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The Neuropsychology of Amphetamine and Opiate Dependence: Implications for Treatment

Karen D Ersche • Barbara J Sahakian

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Abstract Chronic use of amphetamines and/or opiates has been associated with a wide range of cognitive deficits, involving domains of attention, inhibitory control, planning, decision-making, learning and memory. Although both amphetamine and opiate users show marked impairment in various aspects of cognitive function, the impairment profile is distinctly different according to the substance of abuse. In light of evidence showing that cognitive impairment in drug users has a negative impact on treatment engagement and efficacy, we review substance-specific deficits on executive and memory function, and discuss possibilities to address these during treatment intervention.

Keywords Cognition ■ Executive function ■ Substance abuse ■ Amphetamines ■ Opiates ■ Cognitive enhancement

Abbreviations

ACC	anterior cingulate cortex
ADHD	attention deficit hyperactivity disorder
BIS-11	Barratt Impulsiveness Scale, version 11
CANTAB	Cambridge Neuropsychological Test Automated Battery
CGT	Cambridge Gamble Task
CPT	Continuous Performance Test
IDED	Intra-Dimensional/Extra-Dimensional set-shifting test
IGT	Iowa Gambling Task
MRI	magnetic resonance imaging
WCST	Wisconsin Card Sorting Test

K. D. Ersche (S) ■ B. J. Sahakian
School of Clinical Medicine, Department of Psychiatry,
University of Cambridge,
Brain Mapping Unit, Box 255, Addenbrooke's Hospital,
Cambridge, UK
e-mail: ke220@cam.ac.uk

K. D. Ersche ■ B. J. Sahakian
Behavioural and Clinical Neurosciences Institute,
University of Cambridge,
Cambridge, UK

Introduction

According to United Nations estimates, approximately 200 million people worldwide were consuming illegal psychoactive substances at the beginning of the millennium (United Nations Office on Drugs and Crime 2003a). Although not everybody who takes drugs shows addictive behavior, such as compulsive drug seeking or loss of control over drug intake, the damaging effects of repeated drug use are undisputed (United Nations Office on Drugs and Crime 2003b). Such harm includes acute and chronic health problems, caused directly by drug use or indirectly through drug-related accidents (WHO 2004). Furthermore, there is growing evidence that chronic drug use is associated with impaired cognitive function (see for review Rogers and Robbins 2001, 2003; Verdejo-Garcia et al. 2004), which may contribute to negative long-term consequences observed in chronic drug users.

The impact of chronic drug use on cognition has received relatively little attention until recently. Contemporary theories on the neuropathology of drug addiction have highlighted the involvement of cognitive functions such as memory, learning, attention, and inhibitory control in the development of drug dependence (Volkow et al. 2003, 2004a). Advances in the psychometric assessment of neuropsychological functions and computer-based applications of test batteries (e.g., the Cambridge Neuropsycho-

logical Test Automated Battery (CANTAB; http://www.camcog.com) have facilitated research into cognitive impairments associated with drug dependence, and allowed comparisons to be drawn with cognitive profiles observed in other clinical populations. The development of paradigms capable of being applied in both animals and in humans has opened up new avenues, as drug users' behavior observed clinically can be modelled in animals, and findings in animals treated experimentally with drugs could be directly tested in humans (Robbins et al. 1994). Neuroimaging research such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have provided vital insight into the neural substrates and neurochemical processes subserving cognition and have shed light on disrupted neural network in chronic drug users (London et al. 2000; Volkow et al. 2004a).

Comparisons of the cognitive profiles associated with the psychostimulants and narcotics is particularly interesting with regard to the different pharmacological actions and the distinct mechanisms of positive and negative reinforcement implicated in the development of amphetamine and opiate dependence. This article will provide a concise overview of the neuropathology associated with chronic amphetamine and opiate use, review the cognitive systems and their dysregulation by amphetamine and opiates, and will discuss possibilities of how cognitive deficits could be addressed in drug treatment.

Neuropathology Associated with Chronic Amphetamine and Opiate Use

Amphetamines and opiates are widely used (United Nations Office on Drugs and Crime 2003a), and both activate the dopamine system in the midbrain, which is associated with positive reinforcing effects, and therefore, have addictive potential (Di Chiara and Imperato 1986). However, the pharmacological actions of both substances can be differentiated. The acute pharmacological effects of amphetamines are to increase central monoamine neurotransmission by interaction with processes of transmitter release, uptake, and metabolism (Seiden et al. 1993, for review). Opiates, by contrast, exert action mainly through p-opioid receptors, indirectly increasing dopamine but decreasing noradrenaline levels (De Vries and Shippenberg 2002; Maldonado 1997). In view of the distinct pharmacological actions and reinforcement mechanisms implicated in amphetamine and opiate use (Bardo 1998, for review), the neuropathology in chronic users may be different.

