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Published in:
Pharmacology, Biochemistry and Behavior

DOI:
10.1016/j.pbb.2005.02.017

2005

Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions.

Pharmacol Biochem Behav. 2005 Jun;81(2):319-30.

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This review aims to compare cognitive consequence between cannabis, and stimulants and heroin with regards to attention, memory and executive functions. The available studies using brain imaging techniques and neuropsychological tests show that acutely, all drugs create a disharmony in the neuropsychological network, causing a decrease of activity in areas responsible for short-term memory and attention, with the possible exception of heroin. Cannabis induces loss of internal control and cognitive impairment, especially of attention and memory, for the duration of intoxication. Heavy cannabis use is associated with reduced function of the attentional/executive system, as exhibited by decreased mental flexibility, increased perserveration, and reduced learning, to shift and/or sustain attention. Recent investigations on amphetamine/methamphetamine have documented deficits in learning, delayed recall, processing speed, and working memory. MDMA users exhibit difficulties in coding information into long-term memory, displays impaired verbal learning, are more easily distracted, and are less efficient at focusing attention on complex tasks. The degree of executive impairment increases with the severity of use, and the impairments are relatively lasting over time. Chronic cocaine users display impaired attention, learning, memory, reaction time and cognitive flexibility. Heroin addiction may have a negative effect on impulse control, and selective processing.

Index terms: cannabis, methamphetamine, MDMA, cocaine, heroin, cognitive impairment, attention, memory.

1. Introduction

Clinical observations, conventional wisdom, and well-reasoned theoretical mechanisms, suggests that the acute and chronic use of psychoactive substances would impair cognitive functioning of individuals. Could this impairment be a specific effect with regard to specific drugs of abuse or is it a general impact on the brain? This review compares findings from other drugs of abuse according to how cannabis impairs human cognition, with regard to attention, memory and executive functions. The executive functions are a group of superior abilities of organization and integration that have been neuroanatomically associated with different neural interaction pathways involving the prefrontal cortex (Roberts et al. 1998). These include anticipating and establishing goals, designing plans and programs, selfregulation and monitoring of tasks, and effective execution and feedback (Lezak 1995).

To reduce the scope of this review the focus will be on the abuse of amphetamine and methamphetamine, MDMA or similar synthetic amphetamine derivates, cocaine, and heroin.

Recent studies of the acute and chronic effects of specific drugs of abuse on human cognition have shown a cluster of cognitive, behavioural or physiological symptoms. Hall et al. (1999) compared the health effects of cannabis to other drugs by using the same standards that have been used to appraise the health effects of other drugs. The analysis, which was undertaken at the request of the WHO Committee on the health proved difficult. The analysis was hindered by a dearth of epidemiological studies of consequences of cannabis use that would permit quantitative comparisons.

Other attempts to investigate this area have been made by Rogers and Robbins (2001) and Vik et al. (2004), and Verdejo-Garcia (2005). Rogers and Robbins (2001) reviewed the neurocognitive deficits associated with chronic drug misuse and concluded that chronic and heavy use of cannabis may be associated with quite subtle changes in cognitive, particularly attentional function, but whether such changes are permanent remains unclear, that chronic amphetamine abuse is associated with altered functioning of the circuitry, involving the ventral prefrontal cortex (PFC) that mediates decision-making. This is consistent with earlier results indicating that prolonged stimulant use (cocaine) is associated with altered metabolism in the orbital cortex (Volkow et al., 1993). It is also consistent with the finding of high densities of the cannabinoid receptor in the cerebral cortex and hippocampus (Herkenham et al., 1990), hypothesising that cannabinoids are involved in attentional and memory processes. Vik et al. (2004) conclude that acute intoxication and immediate and protracted withdrawal produce transient alterations of cognitions that can persist for weeks to months. Some subtle

residual effects remain for up to 1 year for certain drugs. Evidence of irreversible effects is less clear. In comparison with cannabis and stimulants, there has been substantially less research into neuropsychological deficits in chronic abusers of opiates. Verdejo-Garcia et al. (2005) analyzed the relationship between severity of consumption of different drugs and neuropsychological performance on tasks sensitive to impairment in the executive subprocesses of working memory, response inhibition, cognitive flexibility, and abstract reasoning. The results showed a differential impact of severity of MDMA abuse on working memory and abstract reasoning indices, of cocaine severity on an inhibitory control index and of cannabis on a cognitive flexibility index.

Most of the neurotransmitters affected by drugs of abuse exert their effects through relatively diffuse patterns of innervations across the whole of the forebrain and wider cortical areas. It is therefore unsurprising that there have been relatively few, if any, convincing demonstrations of differences in neurocognitive performance between abusers of different drugs of abuse.

