

Investigating the neurocognitive deficits associated with chronic drug misuse

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Cognitive deficits associated with the chronic abuse of drugs have important theoretical and clinical significance: such deficits reflect changes to the underlying cortical, sub-cortical and neuromodulatory mechanisms that underpin cognition, and also interfere directly with rehabilitative programs. Recent investigations have been made into the neuropsychology of chronic abuse of cannabis, stimulants and opiates. It is suggested that future progress in this area, involving developing advances in brain-imaging and neuropharmacology, will capitalize on experimental demonstrations of specific patterns of impairments in decision-making, attention and memory function.

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Abbreviations

MDMA 3,4-dioxyethylenemethamphetamine
PET positron emission tomography
PFC prefrontal cortex
THC Δ^9 -tetrahydrocannabinol

Introduction

Cognitive impairments may contribute to drug misuse and addiction in at least two ways. First, they may increase the likelihood of drug-seeking behaviour through various kinds of cognitive deficits including, for example, failures of impulse control mechanisms. Second, they may interfere with users' capacity to assimilate and participate in rehabilitation programs that often have an educative and cognitive emphasis [1].

The nature and extent of cognitive deficits in drug abusers, and their relationship to hypothesised neurochemical and morphological pathology, is now a burgeoning area of research that capitalises on advances on all fronts of cognitive neuroscience. These include advances in neuroanatomy and molecular pharmacology [2,3], psychological theory relating to the nature of motivated action and reinforcement mechanisms for drugs of abuse [4], and sophisticated imaging techniques for studying the physiological correlates of cognitive activity in the brain, including positron emission tomography (PET) and functional magnetic resonance imaging modalities [5–7], as well as event-based electroencephalography [8].

Despite the growth of this research and its ability to use such impressive technical resources, however, the study of the neuropsychology of human drug abuse also faces formidable clinical, methodological and theoretical obstacles. In this review, we first describe briefly these obstacles and then consider how recent studies investigating neurocognitive deficits associated with different kinds of drugs have coped with these problems. In separate sections, we consider the neurocognitive correlates of the 'illicit' use of cannabis, stimulants and opiates. We do not discuss the well-documented neurocognitive correlates of prolonged alcohol or nicotine abuse, or the more commonly prescribed drugs liable to abuse such as the benzodiazepines. Relevant reviews have been published elsewhere [9,10]. However, we do refer to the neuropsychological correlates of alcohol abuse in connection with selected stimulant-abuse studies discussed below.

Theoretical and methodological issues

Most of the neurotransmitters affected by drugs of abuse exert their effects through relatively diffuse patterns of innervation 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 classes of drug (e.g. stimulants versus hypnotics/sedatives).

The chronic use of illicit drugs may be associated with a rather generalized profile of neuropsychological deficit; however, there are also important differences in the patterns of innervation associated with different neurotransmitter systems, coupled with corresponding differences in the distributions of various receptor subtypes. For example, dopaminergic innervation tends to be most pronounced in anterior cortical regions, whereas cannabinoid receptors are most densely concentrated in the basal ganglia and the hippocampus, and are relatively absent in the brain stem [11]. Therefore, in addition to whatever general cognitive deficits may be associated with chronic drug misuse, there may be subtle differences associated with the abuse of different classes of drugs that have distinctive modes of actions. Moreover, although most investigations have used traditional neuro-psychological tests whose reliability and sensitivity for neural dysfunction may be quite variable, more recently developed and sensitive neurocognitive instruments may be able to detect specific cognitive changes.

At the outset, it is important to acknowledge that neuropsychological investigations — and for that matter, brain-imaging studies — produce only correlational data. Converging evidence from animal models is needed to

establish that prolonged administration of such drugs produces not only the kind of chemical and morphological changes already widely documented [12], but also cognitive and behavioural changes comparable to those demonstrated in the kind of studies under review here. In the absence of such data, it is tricky to distinguish between neurocognitive deficits that reflect cumulative changes to neurotransmitter function resulting from prolonged abuse and a pre-existing neurocognitive abnormality.