Growing evidence suggests that chronic amphetamine use results in long-lasting changes in dopamine neurotransmission, a neurotransmitter system critically implicated in motor, reward and cognitive functions, thereby contributing to a wide range of behavior patterns (Cools and Robbins 2004; Nieoullon 2002; Robbins 2005). Converging evidence from animal and human research indicates marked dopaminergic dysfunction as reflected by down-regulation of dopamine DI and D2 receptors, glucose metabolism (London et al. 2004; Volkow et al. 2001c; Wang et al. 2004), and perfusion (see for review Baicy and London 2007; Volkow et al. 2004b). Neuroimaging studies using structural MRI have provided further evidence that abnormalities associated with chronic amphetamine exposure are not only functional but also of a morphological nature. Profound reductions in gray matter have been identified in the cingulate, limbic, and paralimbic cortices and the inferior frontal gyrus (Thompson et al. 2004), while striatal volume is significantly increased (Chang et al. 2005; Jemigan et al. 2005). Although the neurotoxicity of amphetamines in humans is still a matter of debate, drug-induced changes in the dopamine system may be dose-dependent (Sung et al. 2007) and be long-lasting (Johanson et al. 2006; McCann et al. 1998; Sekine et al. 2001; Volkow et al. 2001b). Yet, there is converging evidence from studies investigating brain glucose metabolism, brain metabolites, and dopamine transporter density which suggests recovery from some of the drug-induced dopaminergic alterations following protracted abstinence (proton MRS: Nordahl et al. 2005; PET dopamine-ligand: Volkow et al. 2001b; FDG-PET: Wang et al. 2004).

Chronic opiate abuse has been associated with marked changes in the density of p-opioid receptors throughout the brain (Kling et al. 2000; Melichar et al. 2005). Although methadone is used as a substitute for heroin for the treatment of opiate-dependent individuals, the long-lasting effects between these two opiates differ. Thus, methadone administered in a maintenance regimen results in an up-regulation of p-opioid receptors, which persists even after detoxification from opiates (Daglish and Nutt 2003); conversely post-mortem analyses of chronic heroin users have shown a down-regulation of p-opioid receptors (Gabilondo et al. 1994). Regarding monoamines neurotransmission, chronic opiate users has been associated with reduced densities in noradrenaline (a2) and dopamine (D2) receptors (Gabilondo et al. 1994; Wang et al. 1997), but no evidence for neurotoxic effects on dopamine neurons has been identified (Kish et al. 2001). In particular, the effects on the dopamine system overall in opiate users are less pronounced than in stimulant users (Kish et al. 2001). Functional and structural abnormalities in opiate users are less specific than those observed in amphetamine users (Danos et al. 1998a, 1998b; Gerra et al. 1998; Lyoo et al. 2006; Rose et al. 1996; Pezawas et al. 1998).

In summary, neuropathological changes associated with chronic use of amphetamines have been well documented for the midbrain dopamine system and the ascending

dopamingergic pathways. Accordingly, structural and functional anomalies in areas of dopamine pathways, the corticostriatal loops, have been identified in chronic amphetamine users, as measured by neuroimaging techniques. In contrast to the extensive research in psychostimulant users, the neuropathological changes in opiate users have been far less investigated to date. There is however, substantial evidence showing that chronic opiate use is associated with marked changes in the opioid system, while the dopamine system seems to be less affected. Abnormalities in brain structure and function appear to be less pronounced and less specific than in psychostimulant users. In light of differences in pharmacological actions of amphetamines and opiates, and in the neuropathology associated with chronic use of these substances, it may be anticipated that cognitive function would be more severely impaired in chronic users of amphetamines compared to chronic users of opiates.

While this review will focus on the cognitive neuropathological changes associated with amphetamine and opiate dependence in neural networks subserving cognitive function, it should be noted that the adverse effects of chronic abuse of amphetamines and of opiates on the central nervous system are complex (Brust 1998; Neiman et al. 2000), making chronic drug users susceptible to numerous neurological complications which may also affect cognition. These include ischemic and haemorrhagic stroke (Buttner et al. 2000; Buxton & McConachie, 2000; Mathew & Wilson, 1991), cardiovascular problems such as myocardial infarction (Yu et al., 2003), and infectious diseases (Neaigus et al., 2007; Urbina & Jones, 2004). Medical complications are either directly related to the properties of the drug of choice, for example, immunosuppression caused by opiates (Sacerdote, 2006), increased cerebral blood flow caused by amphetamines (Russo et al., 1991), or produced by agents used for the 'cutting' of street drugs (Poulsen et al., 1996). Medical problems may also occur as a consequence of the pattern of drug use, for example, hypoxia following intravenous heroin use (Dursteler-MacFarland et al., 2000), or cardiac pathology following methamphetamine binges (Varner et al., 2002). Furthermore, the drug users' nutritional status (Kumar, 2007; Virmani et al., 2006) and lifestyle may also account for some of the medical problems observed (e.g. a heightened risk of infectious diseases due to needle sharing or promiscuity [Neaigus et al., 2007; Urbina & Jones, 2004; Warner & Srinivasan, 2004]).

The Profile of Cognitive Deficits Associated with Amphetamine and Opiate Dependence

Executive functions represent high-level, dissociable cognitive abilities such as planning, working memory, attentional set shifting, and inhibition of prepotent responses, which are necessary for goal-directed behavior (Baddeley 1986; Burgess 1997). Executive dysfunction has generally been linked with a frontal lobe pathology (see both for review Elliott 2003; Robbins 1996), including chronic substance abuse (Rogers and Robbins 2001). In the following sections, impairments in selected executive and memory domains in chronic users of amphetamines and opiates are discussed.