2. Cannabis

Qualitative analyses of the cognitive consequences of cannabis use made by Hall et al. (1999) conclude, focusing on: *acute effects* that, cannabis induces loss of internal control and cognitive impairment, especially of attention and memory, for the duration of intoxication. Further, according to Hall et al.(1999), the major health and psychological effects of chronic heavy cannabis use, especially daily use over many years, remain uncertain. On the available evidence, the major probable adverse *chronic effects* on cognition appear to be development of a cannabis dependence syndrome, characterized by an inability to abstain from or to control cannabis use; subtle forms of cognitive impairment, most particularly of attention and memory, which persist while the user remains chronically intoxicated, and may or may not be reversible after prolonged abstinence from cannabis.

2.1 Neuropsychological findings

2.1.1 Findings in brain imaging studies with regard to attention, memory and executive functions.

Cognitive deficits associated with the acute and chronic use of cannabis have important theoretical and clinical significance and using brain imaging techniques may reveal

neurotoxic effects of cannabis. Thus, the deficits reflect changes to the underlying cortical, sub-cortical and neuromodulatory mechanisms that underpin cognition.

Although many studies have reported behavioural alterations and cellular effects in connection with cannabis (see reviews in Martin and Cone, 1999; Solowij, 1999) relatively little is still known, but improving, about the neurophysiological effects of cannabis on brain function. Neuroimaging data has been derived from studies focusing both on acute marijuana exposure and on chronic abusers, in resting conditions, where the subject is instructed to lie down, relax and not to think, and in activated conditions with a cognitive challenge paradigm.

2.1.1.1 Resting paradigm

Several studies, with different techniques (CBF, PET SPECT, fMRI), have shown subnormal cerebral blood flow (Tunving et al., 1985; Mathew et al., 1986; Mathew et al., 1989;) or lower cerebellar metabolism (Volkow et al., 1996; Amen and Waugh, 1998) in long-term cannabis users who were assessed within one week of cessation of use. Lundqvist et al. (2001) measured brain blood flow levels after cessation of cannabis use (mean 1.6 days). The findings showed significantly lower mean hemispheric blood flow values and significantly lower frontal values in the cannabis subjects, compared to normal controls. Block et al.(2000a) found that after 26 hours of controlled abstinence, young frequent marijuana users showed hypoactivity relative to controls in a large region of bilateral posterior cerebellar hemispheres, vermis and in left and right ventral prefrontal cortex (Brodmann's area 11). Compared with average whole brain activity in controls, marijuana users showed 9% lower values.

Acute exposure to marijuana has resulted in dose related increases in CBF measures among experienced users (Mathew et al., 1991; Mathew et al., 1993). In a PET study Volkow et al. (1991) showed that effects may be individual related. In a subsequent study Volkow et al. (1996) found, similar to Mathew et al.(1991), that besides an increase in the global metabolism, the users also showed regional metabolic increases in orbitofrontal cortex, prefrontal cortex and basal ganglia, which were not seen in the normal group. Mathew et al. (1997, 1999) also reported regional flow increases that reached statistical significance in frontal regions, insula, cingulate gyrus, and subcortical regions. Block et al. (1999) found that chronic marijuana use was related to decrease memory-related activation in users relative to controls. The results revealed a number of between group differences in prefrontal regions. Block et al. (2000b) also used magnetic resonance imaging (MRI) to investigate brain structure in young currently frequent marijuana users. The users showed no evidence of cerebral atrophy or global or regional changes in tissue volumes compared to controls.

2.1.1.2 Cognitive challenge paradigm

Cognition in an everyday situation demands cognitive effort. It is therefore necessary to involve studies, which have a challenge within their paradigm. Yurgelun-Todd et al. (1999) assessed chronic marijuana smokers twice with functional magnetic resonance imaging (fMRI), after 24 hours and 28 days of abstinence. A visual working memory task with known sensiti0vity was used as a cognitive challenge paradigm. The control subjects produced significant activation in the dorsolateral prefrontal cortex (DLPFC) during the challenge paradigm. Smokers who completed twenty-four hours of washout showed diminished activation in this region. The effect remained diminished after twenty-eight days of washout, although some increase in the DLPFC activation was noted relative to the twenty-four hour time point. In contrast, smokers produced increased activation in the cingulate during both washout conditions, whereas controls did not. These results indicate that even after an extended washout period, specific differential patterns of cortical activation exist in subjects with a history of heavy marijuana use.

Block et al. (2002) measured cerebral blood flow during the performance of verbal memory recall tasks and during a selective attention task Memory-related blood flow in frequent marijuana users showed decreases relative to controls in prefrontal cortex, increases in memory-relevant regions of cerebellum, and altered lateralization in hippocampus. The greatest differences between users and controls occurred in brain activity related to episodic memory encoding.

O'Leary et al. (2002) observed increased rCBF after inhalation of cannabis in orbital and mesial frontal lobes, insula, temporal poles, and anterior cingulate, as well as in the cerebellum. The increases in rCBF in anterior brain regions were predominantly in "paralimbic" regions that may be related to marijuana's mood-related effects. Reduced rCBF was observed both during resting as activated conditions, acutely intoxicated, in brain regions that may be a part of an attentional network (parietal lobe, frontal lobe and thalamus). Reduced rCBF was also observed in temporal lobe auditory regions, in visual cortex. The auditory activation paradigm did not show rCBF increases in temporal lobe auditory regions that were significantly different from a baseline condition. Additionally, marijuana decreased rCBF in comparison to the baseline condition in brain regions that have been found in a number of studies to be involved in attentional modulation of sensory processing. These findings suggest that it may be possible to isolate the mood-enhancing effects of marijuana

(rCBF increases in ventral forebrain) from cannabis´ effect on perception, attention and behaviour (decreased rCBF in sensory regions and attention-related brain systems).

