perry E, Simen A. Preliminary evidence of cannabinoid effects on brain-derived neurotrophic factor (BDNF) levels in humans. *Psychopharmacology* (Berl). 2009;202(4):569-78.

108. Egerton A, Allison C, Brett RR, Pratt JA. Cannabinoids and prefrontal cortical function: Insights from preclinical studies. *Neurosci Biobehav Rev.* 2006;30(5):680-95.

109. Niyuhire F, Varvel SA, Martin BR, Lichtman AH. Exposure to marijuana smoke impairs memory retrieval in mice. *J Pharmacol Exp Ther.* 2007;322(3):1067-75.

110. 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(2):108-11.

111. Amal H, Fridman-Rozevich L, Senn R, Strelnikov A, Gafni M, Keren O, Sarne Y. Long-term consequences of a single treatment of mice with an ultra-low dose of Delta9-tetrahydrocannabinol (THC). *Behav Brain Res.* 2010;206(2):245-53.

112. Kang-Park M, Wilson WA, Kuhn CM, Moore SD, Swartzwelder HS. Differential sensitivity of $GABA_A$ receptor-mediated IPSCs to cannabinoids in hippocampal slices from adolescent and adult rats. *J Neurophysiol.* 2007;98(3):1223-30.

113. Realini N, Rubino T, Parolaro D. Neurobiological alterations at adult age triggered by adolescent exposure to cannabinoids. *Pharmacol Res.* 2009;60(2):132-8.

114. Rubino T, Realini N, Braida D, Guidi S, Capurro V, Vigano, D, Guidali C, Pinter M, Sala M, Bartesaghi R, Parolaro D. Changes in hippocampal morphology and neuroplasticity induced by adolescent THC treatment are associated with cognitive impairment in adulthood. *Hippocampus.* 2009;19(8):763-72.

115. 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(10):1760-9.

116. O'Shea M, Singh ME, McGregor IS, Mallett PE. Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats. *J Psychopharmacol.* 2004;18(4):502-8.

117. Schneider M, Schomig E, Leweke FM. Acute and chronic cannabinoid treatment differentially affects recognition memory and social behavior in pubertal and adult rats. *Addict Biol.* 2008;13(3-4):345-57.

118. Deadwyler SA, Goonawardena AV, Hampson RE. Short-term memory is modulated by the spontaneous release of endocannabinoids: evidence from hippocampal population codes. *Behav Pharmacol.* 2007;18(5-6):571-80.

119. Robinson L, Goonawardena AV, Pertwee RG, Hampson RE, Riedel G. The synthetic cannabinoid HU210 induces spatial memory deficits and suppresses hippocampal firing rate in rats. *Br J Pharmacol.* 2007;151(5):688-700.

120. Varvel SA, Anum E, Niyuhire F, Wise LE, Lichtman AH. Delta-9-THC-induced cognitive deficits in mice are reversed by the GABA(A) antagonist bicuculline. *Psychopharmacology* (Berl). 2005;178(2-3):317-27.

121. Fadda P, Robinson L, Fratta W, Pertwee RG, Riedel G. Differential effects of THC or CBD-rich *cannabis* extract on working memory in rats. *Neuropharmacology.* 2004;47(8):1170-9.

122. Murray RM, Morrison PD, Henquet C, Di Forti M. *Cannabis*, the mind and society: the hash realities. *Nat Rev Neurosci.* 2007;8(11):885-95.

123. Henquet C, Di Forti M, Morrison P, Kuepper R, Murray RM. Gene-environment interplay between *cannabis* and psychosis. *Schizophr Bull.* 2008;34(6):1111-21.

124. Fernandez-Espejo E, Viveros MP, Núñez L, Ellenbroek BA, Rodriguez de Fonseca F. Role of *cannabis* and endocannabinoids in the genesis of schizophrenia. *Psychopharmacology* (Berl). 2009;206(4):531-49.

125. Koethe D, Hoyer C, Leweke FM. The endocannabinoid system as a target for modelling psychosis. *Psychopharmacology* (Berl). 2009;206(4):551-61.

126. Yücel M, Lubman DI, Solowij N, Brewer WJ. Understanding drug addiction: A neuropsychological perspective. *Aust N Z J Psychiatry.* 2007;41(12):957-68.

127. Henquet C, Rosa A, Krabbendam L, Papiol S, Fananás L, Drukker M, Ramaekers JG, van Os J. An experimental study of catechol-O-methyltransferase val(158)met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology.* 2006;31(12):2748-57.

128. Bhattacharyya S, Crippa JA, Martin-Santos R, Winton-Brown T, Fusar-Poli P. Imaging the neural effects of cannabinoids: Current status and future opportunities for psychopharmacology. *Curr Pharmaceut Design*. 2009;15(22):2603-14.