Cognitive Flexibility

Cognitive flexibility has been defined as 'the ability to shift avenues of thought and action in order to perceive, process, and respond to situations in different ways' (Eslinger and Grattan 1993). The Wisconsin Cart Sorting Test (WCST) (Grant and Berg 1948) and the intra-dimensional/extra-dimensional (IDED) set-shifting task of the CANTAB test battery (Downes et al. 1989; Rogers et al. 2000b) both shown in Fig. 1, have been widely used to assess cognitive flexibility in laboratory settings. The latter paradigm specifically measures the ability to shift away from a previously relevant stimulus dimension towards a newly relevant dimension (i.e., extra-dimensional [ED]-shift), which is formally akin to a category shift on the WCST and has been associated with dorsolateral prefrontal cortex function (Konishi et al. 1998a; Rogers et al. 2000b). The IDED task, in particular, has proven suitable for translational medicine approach (Birrell and Brown 2000; Dias et al. 1997). Studies with current amphetamine/methamphetamine users have shown marginal to severe impairment on cognitive flexibility (Ersche et al. 2006a; Omstein et al. 2000; Simon et al. 2000), although these deficits were not evident in abstinent amphetamine/methamphetamine users (Hoffman et al. 2006). Interestingly, there is some evidence indicating that impaired cognitive flexibility in methamphetamine users is associated with male, but not with female gender (Kim et al. 2005b). This proposal finds support from experimental animal studies showing greater neurotoxic damage of methamphetamine to male than to female brains following administration of the same amount of the drug in animals of the same age (Wagner et al. 1993). It may therefore be that factors such as heavier drug use or an earlier age of onset only partly account for the more severe cognitive impairment in male methamphetamine users. Taken together, this may suggest that amphetamine exposure in male stimulant users acutely impairs the shifting of a mental set, while protracted abstinence from amphetamines may restore attentional set-shifting function. Compromised cognitive flexibility in abstinent methamphetamine users has been shown to be associated with decreased frontal white matter metabolism (Kim et al.

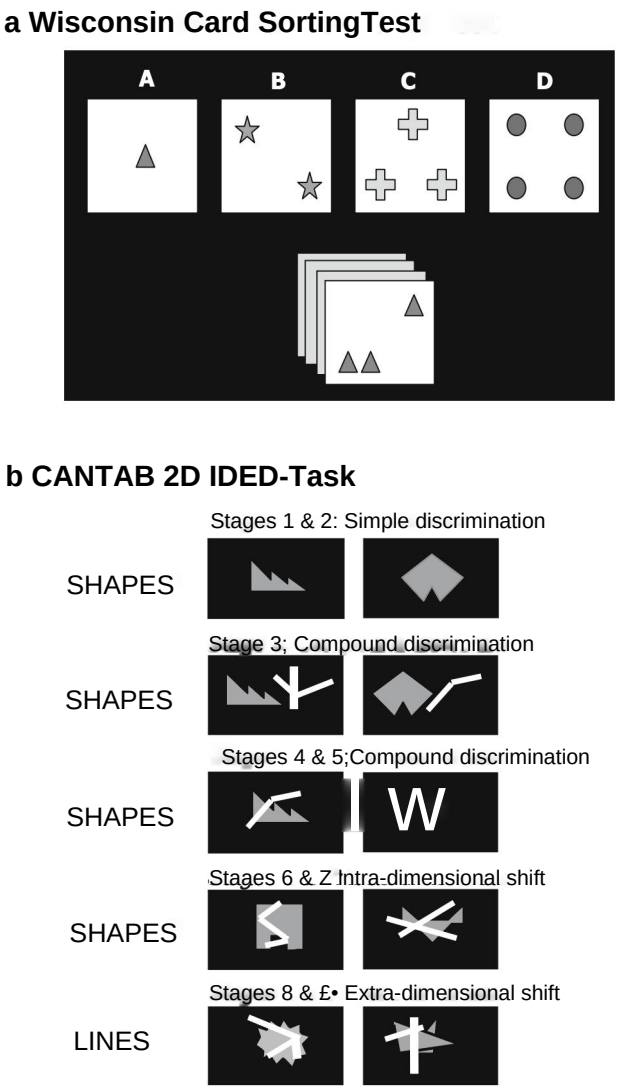

Fig. 1 a In the Wisconsin Card Sorting Test, participants are presented with a deck of cards, showing stimuli that differ along the dimensions of color, shape and number. Participants are asked to match each of the cards of the deck to one of the stimulus cards A-D displayed in front of them. Feedback informs participants of the correctness of their choices. Successful matching requires the learning of a sorting rule and the adaptation of the matching strategy when the sorting rule changes, b In the CANTAB 2D-IDED task, participants are trained to discriminate stimuli that differ along the dimensions of shapes and lines. Feedback teaches participants which stimulus is correct, and after six correct responses, the stimuli and/or rules are changed. Shapes remain the relevant dimension (i.e., shifts are intra-dimensional within the same dimension) until stage 8, when the new dimension, the white lines, become the relevant dimension (i.e., extra-dimensional shift)

2005a) and reduced gray matter density in the middle frontal cortex (Kim et al. 2006). The fact that task performance improves with protracted drug abstinence (Kim et al. 2006), and may even reach normal level (Hoffman et al. 2006; Johanson et al. 2006; Toomey et al. 2003), is interesting, given the relationship between performance and D2 receptor availability (Mehta et al. 1999, 2004; Volkow et al. 1998). One may speculate whether the improved task performance during protracted abstinence in amphetamine users is concomitant with recovery in dopamine transmission (Volkow et al. 2001b; Wang et al. 2004). In contrast to the findings in amphetamine users, most studies in current and former opiate users did not identify impairments on cognitive flexibility, suggesting that chronic opiate consumption does not have an impact on attentional set-shifting (Ersche et al. 2006a; Pau et al. 2002; Rotheram-Fuller et al. 2004; Verdejo-Garcia et al. 2005; Verdejo-Garcia and Perez-Garcia 2006).