Two studies by O'Leary et al. (2000; 2002) utilizing an auditory attention task, found increased regional cerebral blood flow in orbital and mesial frontal lobes, insula, temporal poles, anterior cingulate, and cerebellum, but decreased blood flow in temporal lobe auditory regions, visual cortex, and regions associated with attention . The same group (O'Leary et al., 2003) found increased forebrain and cerebellar blood flow, but decreased frontal blood flow in acutely intoxicated cannabis user performing a counting task.

Eldreth et al. (2004) used PET and a modified version of the Stroop task to determine if 25-day abstinent heavy marijuana users have persistent deficits in executive cognitive functioning (ECF) and brain activity. The 25-day abstinent marijuana users showed no deficits in performance on the modified version of the Stroop task when compared to the comparison group. Despite the lack of performance differences, the marijuana users showed hypoactivity in the left perigenual anterior cingulate cortex and the left lateral prefrontal cortex and hyperactivity in the hippocampus bilaterally, when compared to the comparison group. These results suggest that marijuana users display persistent metabolic alterations in brain regions responsible for ECF. It may be that marijuana users recruit an alternative neural network as a compensatory mechanism during performance on a modified version of the Stroop task. Kanayama et al. (2004) found in an fMRI study that heavy long-term cannabis abusers displayed greater and more widespread brain activation than normal subjects attempting to perform a spatial working memory task. This observation suggests that heavy long-term cannabis abusers may experience subtle neurophysiological deficits, and that they compensate for these deficits by "working harder"-calling upon additional brain regions to meet the demands of the task.

Brain imaging studies also discuss how long the washout period is. Loeber and Yurgelun-Todd (1999) postulate that a washout period of three days is the minimum required in order to have negligible levels of metabolites in the body. In another study, using a challenge paradigm, Yurgelun-Todd et al. (1999) found that even after an extended washout period (28 days), specific differential patterns of cortical activation exist in subjects with a history of heavy marijuana use.

2.1.2 Findings with neuropsychological tests assessing attention, memory and executive functions.

After defining that both resting and activated paradigms show decreased metabolism in areas responsible for attention, memory and executive function. It is an interesting task to see if this is noticeable using special tests addressing these issues. Several neuropsychological studies suggest that long-term cannabis use may produce working memory impairments and attentional dysfunction. In studies on adolescents, Schwartz et al (1989) reported the results of a small but carefully controlled study of persistent memory impairment. The adolescents themselves reported such deficits as persisting for at least 3-4 weeks after last using cannabis. Cannabis users were selectively impaired on the Benton Visual Retention test and the Wechsler Memory Scale Prose Passages. Deficits lessened but were still detectable 6 weeks later; the cannabis group did show improvement over time, but this failed to reach statistical significance.

Block and Ghoneim (1993) have found that, relative to a matched group of healthy, non-drug-using controls, heavy marijuana use is associated with small but significant impairments in memory retrieval, verbal expression and mathematical reasoning, in combination with small improvements in concept formation (i.e. abstraction).

Solowij et al. (1995), using a design involving groups of light and heavy users, have provided evidence that heavy, chronic use of cannabis may be associated with relatively subtle dysfunctions of attentional processing, as indexed by changes in event-related potentials across the scalp, particularly involving the positive potential at around 300 ms following stimulus presentation (P300) and the negative potential preceding it. This evidence was interpreted to indicate problems in the efficient selection of relevant stimulus information and in filtering out irrelevant material.

Pope and Yurgelun-Todd (1996) detected specific impairments of attention, memory and frontal lobe function in heavy marijuana-using college students by means of selected neuropsychological test. Their results suggested that heavy cannabis use was associated with reduced function of the attentional/executive system, as exhibited by decreased mental flexibility and increased perserveration and reduced learning. They also suggested that the most pronounced effects may be on the abilities to shift and/or sustain attention, functions associated with the prefrontal cortex. These results indicate that attentional processing may be particularly affected. Some cognitive deficits appear detectable at least 7 days after heavy cannabis use but appear reversible and related to recent cannabis exposure rather than irreversible and related to cumulative lifetime use (Pope et al., 2001).

Bolla et al. (2002) found as joints smoked per week increased, performance decreased on tests measuring memory, executive functioning in 28-days abstinent heavy marijuana abusers.

Solowij et al. (2002) found that long term cannabis users show impairments in memory and attention that endure beyond the period of intoxication and worsen with increasing years of regular cannabis use.