Finally, workers in the field have also been faced with the need to make decisions about a complicated set of clinical variables, the two most obvious being the duration of time between last use of drug and assessment, and the need to control for poly-drug abuse. Other problems commonly associated with neuropsychological research into psychiatric populations include elevated rates of co-morbid psychiatric disorders that tend to compromise interpretation of results in the absence of carefully matched positive control groups, as well as variable levels of concurrent medication for co-morbid disorders and for substance abuse itself (e.g. methadone treatments). No published study has been able to address adequately all of these challenges simultaneously, so the best research in this area has necessarily been concerned with fairly precisely framed issues. The most recent publications on the neurocognitive deficits in substance abuse reflect its clinical diversity and involve many different methodological designs, including cross-sectional and prospective longitudinal studies.

Cannabis

Previous reviews have concluded that early studies into the effects of prolonged cannabis use provided only very weak evidence that neurocognitive deficits persisted beyond the residual effects of drug taken within the previous 12–24 hours [13]. However, Block and Ghoneim [14] 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). Their conclusions have been bolstered by the findings of a large prospective study involving both younger and older cohorts of Costa Rican cannabis users and appropriately matched non-using control groups [15]. In this latter study, a comparison of the differences between both user groups and their respective controls suggested that prolonged use of cannabis is associated with memory deficits on free-recall and list-learning tasks, and difficulties on both selective and divided attention tasks.

Solowij *et al.* [16], using a design involving very well-matched 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. Further work suggests that these deficits may endure over time [17].

Most recently, Ehrenreich *et al.* [18] have reported that deficits in human visual scanning (which undergoes maturation between 12–15 years of age) are best predicted by earlier onset of cannabis use (before 16 years of age versus after 16 years), suggesting that early use is associated with later cognitive dysfunction. These results are also consistent with the above claims that attentional processing may be particularly affected [15,19]. In the main, researchers have concluded that neurocognitive changes that can be reasonably attributed to chronic cannabis use are subtle compared, for example, with those seen in neurological illness [15], and depend on prolonged and quite heavy levels of consumption [19].

Establishing the neural basis for any cognitive changes associated with chronic use of cannabis remains difficult. Only a few investigations have used neuroimaging procedures, including cerebral blood flow and PET protocols, to explore structural or functional changes associated with prolonged use. Volkow *et al.* [20], extending preliminary work, reported lower baseline cerebellar metabolism in chronic users than in controls, but greater increases in prefrontal (orbitofrontal) areas and the basal ganglia after administration of Δ^9 -tetrahydrocannabinol (THC). The latter finding suggests that alterations in the processing of fronto-striatal circuitry may mediate the clinical manifestations of cannabis use involving behavioural dysregulation. The recent finding that repeated administration of THC in rats reduced prefrontal dopamine metabolism [21] provides support for this possibility.

Within the past few years, additional evidence for altered cerebellar activity in chronic cannabis users has accumulated [22]; however, evidence for structural changes in humans may depend on length of use. Wilson *et al.* [23] have reported PET findings indicating that early onset of cannabis use (<17 years) is associated with structural abnormalities including reduced whole brain volume and percentage of grey matter, but higher global cerebral blood flow; whereas Block *et al.* [24] report data, obtained with magnetic resonance imaging, that frequent use of marijuana in younger subjects is associated only with lower ventricular cerebrospinal fluid volume.

In summary, recent data indicate 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. The marked concentration of recent research on altered attention, and the relatively unquestioned assumption that such changes can account for the disrupted memory associated with misuse of cannabis, has meant that more recently developed assays of mnemonic function have been neglected.