The WCST and IDED tasks also assess the capacity to relearn a stimulus-reward association by inhibition of the previously reinforced dimension (i.e. reversal shift), which is subserved by orbitofrontal-striatal pathways (Dias et al. 1997; Rogers et al. 2000a). Neither amphetamine nor opiate users were measurably impaired on the reversal shift in the IDED task (Ersche et al. 2006a; Johanson et al. 2006; Omstein et al. 2000). Although impaired response reversal on the WCST is thought to reflect a high level of attentional disturbance compared with perseverative responding during reversal learning tasks (Nagahama et al. 2001), it is of note that neither amphetamine nor opiate users showed impairment in response reversal during a probabilistic response reversal learning task (Ersche et al. under review). However, it has to be acknowledged that some studies have reported increased perseverative responding on the WCST in methadone-maintained opiate users (Darke et al. 2000; Lyvers and Yakimoff 2003; Pirastu et al. 2006). Response perseveration on the WCST has been associated with early methadone withdrawal (Lyvers and Yakimoff 2003), comorbid alcohol dependence and previous heroin overdoses (Darke et al. 2000) but does not seem to be a characteristic behavioral correlate of opiate dependence.

Inhibitory Control

A hallmark of drug dependence is the loss of control over substance intake, despite the negative consequences involved (American Psychiatric Association 1994). Lack of inhibition has been regarded as a key element of drug addiction, including the suppression of emotional, cognitive and behavioral responses (Goldstein and Volkow 2002; Jentsch and Taylor 1999). Inhibitory control can be investigated in the behavioral and cognitive domains.

Behavioral Inhibition

Behavioral or motor response inhibition is defined as the process required to stop a planned movement (see Aron et al.

2004; Chamberlain and Sahakian 2007) and is assessed using paradigms such as the Go-Nogo or Stop-Signal Reaction Time task (Dougherty et al. 2003; Evenden 1999; Hom et al. 2003). As shown in Fig. 2b, in the Go-Nogo task, participants have to respond quickly to visual 'go' cues but suppress the prepared response whenever a 'nogo' cue occurs on the computer screen. The index of behavioral inhibition is the number of false responses on 'nogo' trials (i.e., commission errors), which has been associated with activation in inferior frontal gyrus (Chikazoe et al. 2007; Konishi et al. 1998b). To our knowledge, no neuroimaging studies have investigated the neural correlates during 'go-nogo' performance in methamphetamine users. Cocaine users, however, exhibit not only significant inhibition failure by making more false responses on 'nogo' trials than controls, but also show significant inattention to 'go' cues, as reflected in a higher rate of false misses (i.e., omission errors) (Kaufman et al. 2003). Interestingly, attenuated error-related activation in the anterior cingulate cortex (ACC) was detected during 'go-nogo' performance, suggesting disturbances in the processing of errors (Kaufman et al. 2003). Alternatively, the attenuated error-related activation may also indicate that cocaine users had difficulty differentiating target from non-target stimuli, since the ACC is thought to play a key role in conflict and action monitoring (e.g. Carter et al. 1998; Gehring and Knight 2000). Remarkably, task-related activation in regions that have previously been implicated in behavioral inhibition during 'go-nogo' performance, such as the right inferior frontal gyrus, did not differ between cocaine users and controls. Thus, it is not clear whether inhibition failure during 'go-nogo' performance reflects attentional problems and/or inefficient inhibitory control.

The Stop-Signal task, in contrast to the Go-Nogo task, does not involve switching between target and non-target stimuli, but requires participants to respond quickly to 'go' cues unless they hear a beep (in 25% of trials), which provides the signal to suppress this prepared motor response (see Fig. 2a). The stop-signal reaction time indexes the time that an individual needs to withhold the prepotent response, which is associated with the integrity of the right inferior frontal gyrus (Aron et al. 2004; Chamberlain and Sahakian 2007; Rubia et al. 2003). Both methamphetamine and cocaine users have a significantly longer stopping process than controls, as reflected by a significantly longer stop-signal reaction time, suggesting that response inhibition is compromised in psychostimulant users independently from attentional processing (Fillmore and Rush 2002; Monterosso et al. 2005). Inhibition failure on the Stop-Signal task is associated with the previous amount of methamphetamine consumed (Monterosso et al. 2005), and may reflect dose-dependent neuroadaptive changes underlying poor behavioral inhibition in chronic users of methamphetamine. Indeed, functional and structural abnormalities have been identified in the inferior frontal gyrus in methamphetamine users (Thompson et al. 2004; Volkow et al. 2001a), which fuel speculation that disruptions in the neural network involving the inferior frontal gyrus may underlie the poor behavioral inhibitory control in chronic methamphetamine users (Monterosso et al. 2005).