Ilan et al. (2004) studied the effects of marijuana on neurophysiological signals of working and episodic memory. The results suggested that marijuana disrupted both sustained and transient attention processes resulting in impaired memory task performance. In subjects most affected by marijuana a pronounced ERP difference between previously studied words and new distracter words was also reduced, suggesting disruption of neural mechanisms underlying memory for recent study episodes.

2.2 Summary of cannabis and effects on attention, memory and executive functioning

Both neuropsychological assessment studies and studies based on brain imaging techniques indicate that deficits in attention, memory and executive functioning. Acute neuropsychological effects (within 12-24 hours) of cannabis use include deficits in attention, executive functioning, and short-term memory (Pope et al., 1995; O'Leary et al., 2002).

Some studies indicate long-term effects (after 24 hours – 28 days) on short-memory and attention (Schwartz et al., 1989; Pope et al., 2001; Bolla et al., 2002; Eldreth et al., 2004). Solowij et al. (2002) found that these deficits may last beyond the period of intoxication and cumulate with years of use. This is a recent developed field of investigation, thus future research may reveal more subtle deficits in neurocognitive functioning as the assessments processes improves.

Interesting findings for future research is reported by Eldreth et al. (2004) and Kanayama et al. (2004), hypothesising that marijuana user may recruit an alternative neural network as a compensatory mechanism during performance of tasks of attention.

3. Stimulants

3.1 Amphetamine and methamphetamine

Neuroimaging studies have demonstrated that methamphetamine user exhibit various abnormalities in brain function relative to healthy controls. These include alterations in frontal, temporal, and subcortical brain metabolism (Gouzoulis-Mayfrank et al., 1999; Iyo et al., 1997; Volkow et al., 2001a), changes in brain metabolites suggestive of neuronal injury in the basal ganglia and frontal cortex (Ernst et al., 2000), and decreased density of

dopaminergic neurons in the caudate and putamen (McCann et al., 1998; Sekine et al., 2001; Volkow et al., 2001b).

Volkow (Volkow et al., 2001b) assessed the effects of protracted abstinence on the loss of DA transporters in striatum, in methamphetamine abusers using positron emission tomography. Brain dopamine (DA) transporters in five methamphetamine abusers evaluated during short abstinence (<6 months) and then retested during protracted abstinence (12-17 months) showed significant increases with protracted abstinence (caudate, +19%; putamen, +16%). Although performance in some of the tests for which the researchers observed an association with DA transporters showed some improvement, this effect was not significant. The DA transporter increases with abstinence could indicate that methamphetamine-induced DA transporter loss reflects temporary adaptive changes (i.e., downregulation), that the loss reflects DA terminal damage but that terminals can recover, or that remaining viable terminals increase synaptic arborization. Because neuropsychological tests did not improve to the same extent, this suggests that the increase of the DA transporters was not sufficient for complete function recovery.

Few studies have explicitly attempted to examine the cognitive functioning of methamphetamine users, recent investigations have documented deficits in learning, delayed recall, processing speed, and working memory (Rippeth et al., 2004; Simon et al., 2000).

Marijuana is the most common secondary drug of abuse among methamphetamine users (Simon et al., 2000). Gonzales et al. (2004) measured neurocognitive performance of methamphetamine users discordant for history of marijuana exposure. A comprehensive neuropsychological battery was administered and performance was quantified for five cognitive ability areas. A group using methamphetamine and marijuana demonstrated the greatest neuropsychological impairment, with statistically significant differences observed between the methamphetamine users only and control group in learning, retention/retrieval, and a summary score of global neuropsychological performance. However, methamphetamine and marijuana group did not differ significantly from the control or methamphetamine users only on any neuropsychological ability.

The association between level of dopamine D2 receptors and metabolism in the orbitofrontal cortex in methamphetamine abusers, which replicates previous findings in cocaine abusers, suggests that D2 receptor-mediated dysregulation of the orbitofrontal cortex could underlie a common mechanism for loss of control and compulsive drug intake in drug-addicted subjects (Volkow et al., 2001a). Further, chronic methamphetamine use may cause dopamine transporter reduction in the orbitofrontal cortex, dorsolateral prefrontal cortex, and

amygdala in the brain. Psychiatric symptoms in methamphetamine users may be attributable to the decrease in dopamine transporter density in the orbitofrontal cortex and the dorsolateral prefrontal cortex (Sekine et al., 2003).

3.2 MDMA (3,4-methylenedioxymethamphetamine, ecstasy)

Of the designer drugs, the amphetamine analogues are the most popular and extensively studied, ecstasy in particular. They are used recreationally with increasing popularity despite animal studies showing neurotoxic effects to serotonin (5-HT) and/or DA neurons. Most of these studies provide suggestive evidence that MDMA is neurotoxic to 5-HT neurones, and (meth)amphetamine to DA neurones in humans. These effects seem to be dose-related, leading to functional impairments such as memory loss, and are reversible in several brain regions. Reneman et al. (2001) found in a PET-study an indication that heavy use of MDMA is associated with neurotoxic effects on serotonin neurons that women might be more susceptible than men, and that MDMA-induced neurotoxic changes in several brain regions of female ex-MDMA users are reversible. McCardle et al. (2004) suggests that MDMA users exhibit difficulties in coding information into long-term memory, display impaired verbal learning, are more easily distracted, and are less efficient at focusing attention on complex tasks.