Stimulants

Reflecting the massive increase in cocaine use during the early 1980s, research into the cognitive effects of prolonged stimulant abuse has been dominated by the search for characteristic patterns of deficits following chronic cocaine abuse, highlighting problems in visuo-motor performance, attention and verbal memory [25–27]. Length of abstinence has been a common theme with some claims that residual deficits persist over months of abstinence [28,29]. The issue of whether or not cocaine abusers continue to show neuropsychological deficits beyond their period of immediate withdrawal has some importance in the light of influential research indicating that regional cerebral blood flow is reduced in the frontal cortex of abstinent cocaine abusers [30–32]. Volkow *et al.* [31] used PET, 2-deoxy-2-[¹⁸F]fluoro-D-glucose (FDG) and [¹⁸F]fluoro-D-glucose methodology in 20 male chronic cocaine abusers and 38 male control subjects to show that reduced D2 receptor availability correlates with reduced metabolism in the orbital prefrontal cortex. Moreover, these reductions in D2 receptor availability remained evident during 3–4 months of detoxification, suggesting that cocaine abuse is associated with persisting changes in receptor function that may in turn disrupt the operation of frontostriatal circuitry.

Interpreting the neural basis for the deficits associated with cocaine use is complicated by cocaine's association with a variety of pathologies that might impair cognition through cerebral vasculitis, stroke, seizures and intracranial haemorrhage. Additionally, some researchers have proposed that the concurrent use of cocaine and alcohol might also impair cognitive function through the neurotoxic effects of cocaethylene [33]; however, there is mixed evidence that the joint abuse of both substances produces larger cognitive deficits than the abuse of cocaine alone [34,35].

Within the past two years, several studies have adopted the approach of choosing some set of neurocognitive outcome measures — encompassing many different traditional indices of verbal memory, visual memory, executive functioning, visuo-construction and visuo-perception, psychomotor speed and manual dexterity — and then regressing these performance measures against not only demographic and psychometric measures expected to be of influence such as age, gender, level of attained education and ethnicity, but also drug-related variables such as frequency of use, intensity of use and duration of use. The results suggest that greater intensity of earlier cocaine use in abstinent users is associated with more marked deficits on those measures associated with executive control, visuo-spatial abilities, psychomotor speed and manual dexterity ([36••]; see also [37]). Further research has suggested that dose-related deficits in verbal learning and memory remain over four weeks of abstinence [38].

Misuse of amphetamine has long been associated with profound psychological disturbance [39]; however, recent research has revealed more precisely the character of the neuropsychological deficits seen in groups of chronic

amphetamine abusers. Starting with the observation that chronic drug abusers exhibit several of the behavioural changes associated with focal lesions of the frontal lobes — lack of behavioural regulation, altered decision-making and a lack of concern for the consequences of actions — Rogers *et al.* [40••] proposed that such individuals should also show deficits on neuropsychological measures of such functions that depend on the frontal lobes.

These authors examined performance in a computerised decision-making task in independent samples of amphetamine-dependent individuals, opiate-dependent individuals, patients with focal lesions of the dorsolateral prefrontal cortex (PFC), patients with lesions of the orbital PFC, and non-drug-using controls. Validatory work indicated that the patients with the orbital lesions took significantly longer to make their decisions than both the patients with dorsolateral lesions and the normal controls, and were more likely to choose the response option that was least likely to lead to reward. Both drug-dependent groups showed the same increase in the time taken to make decisions as the patients with the orbital lesions but, importantly, only the chronic amphetamine abusers exhibited the same tendency to choose the less adventitious responses.

These data suggest that chronic amphetamine abuse is associated with altered functioning of the circuitry, involving the ventral PFC, that mediates decision-making, and are consistent with earlier results indicating that prolonged stimulant use (cocaine) is associated with altered metabolism in the orbital cortex [31]. The finding that analogous deficits in decision-making were demonstrated by non-using controls who underwent rapid dietary tryptophan depletion, leading to reduced central serotonin function [41], suggests that altered neuromodulation of this circuitry underpins these deficits. Supportive evidence has been provided by recent autopsy data indicating reduced cortical monoamines (serotonin in the orbital prefrontal cortex, dopamine in the striatum) in the brains of methamphetamine abusers [42,43].