In contrast to the accumulating evidence for response inhibition impairments in chronic psychostimulant users (e.g., Hester and Garavan 2004; Hester et al. 2007; Fillmore and

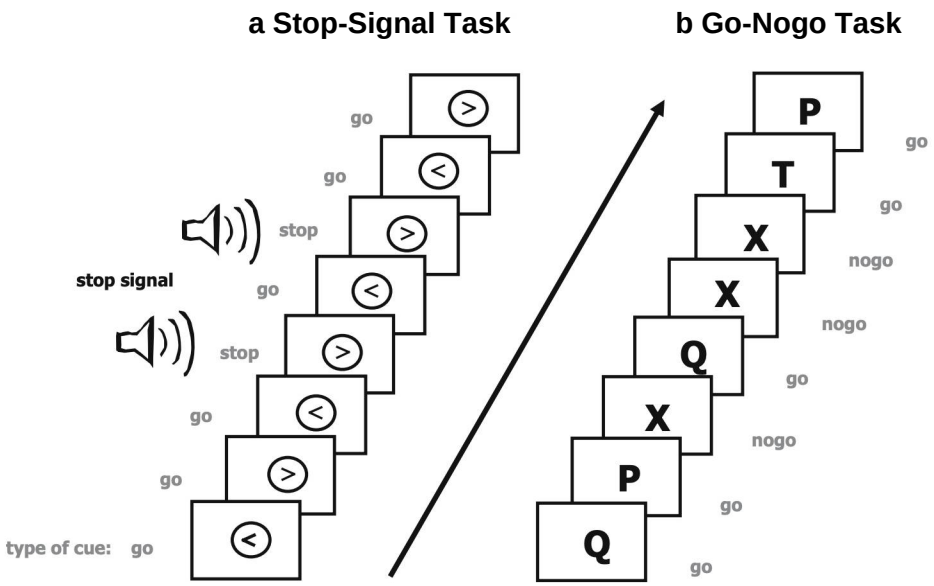

Fig. 2 a In the Stop-Signal task, participants are presented with a series of stimuli and are instructed to press the button on the left of the response panel when the arrow on the screen is pointing to the left, and to press the button on the right when the arrow is pointing to the right. After a practice session of 16 'go' trials, participants are instructed to withhold their responses when they hear a stop-signal (which occurs in 25% of the trials in the form of an auditory 'beep' sound-a 300 Hz tone), b In the Go-Nogo task, participants are presented with a series of letters, and are instructed to press a button as quickly and accurately as possible in response to any letter presented except to the letter X

Rush 2002; Kaufman et al. 2003; Monterosso et al. 2005), the majority of studies did not find behavioral inhibition deficits in opiate users (Forman et al. 2004; Fishbein et al. 2007; Lee et al. 2005; Verdejo-Garcia et al. 2007).

Cognitive Inhibition

In the cognitive domain, inhibitory control is frequently assessed by the Stroop test (Stroop 1992), which requires participants to suppress a salient but conflicting stimulus property while identifying a less salient one (e.g., reading the word 'blue' that is written in red ink requires more cognitive effort, so-called interference control, than reading the word 'blue' when written in blue ink). Neuroimaging research has shown that the ACC is critically involved in the detection of the conflict between task-relevant and task-irrelevant stimulus properties during the Stroop task (Bench et al. 1993; Leung et al. 2000; Pardo et al. 1990). Growing evidence indicates that cognitive control is compromised in both amphetamine (Salo et al. 2002, 2007; Simon et al. 2002) and opiate users (Fishbein et al. 2007; Mintzer and Stitzer 2002; Prosser et al. 2006; Verdejo-Garcia et al. 2007). For example, poor interference control has been associated with decreased concentrations of N-acetylaspartate in the ACC in methamphetamine users (Salo et al. 2007; Taylor et al. 2004), which has been considered a marker of neuronal loss (Tsai and Coyle 1995). This finding is in keeping with the structural and functional abnormalities in the ACC previously observed in methamphetamine users (Hwang et al. 2006; London et al. 2004, 2005; Nordahl et al. 2002; Thompson et al. 2004), elucidating the underpinnings of the impaired ability to effectively monitor situations of conflict in this drug user group (Salo et al. 2005). Some studies, however, did not find impaired interference control in recently abstinent methamphetamine users (Chang et al. 2002; Hoffman et al. 2006; Kalechstein et al. 2003), which may suggest partial recovery of brain function following abstinence from methamphetamine (Nordahl et al. 2005; Wang et al. 2004).