Parrott and Lasky (1998) assessed the effects upon mood and cognition, before, during and after a Saturday night dance. Three groups of young people were compared. Each subject completed a cognitive test and mood scale battery four times: an initial drug-free baseline, at a Saturday night dance/club (on-drug), then 2 days later, and 7 days later. The consumption of cannabis and cocaine at the club was similar across groups. However 2 days afterwards, cognitive performance on both tasks (verbal recall, visual scanning) was significantly reduced on-MDMA. Memory recall was also significantly impaired in drug-free MDMA users, with regular ecstasy users displaying the worst memory scores at every test session. This agrees with previous findings of memory impairments in drug-free ecstasy users. Von Geusau et al. (2004) found that male MDMA users performed significantly worse on the tasks that tap on cognitive flexibility and on the combined executive function tasks. Female users showed no impairments on any of the tasks. The authors conclude that the data suggest that a history of MDMA use selectively impairs executive function. In male users, cognitive flexibility was impaired and increased perseverative behaviour was observed. The inability to adjust behaviour rapidly and flexibly may have repercussions for daily life activities.

3.3 Cocaine

Cocaine induces constriction of coronary and cerebral vessels in both humans and in animal models (Vitullo et al., 1989; Flores et al. 1990), reflecting the ability to use cognitive capacity. Several studies demonstrate both deficits in neuropsychological performance and abnormalities in brain perfusion or metabolism in chronic cocaine abusers and that both of these flow deficits can improve during abstinence (Holman et al., 1993; O'Malley et al., 1992).

Several studies have reported impaired cognitive function in stimulant (cocaine) abusers (Washton and Tatarsky 1984; Ardila et al. 1991; Mittenberg and Motta 1993). Mittenberg and Motta (1993) found significant residual impairment in verbal learning efficiency subsequent to chronic cocaine use that result from memory storage difficulties rather than attentional impairment or general intellectual reduction. Ardila et al. (1991) gave a basic neuropsychological assessment battery to thirty-seven chronic freebase cocaine ("crack") abusers. The following tests were used: Wechsler Memory Scale, Rey-Osterrieth Complex Figure (copy and immediate reproduction), Verbal Fluency (semantic and phonologic), Boston Naming Test, Wisconsin Card Sorting Test, and Digit-symbol from the WISC. In general, performance was lower than expected according to their age and educational level. Subjects showed significant impairment in short-term verbal memory and attention subtests. Neuropsychological test scores were correlated with lifetime amount of cocaine used, suggesting a direct relationship between cocaine abuse and cognitive impairment. A pattern of cognitive decline is proposed. One hundred and eighty-three participants were divided into three groups containing: 61 cocaine-dependent; 59 polydrug-dependent; and 63 normal subjects. All were evaluated using a basic neuropsychological assessment battery. The two dependent groups exhibited significantly lower scores on short-term memory, attention, and concept formation tests. Performance on some subtests correlated negatively with the length of dependency in both groups and frequency of substance use. Test scores were found to correlate with lifetime cocaine abuse, suggesting a relationship between drug abuse and cognitive dysfunction. O'Malley et al. (1992) found mild but significant impairments in tests of attention and memory in 20 heavy cocaine abusers. These subjects also performed poorly on the Category test, but surprisingly were superior in verbal fluency tests. Shortly after cessation, patients (Hoff et al., 1996) display impairment on measures of spatial but not verbal memory, and cognitive flexibility.

4. Heroin

In order to study selective processing of disorder related stimuli on anxiety, depression, and eating disorders, Franken et al. (2000) investigated the role of processing bias of attention in an abnormal motivational system. Heroin dependent participants showed a considerable attentional bias for supraliminally presented heroin cues. However, there was no evidence for a preattentive bias on the subliminal presented cues. Reaction time on heroin cues was significantly predicted by heroin craving-levels. Results indicate that selective processing may be related to motivational induced states in general.

Pau et al. (2002) examined the impact of heroin on frontal executive functioning in three cognitive domains, namely attention, impulse control, and mental flexibility and abstract reasoning. The findings indicate that heroin addiction has a negative effect on impulse control, while attention and mental flexibility/abstract reasoning ability were not affected.

Davis et al. (2002) examined cognitive functioning in people with a current or past history of opiate abuse using a range of neuropsychological tests. The findings in the study suggest subtle impulse control difficulty as a result of five years of heroin use. Other cognitive skills studied, including attention and mental flexibility/abstract reasoning, appeared to be unaffected.

Franken et al. (2003) investigated heroin related visual information processing by employing event related potentials (ERPs). Patients exhibited larger slow positive wave (SPW) components of the ERP on heroin related pictures than on neutral pictures compared to controls, which suggests that these heroin cues are selected by the brain for sustained attentive processing. Within heroin dependent patients, mean SPW response to heroin pictures was correlated with post-experiment craving. The authors conclude that information processing of drug-related information is abnormal in heroin dependent patients.