Follow-up work indicates that both chronic amphetamine and chronic opiate abusers also exhibit marked deficits on a range of neuropsychological tasks, involving attentional control, planning and spatial working memory, that have been shown previously in both neurological and imaging studies to depend on the integrity of the frontal lobes [44••]. As with the decision-making deficits that were more marked in the amphetamine abusers than in the opiate abusers, however, there were subtle differences in the profile of deficits of the amphetamine abusers compared with those of the opiate abusers: namely, the amphetamine abusers had more marked problems in the control of an attentional bias but milder deficits in the use of strategy in a spatial memory task as compared with the opiate abusers. Recent work has extended the ERP methodology previously used in chronic cannabis users [19] to demonstrate problems in attentional mechanisms of amphetamine

abusers, as measured by increased processing negativity and reduced P300 amplitude in a signal attention task [8].

The finding that both amphetamine and opiate abusers display quite widespread deficits in frontal lobe function is consistent with the proposal that chronic drug abuse is somehow associated with altered monoamine activity that might, through relatively diffuse patterns of innervation across the forebrain and frontal cortex, mediate deficits in behavioural organisation. Moreover, Grant *et al.* [45**] have shown that a group of polydrug abusers with high levels of stimulant abuse were impaired on another decision-making measure also known to be sensitive to orbital prefrontal pathology [46] but not on the Wisconsin Card Sorting Task, a traditional but unreliable measure of concept formation and cognitive flexibility [47]. Finally, Bechara *et al.* [48**] have shown that a group of polydrug abusers, with histories of both stimulant and alcohol abuse, were impaired on the same decision-making measure as used by Grant *et al.* [45**]. As three separate studies, using different and complementary measures, have now shown consistent deficits in the decision-making function of chronic drug abusers, brain-imaging studies should be carried out to establish that these deficits are mediated by altered orbital functioning [49*].

Of course, neuropsychological data cannot settle the issue of whether these deficits are caused by chronic drug abuse or whether they possibly reflect some pre-existing cognitive vulnerability that contributes to later drug-seeking behaviour. However, recent work with animal models has extended the now well-known demonstrations that repeated administrations of methamphetamine produce reduced levels of monoamines in the frontal cortex [12], by indicating functional deficits in the same animals. Thus, repeated phencyclidine treatment has been found to reduce both prefrontal dopamine [50] and performance in an object-retrieval memory task [51*], and to impair inhibition of a conditioned response [52]. In addition, the administration of escalating doses of amphetamine to rhesus monkeys has been found to alter, for up to 28 days, behavioural responses to later amphetamine challenge [53*].

Other studies have extended the evidence for structural change after repeated injections of psychostimulants, including cocaine, by demonstrating morphological changes in the dendritic branching in the ventral striatum and frontal cortex [54**], further highlighting the possibility that chronic psychostimulant abuse may produce brain changes that mediate cognitive deficits. Depleted monoamines have also been demonstrated in monkeys after repeated doses of amphetamine at doses comparable to those used recreationally by humans [55]. Therefore, there is support for a 'working hypothesis' that neuropsychological deficits in stimulant abusers reflect cumulative changes to ascending chemical pathways modulating frontal lobe functions.

Accumulating evidence suggests that repeated exposure to 3,4-dioxyethylenemethamphetamine (MDMA; 'ecstasy')

also produces both long-lasting reductions in markers of serotonergic function and permanent morphological changes [56]. Converging research with human MDMA users using brain-imaging and ligand technologies has demonstrated reduced serotonin receptor binding, possibly attributable to repeated exposure to the drug [57]. Consistent with such changes in neuromodulatory actions of the serotonergic system, several studies have now shown that MDMA users exhibit impairments in tests of short-term memory and more complex attentional functioning, as compared with non-drug-using controls and other drug-abusing groups [58–61].