Profound impairment in suppressing conflicting information on the standard color Stroop task has been identified in opiate users (Fishbein et al. 2007; Mintzer and Stitzer 2002; Prosser et al. 2006; Verdejo-Garcia et al. 2007). The type of opiate used does not seem to influence performance on the Stoop task (Gruber et al. 2006; Verdejo-Garcia et al. 2005). Given the key role of the ACC in conflict monitoring, one may speculate that dysfunction in this area also accounts for the poor performance on the Stroop test in opiate users. Indeed, there is now growing evidence suggesting that ACC function may be compromised in opiate users (Ersche et al. 2006b; Forman et al. 2004; Lee et al. 2005; Yucel et al. 2007). For example, opiate users showed attenuated error-related activation in the ACC during the Go-Nogo task (Forman et al. 2004) and lack a normal relationship between activation of ACC and adaptive responding to negative feedback (Ersche et al. 2006b) and to errors (Yucel et al. 2007). Reduced levels of the metabolite N-acetylaspartate have also been reported in chronic opiate users (Haselhorst et al. 2002; Yucel et al. 2007), but in contrast to methamphetamine users (Salo et al. 2007), these abnormalities were not associated with behavioral performance. At present, the nature of underlying biochemical abnormalities such as the significant reductions in N-acetylaspartate in chronic drug users is still unclear. Given that the ACC has a high density of opioid receptors (see Vogt et al. 1995), and has been implicated in opioid analgesia (Casey et al. 2000; Petrovic et al. 2002), it seems conceivable that chronic exposure to opiate agonists such as methadone and heroin, modulates ACC function during cognitively challenging tasks such as the Stroop task. Previous research has shown that task-related activation during the Stroop task overlaps with the neural network involved in processing of pain (Derbyshire et al. 1998) and opioid analgesia respectively (Petrovic et al. 2002).

Sustained Attention

Sustained attention characterizes a state of 'readiness to detect rarely and unpredictably occurring signals over prolonged periods of time' (Sarter et al. 2001) and has frequently been assessed by various versions of the Continuous Performance Test (CPT) (see Borgaro et al. 2003). In this test, participants are required to maintain vigilance and to react when target stimuli are presented but to avoid responding when distractors occur. Performance is usually assessed by signal detection index (d') which takes into account the number of missed targets and the number of false alarms. London et al. (2005) has recently shown that methamphetamine users made significantly more errors on an auditory version of the CPT than non-drug taking controls. Most importantly, the authors found that d' was significantly smaller in methamphetamine users than in controls, providing evidence for impairments in methamphetamine users' ability to discriminate targets from non-targets. Poor test performance was further reflected in abnormal glucose metabolism in the ACC, insula and orbitofrontal cortex at rest. Interestingly, compared with controls, glucose metabolism in the ACC was significantly reduced, and correlated negatively with the recent amount of methamphetamine used (London et al. 2004). Methamphetamine users with relatively elevated glucose metabolism at rest made significantly fewer errors during the task (London et al. 2005). This may suggest that drug users with a smaller consumption of methamphetamine were able to compensate for an underlying neuropathology; a plausible

proposal given that methamphetamine-induced neural damage in the frontal lobe, including the ACC, has shown to be dose-dependent (Oh et al. 2005; Sung et al. 2007). It is important to note that the aforementioned group differences on the CPT became only apparent over a 30-minute testing session (London et al. 2005), but not during a 15-minute session (London et al. 2004), which suggests that methamphetamine users are to some extent able to compensate for the underlying neuropathology.

Although the length of the administered version of the CPT is likely to determine the detection of deficits in sustained attention in stimulant users, the nature of the impairments identified is still unknown. It is important to acknowledge that not all studies find impairments in measures of signal detection (cT) on the CPT in stimulant users. For example, Levine et al. (2006) identified inattentiveness in stimulant users by increased numbers of omission errors and great reaction time variability, although measures of discrimination targets and non-targets did not differ from controls. In light of the dose-dependent effects of methamphetamine on ACC, one may speculate whether the type of stimulants used (i.e., amphetamine versus cocaine) or the pattern of drug use (i.e., chronic versus recreational use) might account for differences in performance profiles observed. Although poor performance in the detection of targets has repeatedly been found in methadone-maintained opiate users (Forman et al. 2004; Mintzer and Stitzer 2002), relatively little is known about the underlying neuropathology of these impairments in opiate users. Abnormalities in glucose metabolism and brain metabolites in the ACC of opiate users have been reported (Galynker et al. 2000; Yucel et al. 2007) and it is conceivable that opiate users need to compensate for ACC dysfunction in order to meet attentional demands. Functional MRI studies in opiate users have provided preliminary evidence for this assertion, since task related under-activation of the ACC has been associated with deficits in the detection of targets (Forman et al. 2004). Normal task-related activation in the ACC, concomitant with additional recruitment of brain regions that are not typically activated by non-drug users, however, is associated with normal performance in opiate users (Yucel et al. 2007). Although attentional dysfunction has repeatedly been identified in laboratory settings (Forman et al. 2004; Mintzer and Stitzer 2002), driving ability (which requires sustained attention) is considered to be intact in chronic opiate users (Fishbain et al. 2003; Stout and Farrell 2003). It may be that the compensatory recruitment of brain areas enables opiate users to drive safely without being involved in significantly more road accidents than non-drug users (see Fishbain et al. 2003). In summary, more research is needed to better understand the engagement of neural networks during forms of attentional processing in opiate dependent individuals.