Heavier use of opiates in long-term users has been shown to be associated with greater likelihood of neuropsychological impairment as assessed by at battery including WAIS, aphasia tests, and the Halstead battery (Grant et al., 1977). Hill et al. (1979) who studied opiate abusers with an almost exclusive drug preference for heroin found that they were impaired on Tactual Performance for memory and location and Tapping Tests, but not on the Category Test, a measure of abstract reasoning ability. They concluded that, since performance on the Category Test is thought to be related to damage to the frontal lobes, this

brain region may be less affected by opiate abuse. This conclusion is supported by some extent by results from studies that have failed to detect a difference between opiate users and controls on other measures of neuropsychological functioning thought to correlate with frontal lobe damage; for example, abstract thinking (Bruhn and Maage, 1975) or verbal fluency (Rounsaville et al., 1982).

An interesting study was performed by Ornstein et al. (2000) comparing groups of subjects whose primary drug of abuse was amphetamine or heroin, together with age- and IQ-matched control subjects. The study consisted of a neuropsychological test battery which included both conventional tests and also computerised tests of recognition memory, spatial working memory, planning, sequence generation, visual discrimination learning, and attentional set-shifting. Many of these tests have previously been shown to be sensitive to cortical damage (including selective lesions of the temporal or frontal lobes) and to cognitive deficits in dementia, basal ganglia disease, and neuropsychiatric disorder. Qualitative differences, as well as some commonalities, were found in the profile of cognitive impairment between the two groups.

The chronic amphetamine abusers were significantly impaired in performance on the extra-dimensional shift task (a core component of the Wisconsin Card Sort Test) whereas in contrast, the heroin abusers were impaired in learning the normally easier intra-dimensional shift component. Both groups were impaired in some of tests of spatial working memory. However, the amphetamine group, unlike the heroin group, were not deficient in an index of strategic performance on this test. The heroin group failed to show significant improvement between two blocks of a sequence generation task after training and additionally exhibited more perseverative behaviour on this task. The two groups were profoundly, but equivalently impaired on a test of pattern recognition memory sensitive to temporal lobe dysfunction. These results indicate that chronic drug use may lead to distinct patterns of cognitive impairment that may be associated with dysfunction of different components of cortico-striatal circuitry. In verbal fluency the chronic drug abuse groups both generated fewer words than the controls. This effect was significant in the case of the letter fluency (FAS) component, but not in the case of the semantic (‘animal’) component of the task. The combined (amphetamine and heroin) drug abuse was impaired on pattern and spatial recognition memory compared to their control subjects.

4. Discussion

Searching PubMed (January 2005) for attention and memory, gives the following top five in the abuse perspective; cannabis, cocaine, ecstasy, methamphetamine, heroin. The order probably well illustrates the prevalence of the drugs. When executive functioning was added to the search, only ten studies for all the above mentioned drugs together were found. This indicates paucity in studies assessing drug abuser and executive functioning. The brain imaging studies contain the same technique but have different angles of approach, which gives many pieces to fit together. The neuropsychological tests are assessing different aspects of attention, memory processes, and executive functions, which provides even more pieces to fit together. Additionally, it may be that the neuropsychological tests are not sensitive enough to detect subtle deficits, even if these subtle deficits are illustrated in brain imaging studies and are well known in clinical settings.

4.1 Areas of interest

The localisation of the cannabinoid receptor with high densities in basal ganglia, cerebral cortex and hippocampus (Herkenham et al., 1990) is an indication of cannabinoid involvement in attentional and memory processes. The cannabinoids probably interfere with the normal processing of sensory information by interrupting the transmission of neural activity between the hippocampus, cortex and other brain regions, causing a fragmentation of the neuropsychological network.

The cortical distribution of dopaminergic and opiate receptors (Joyce and Meador-Woodruff, 1997) might be expected to lead to different patterns of cognitive impairment among stimulants and opiate abusers. For example, dopamine (DA) D1 receptors are mainly present in the anterior neocortex (especially prefrontal cortex). Subcortically, stimulants and opiates have distinct effects in the nucleus accumbens, but share some common actions, for example in boosting the activity of the mesolimbic dopamine system (Koob and LeMoal 1997; Wise and Bozarth 1984).

Consequently, some similarities in the profiles of neuropsychological impairment might also result from long-term abuse of these drugs. Chronic abuse of stimulants, and also opiates, may lead to changes in neurotransmission present in DA terminals such as nucleus accumbens, caudate-putamen, and frontal cortex, leading to disruptive functioning of cortico-striatal loops subserving cognitive and affective information processing (Sorg et al., 1997). Lower levels of dopamine D2 receptor availability have been previously reported in cocaine abusers, alcoholics, and heroine abusers (Volkow et al., 2001a).