The neural basis of deficits in MDMA users is unclear at the current time, with one recent study that controlled for use of other illicit drugs, as well as personality variables associated with drug use, indicating that established and prolonged MDMA use may not be associated differentially with widespread deficits on, for example, tasks of frontal lobe function, but may be associated with problems in impulse control mechanisms [62]. These problems may also be associated with deficits in affective learning, which have been shown recently to be sensitive to serotonergic manipulations in healthy volunteers [63].

Opiates

In comparison with cannabis and stimulants, there has been substantially less research into neuropsychological deficits in chronic abusers of opiates. Early studies found some evidence that opiate abusers are more likely to be impaired on batteries of traditional neuropsychological tests such as the Halstead battery, and the Wechsler Adult Intelligence Scale (WAIS) and aphasia tests [64], whereas Hill and Mikhael [65] found evidence of impairment in some measures of memory but relatively few impairments in tasks involving abstraction and reasoning such as the Category tests.

The lack of impairment on tasks of abstraction has led other investigators to conclude that opiate abuse is not associated with deficient frontal lobe functioning [66,67]. As we have seen, however, the development of more sensitive measures has demonstrated that opiate abusers do have marked deficits in frontal lobe functioning, relative to healthy control subjects, even though these deficits may not include problems with altered attentional control or altered decision-making [40**,44**]. Finally, the finding that opiate abusers were not as impaired as stimulant abusers on the decision-making task should not be taken as evidence that opiate abusers do not have problems with choices involving motivationally significant outcomes. Madden *et al.* [68] provided evidence that, given notional choices between small, immediate rewards and large delayed rewards, opiate abusers tend to choose the smaller rewards rather more frequently than did non-drug-using controls, and that this effect is enhanced when the reward itself is heroin as opposed to monetary rewards. Further research with such procedures is required to indicate whether this pattern of choices reflects an

increased trait impulsivity as reflected in personality inventories and previously seen in other populations of drug abusers [69].

Inevitably, the interpretation of neuropsychological deficits in opiate abusers is complicated by the high incidence of methadone treatment, which may exaggerate cognitive deficits through its own pharmacological actions; however, formal studies to address this issue have not been attempted. Although the evidence for persisting structural or functional changes in brain function following repeated administration of opiates is more limited than that after stimulant administration, recent work has indicated that repeated administration of morphine can lead to morphological change in the frontal cortex of rats [70•]. Work with animal models, perhaps involving the discounting paradigm described above [68], are needed to establish whether these morphological changes can induce cognitive changes analogous to those seen in humans.

Conclusions

Progress in preventing and treating drug misuse and addiction requires a fuller understanding of the significance of cognitive dysfunction in the onset and maintenance of drug-seeking behaviour. At the clinical level, diagnostic systems need to be refined to characterize further the nature of substance abuse disorders at various stages of pathology so that the clinical impact of cognitive dysfunction can be more fully appreciated. Neuropsychological deficits associated with drug abuse involving attentional, mnemonic and response-based mechanisms often appear to be relatively subtle across drug preference and to have an uncertain relationship with the abstinent state. Therefore, experimentation will require the study of groups, however hard to identify, with more consistent and homogenous patterns of drug use, as well as more detailed investigation of the acute cognitive effects of drugs of abuse and of concurrent medication.