Strategic Planning

The ability to 'think ahead' and actively search for an appropriate solution is an essential part of goal directed behavior, and is required in many daily activities (Owen 1997). The Tower of London test (Shallice 1982; Owen et al. 1990), or the more difficult version, the one-touch Tower of London (Owen et al. 1995), are widely used means to assess strategic planning in laboratory settings. Multiple lines of evidence indicate that planning performance on the Tower of London is subserved by a neural network including the dorsolateral prefrontal cortex (Baker et al. 1996; Dagher et al. 2001; Manes et al. 2002). Both amphetamine and opiate users, regardless of current drug status, solved significantly fewer problems correctly on the one-touch Tower of London, and therefore needed more attempts in order to generate correct answers compared to controls (Ersche et al. 2006a; Omstein et al. 2000). This behavioral deficit occurred in the absence of latency differences between the groups and, as such, was not secondary to motor impulsivity (Ersche et al. 2006a). Whilst amphetamine and opiate users were equally impaired on planning problems of medium and high levels of difficulty, amphetamine users also struggled with generating solutions for the relatively easy three-move problems (Ersche et al. 2006a). The first stages of the Tower of London (i.e., one- to three-move problems) require relatively little planning ability, since they can easily be solved by a visual matching-to-sample strategy (Owen 1997). In light of accumulating evidence showing that basic visuospatial function, as assessed by the Rey-Osterrieth Complex Figure Test (see Stem et al. 1994), is not impaired in amphetamine users (Chang et al. 2005; Hoffman et al. 2006; Kalechstein et al. 2003; Toomey et al. 2003), it is conceivable that the poor performance of amphetamine users at this low level of difficulty may reflect either an over-confident approach towards the solution or an inefficiency in concentrating on the task demands. High-level cognitive planning, as assessed on the Tower of London by planning problems requiring mental organization of four to six-sequences of moves, overlaps with different aspects of working memory (Owen 1997; Robbins et al. 1998). Therefore, it may not be surprising that amphetamine and opiate users have also shown poor performance on tasks requiring complex spatial working memory function and visuo-spatial strategy generation (Omstein et al. 2000). The marked impairment in solving planning problems on the Tower of London exemplifies the difficulty of drug users to mentally organize behavior to achieve a goal through a series of intermediate steps.

The fact that planning impairment was not only observed in current users of amphetamine and opiates but also in a group of former drug users who had been drug abstinent for an average of eight years, may indicate that impairments do

not simply reflect the current effect of the drug. Longitudinal studies are needed to settle the question whether neurocognitive impairment was caused by chronic drug exposure or predated drug-taking, or even represents a combination of both. Lack of planning and forethought has also been considered being a component of impulsive behavior (Dickman 1990; Evenden 1999). As a personality trait, non-planning is assessed by subscale of the Barratt Impulsiveness Scale (BIS-11) (Patton et al. 1995). Both chronic amphetamine users and opiate users not only report higher overall levels of impulsivity compared with non-drug using controls, they also score higher on the non-planning subscale of BIS-11 (Clark et al. 2006). In light of the poor performance during strategic planning, one may speculate whether this impairment may contribute to the impulsive behavior pattern frequently reported by chronic drug users.

Decision-Making

The ability to make decisions is a key element in human behavior because the way people behave socially, financially, ecologically, and politically largely depends on this ability (Hastie 2001; Mellers et al. 1998). Because decisions are usually made with a view to a favorable outcome, rewards provide the motivation to make decisions. Cognition is necessary to appraise the options and alternatives, assessing the means to achieve them and evaluate the consequences involved with each choice (Ernst and Paulus 2005; Hastie 2001).

Neuropsychological studies have been investigating decision-making abilities in chronic drug users with different experimental paradigms, providing evidence that decision-making performance differs between the type of substance used. For example, the Iowa Gambling Task (IGT) (Bechara et al. 1997), shown in Fig. 3a, requires a series of card selections to be made concerning winning and losing monetary rewards. Optimal performance requires switching from selecting cards from high gain/high loss decks to low gain/low loss but more profitable decks. The main measure is the net-score, which is calculated from the total number of cards selected from the two advantageous minus the two disadvantageous decks, reflecting the decision-making strategy across the task. There are inconsistencies in drug users' decision-making strategies on the IGT across studies, and not all report the net-score. Among those studies that report the net-score, some did not find a measurable decision-making impairment in psychostimulant, opiate, and polydrug users (Adinoff et al. 2003; Bolla et al. 2003; Ernst et al. 2003; Mintzer and Stitzer 2002; Mintzer et al. 2005), whereas others found significantly smaller but positive net-scores in