Goldstein and Volkow (2002) found in a review of drug addiction and its underlying neurobiological basis that the orbitofrontal cortex and the anterior cingulated gyros, which are regions neuroanatomically, connected with limbic structures, are the frontal cortical areas most frequently implicated in drug addiction. They are activated in addicted subjects during intoxication, craving, and bingeing, and they are deactivated during withdrawal. These regions are also involved in higher-order cognitive and motivational functions, such as the ability to track, update, and modulate the salience of a reinforcer as a function of context and expectation and the ability to control and exhibit prepotent response. In addition, imaging studies have also documented a role of dopamine in motivation, which appears to be encoded both by fast as well as smooth DA increases (Volkow et al., 2004a; Volkow et al. 2004 b). Hippocampus has an important role in inhibiting previously acquired and now irrelevant responses, among other functions in organizing memories (Douglas, 1967; Eichenbaum and Cohen, 2001) and that interfering with hippocampal functioning can increase behaviours that are not hippocampus-dependent (Packard et al., 1989).Thus, there are reasons to suspect a relationship between prefrontal dysfunction and drug use in normal individuals. In the following section the different drugs of abuse will summarized and discussed.

4.2 Cannabis

Brain imaging studies of cannabis users have demonstrated altered function, blood flow, and metabolism in prefrontal and cerebellar regions (Loeber and Yurgelun-Todd, 1999; Block et al., 1999; Block et al., 2000a; Block et al., 2000 b; Lundqvist et al., 2001). Thus, cannabis produces various metabolic changes in the brain. Long-term cannabis users appear to have lower resting levels of CBF compared with non-smokers. Cannabis increases CBF and brain metabolism in experienced users, while it decreases CBF in non-users. These effects have been particularly apparent in frontal cortical areas. Decreases in rCBF were localized to brain regions that mediate sensory processing and attention.

Studies using a challenge paradigm indicate that even after an extended washout period, specific differential patterns of cortical activation exist in subjects with a history of heavy marijuana use. During a challenge paradigm smokers who completed twenty-four hours of washout showed diminished activation in dorsolateral prefrontal cortex (DLPFC). The effect remained diminished after twenty-eight days of washout, although some increase in the DLPFC activation was noted relative to the twenty-four hour time point (Yurgelun-Todd et al., 1999). Memory-related blood flow in frequent marijuana users showed decreases relative

to controls in prefrontal cortex, increases in memory-relevant regions of cerebellum, and altered lateralization in hippocampus (Block et al., 2002). The greatest differences between users and controls occurred in brain activity related to episodic memory encoding.

It may be that marijuana users recruit an alternative neural network as a compensatory mechanism during performance on a modified version of the Stroop task (Eldreth et al., 2004). This observation suggests that heavy long-term cannabis abusers may experience subtle neurophysiological deficits, and that they compensate for these deficits by "working harder"-calling upon additional brain regions to meet the demands of the task (Kanayama et al., 2004).

There is good consensus that heavy cannabis use produces residual neuropsychological deficits on measures such as memory of word lists (Pope et al., 1995; Pope and Yurgelun-Todd, 1996; Fletcher et al, 1996; Pope et al:, 2001, Solowij et al., 2002), selective and divided attention tasks (Fletcher et al., 1996; Pope et al., 2001) that may last for many days after cessation. Pope et al (2001) found no evidence of persistent impairment after 28 days abstinence but Pope et al (2002) report from a further analysis of the data from the same sample, persistent deficits among those who commenced cannabis use prior to the age of 17. Bolla et al (2002) found persistent dose-related decrements in neuropsychological performance after 28 days abstinence using a very similar neuropsychological test battery. Solowij (1995) found partial recovery but persistence of some selective attention deficits after a mean 2 years abstinence. However, at present consensus is still lacking on the question of whether increasing duration of cannabis exposure causes increasing cognitive deficits. To date the result of different studies indicate that cannabis-associated cognitive deficits are reversible and related to recent cannabis exposure (Pope et al., 2002). Two sophisticated studies have produced (Solowij et al., 2002; Pope et al., 2002) somewhat different findings in this question. Studies failing to detect cognitive decline associated with cannabis use (Lyketsos et al., 1999) may reflect insufficient heavy or chronic use of cannabis in the sample or the use of insensitive assessments instruments (Solowij and Grenyer, 2002).

4.3 Amphetamine and methamphetamine

Neuroimaging studies have demonstrated alterations in frontal, temporal, and subcortical brain metabolism (Gouzoulis-Mayfrank et al., 1999; Iyo et al., 1997; Volkow et al., 2001a), changes in brain metabolites suggestive of neuronal injury in the basal ganglia and frontal cortex (Ernst et al., 2000), and decreased density of dopaminergic neurons in the caudate and

putamen (McCann et al., 1998; Sekine et al., 2001; Volkow et al., 2001b). The DA transporter increases with abstinence could indicate that methamphetamine-induced DA transporter loss reflects temporary adaptive changes (i.e., downregulation), that the loss reflects DA terminal damage but that terminals can recover, or that remaining viable terminals increase synaptic arborization (Volkow et al., 2001b). Because neuropsychological tests did not improve to the same extent, this suggests that the increase of the DA transporters was not sufficient for complete function recovery. Recent investigations have documented deficits in learning, delayed recall, processing speed, and working memory (Rippeth et al., 2004; Simon et al., 2000) and the psychiatric symptoms in methamphetamine users may be attributable to the decrease in dopamine transporter density in the orbitofrontal cortex and the dorsolateral prefrontal cortex (Sekine et al., 2003).