The next stage for research in this area will be to provide convincing links between cognitive deficits and underlying changes in brain physiology as most clearly revealed by imaging modalities. Clues about the nature of these links can be found in the growing evidence that substance abuse is likely to involve changes within multiple levels of the neurocognitive system, including the limbic-striatal circuitry mediating incentive/motivational processes in respect of the drugs of abuse, and the fronto-striatal circuitry mediating attentional, decisional and output mechanisms [71•]. In this context, the recent suggestion that dysfunctional D2 receptors in the striatum produce disturbances in circuitry extending to the orbital cortex provides insight into how deficits in both systems may synergise to mediate cognitive dysfunction [72••], with the conjoint use of monoaminergic agents — such as methylphenidate — being one means of exploring the pharmacological treatments necessary to correct these disturbances [73••]. Also, rapidly developing research into genetically mediated individual differences in receptor

function, together with animal models using cognitive and behavioural paradigms with proven construct validity, will help establish whether these neurocognitive deficits pre-date drug seeking or are the result of prolonged, illicit drug exposure.

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- This well-designed study compares the decision-making function and cognitive flexibility of a group of 30 polydrug abusers with that of 24 healthy controls, using a 'gambling task' [46] and the Wisconsin Card Sorting Test [47]. Specific deficits are evident in decision-making but not in cognitive flexibility. As decision-making is measured by a gambling task with well-established sensitivity to orbital cortical damage [46,48], these data provide strong evidence that substance abuse may be associated with altered processing in neural circuitry encompassing the inferior frontal lobes.
- A comprehensive comparison between the profiles of neurocognitive deficits in 23 chronic amphetamine abusers, 22 chronic opiate abusers and groups of non-drug-using controls, which assessed recognition memory, spatial working memory, planning, sequence-generation and learning, visual discrimination learning, and attentional-set shifting with neuropsychological instruments validated in studies with neurological patients and studies with brain-imaging techniques in normal volunteers. Both groups are impaired at spatial working memory tasks. The amphetamine abusers are worse than both the opiate abusers and the controls at shifting an attentional set, whereas the opiate abusers are worse at generalizing an already acquired attentional set to new learning and are also impaired in acquiring strategy in the sequence-generation task. These results suggest that there is general impairment common to amphetamine and opiate abusers, with some evidence of specific deficits in each case.
- This study examines 30 abstinent chronic cocaine abusers and 21 non-drug-using controls subjects matched for age, education and intelligence. Multiple regression analysis indicates that chronic cocaine use is associated with persisting deficits in visuo-spatial function, response speed and motor co-ordination, and that these deficits are most pronounced in heavy users. Although dependent upon the veracity of patient report, this approach permits the identification of relationships between different patterns of drug abuse in various clinical settings and specific patterns of cognitive deficits.
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This is a stimulating review offering the hypothesis that altered neuromodulation of frontostriatal circuitries, a result of prolonged substance abuse, produces an imbalance between heightened incentive, motivational properties of drug and conditioned stimuli, and a significantly reduced capacity to modulate the motivational effects of such stimuli on ongoing behaviour and cognition (e.g. through inhibitory mechanisms). Cited data indicate how animal models may be able to unpick those aspects of cognitive dysfunction in substance abuse that reflect the effects of drug as opposed to pre-existing vulnerability.
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This is an excellent review of the most recent brain-imaging research into substance abuse. The authors suggest that inconsistent activation of reinforcement circuits involving the nucleus accumbens and amygdala, following drug

use, produces dysfunction in the orbital prefrontal cortex through circuitry involving the striatum, thalamus and orbital prefrontal cortex. Altered orbital prefrontal cortex activity, governed by D2 receptors, is associated with intensity of craving, suggesting that the characteristic compulsion and loss of control associated with addicted state is mediated by dysfunctional orbital cortical fields.

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To assess whether the decreased D2 receptor density in the striatum and the reduced metabolism in the cingulate cortex and frontal cortex of chronic cocaine abusers could be remediated with methylphenidate, the authors administered methylphenidate to 20 cocaine abusers while measuring D2 receptor availability with [^{11}C]raclopride, a D2-receptor antagonist. Methylphenidate induced variable changes in brain metabolism depending on levels of D2 availability; these changes correlated with craving in the case of the right orbital prefrontal cortex and right striatum, and with mood in the case of prefrontal metabolism more generally.