4.4 MDMA (3,4-methylenedioxymethamphetamine, ecstasy)

MDMA users are suggested to exhibit difficulties in coding information into long-term memory; display impaired verbal learning, more easily distracted, and less efficient at focusing attention on complex tasks (McCardle et al., 2004). The majority of the MDMA studies indicate that the degree of executive impairment increases with the severity of use, and that the impairments are relatively lasting over time. Some studies indicate sex differences (Reneman et al., 2001; Von Geusau et al., 2004), that women might be more susceptible than men, and that men performed significantly worse on the tasks that tap on cognitive flexibility and on the combined executive function tasks. In male users, cognitive flexibility was impaired and increased perseverative behaviour was observed. The inability to adjust behaviour rapidly and flexibly may have repercussions for daily life activities.

4.5 Cocaine

Chronic cocaine users display impaired attention, learning, memory, reaction time and cognitive flexibility. Shortly after cessation, patients (Hoff et al., 1996) display impairment on measures of spatial but not verbal memory, and cognitive flexibility. Roselli and Ardila (1996) reported significant correlations between the chronicity of use of cocaine and other drugs and moderate executive performance deteriorations, evaluated by the Wisconsin Card Sorting Test (WCST).

4.6 Heroin

Findings indicate that heroin addiction has a negative effect on impulse control (Pau et al., 2002). With regard to opioid and amphetamine users, Ornstein et al. (2000) showed the existence of alterations in the executive processes of attentional set shifting and sequence generation. Pau et al. (2002) have also found a significant correlation between opioid abuse and executive functioning impairment, and that reaction time on heroin cues was significantly predicted by heroin craving-levels (Franken et al., 2000). This indicates that selective processing may be related to motivational induced states in general (Franken et al., 2000). Subtle impulse control difficulty as a result of five years of heroin use, but other cognitive skills studied, including attention and mental flexibility/abstract reasoning, appeared to be unaffected (Davis et al., 2002).

4.7 Concomitant use of cannabis or alcohol

Studies focusing on concomitant use or polydrug use have tried to differentiate between effects of different drugs used simultaneously. A group using methamphetamine and marijuana demonstrated the greatest neuropsychological impairment, with statistically significant differences observed between the methamphetamine users only and control group in learning, retention/retrieval, and a summary score of global neuropsychological performance (Gonzales et al., 2004).

Several studies report MDMA and concomitant cannabis use. The main finding was that cannabis users, whether or not they also used MDMA, showed significantly impaired memory function on word free-recall and on immediate and delayed story recall compared to non-users (Dafters et al., 2004). The results suggest that cannabis is an important confounds in studies of MDMA-related cognitive impairment, and that previously reported cognitive impairment in MDMA users may have been caused by coincident cannabis use.

The concomitant use of cocaine and alcohol may have additive negative effects on the brain as compared to the use of only one of these two substances (Bolla et al., 2000). After controlling for the effects of age, sex, and intelligence on performance, the authors found dose-related associations between neurobehavioral performance and cocaine dose and alcohol dose. When the influences of cocaine and alcohol on neurobehavioral performance were taken separately, cocaine and alcohol each selectively affected performance on different neurobehavioral tests after 1 to 3 days of abstinence, with these effects persisting after 4 weeks of abstinence.

4.7 Concluding remarks

The scope of this review does not include a report on or discussion of the effects of polydrug use on attention, memory and executive functions, nor the interaction between opioid and cannabinoid systems. In the section concerning the areas involved in those processes indicate that the difficulties will worsen with drugs added. There is a consensus that all drugs create a disharmony in the neuropsychological network, causing a decrease of activity in areas responsible for short-term memory, attention, and executive functioning with the possible exception of heroin. It is worth pointing out the effort made in many of these studies to relate quantity and chronicity measures of drug use with the magnitude of the neuropsychological impairments. Due to the absence of a more profound knowledge about the cause–effect relationships in the area of the neuropsychology of drug dependence, and the considerable methodological difficulties associated to longitudinal studies, these chronicity and severity-related measures can provide important support for the hypothesis that drugs generate neuropsychological alterations, and not the other way around. Brain Imaging Techniques on the other hand reveal that changes in brain function differs between drugs, but neuropsychological assessments show similar results or no changes in function. The results yielded by these neuropsychological studies have shown the existence of significant impairments in the executive functioning of users of a number of substances.

Despite the wealth of research, there are obviously many questions unanswered within the area of cognitive impairment induced by drug use, especially when it is considered to be subtle. The development of parameters of use that are associated with short- or long-lasting cognitive and brain dysfunction will provide more answers to the question when a cognitive function starts to get impaired.

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