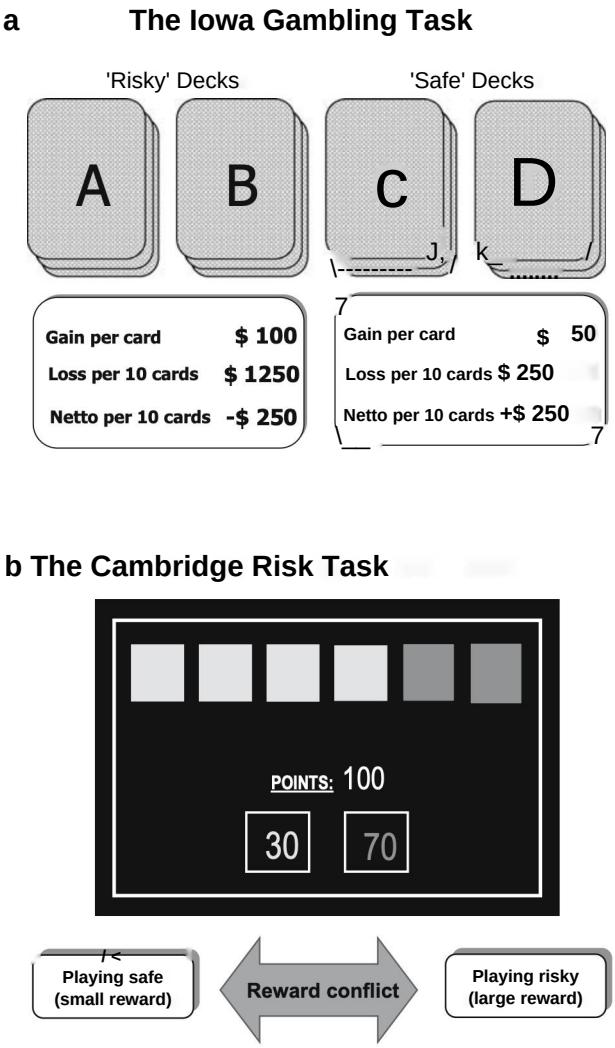

Fig. 3 a In the Iowa Gambling task, participants are presented with four card decks and asked to make series of card selections concerning winning and losing monetary rewards. Participants are not told that there are 'safe' and 'risky' decks. Over the course of the task, participants generally develop a preference for the 'safe' decks (C and D) over the risky decks (A and B). The net-score, which is calculated from the total number of cards selected from 'safe' minus 'risky' decks, reflects the decision-making strategy across the task, b The Risk Task requires participants to choose between two mutually exclusive options with different probabilities of reward and punishment. On each trial, an array of six boxes is presented on the screen, with a ratio of red and blue boxes that varies from trial to trial (5:1, 4:2, 3:3 boxes). Participants are told that the computer had hidden a yellow token, at random, behind one of the six boxes and they need to decide whether the token is hidden behind a red or blue box. Their decision on each trial is shaped by a fixed bet, associated with each alternative, regarding the magnitude of potential gain or loss (90:10, 80:20, 70:30; 60:40, 50:50 points). Feedback is provided by the way of gain or loss of points following each trial. Since the least likely option is always associated with the large reward value, participants are facing a reward-conflict situation

these groups of drug users compared with controls (Bechara et al. 2001; Grant et al. 2000; Pirastu et al. 2006; Verdejo-Garcia and Perez-Garcia 2006), reflecting a disadvantageous decision-making strategy. It seems that only subgroups of polydrug users (Bechara et al. 2002) and subgroups of opiate users (Rotheram-Fuller et al. 2004; Pirastu et al. 2006) have negative net-scores, indicating that these drug users preferably chose cards from the 'risky decks.' Negative net-scores have also been identified in other clinical groups, for example in suicide attempters, independently from their drug using habits (Jollant et al. 2005) and in psychopathic individuals (Mitchell et al. 2002 e.g.; van Honk et al. 2002). Interestingly, Vassileva et al. (2007) have recently shown significant differences in decision-making strategies between psychopathic and non-psychopathic opiate users. While the psychopathic opiate users consistently selected cards from risky decks, the non-psychopathic opiate users successfully adjusted their decision-making strategy in the course of the task toward the advantageous decks. This selection strategy suggests difficulties in the learning reward-contingencies, which at the beginning of the task have resulted in risky decisions. Taken together, accumulating evidence indicates that drug abuse per se does not mediate decision-making on the IGT but it may act as a moderator, aggravating existing decision-making impairments.

One major drawback of the IGT is that volunteers need to leam reward-punishment associations over the course of the task, which means that individuals who are poor learners may develop a less successful decision-making strategy than good learners (Clark and Robbins 2002). Consequently, the Cambridge Gamble Task (CGT) (Rogers et al. 1999a) and the Risk Task (Rogers et al. 1999b) have been developed to investigate decision-making independently from learning. In the CGT, participants make choices between two mutually exclusive options and place bets on the expected outcome. Learning on the CGT is obviated by providing information about outcome probabilities and reward values on the screen and by the fact that each trial is independent from its predecessor. The Risk Task is a variant of the CGT, which investigates decision-making in a reward-conflict situation (see Fig. 3b). Research findings regarding decision-making in chronic drug users, using either the CGT or the Risk Task, are strikingly similar to findings on the IGT. Chronic amphetamine users, but not opiate users, showed disadvantageous decision-making (Rogers et al. 1999a). Amphetamine users overall selected the likely small reward option less frequently (i.e., in only 85% of trials) than opiate users (92%) and controls (95%), but showed no signs of impaired risk adjustment (Rogers et al. 1999a). In other words, although amphetamine users chose disadvantageously, they neither increased their gambles on the less favorable options nor did they significantly choose against the odds on the risky conditions. Disadvantageous decision-making strategy in amphetamine users on the CGT and Risk Task appears to be due to impairment in correctly estimating outcome probabilities and may not reflect a reward-seeking strategy per se. This proposal finds support from neuroimaging research, showing that methamphetamine users were not different regarding the sensitivity to positive or negative feedback, but showed disruptions in the neural network implicated in processing of feedback information, on the basis of which outcome probabilities were estimated (Paulus et al. 2002, 2003). Disadvantageous choices particularly in amphetamine users were also evident on the Risk Task (Ersche et al. 2005a, 2005b). For example, in a neuroimaging study, amphetamine users selected the most favorable option in 72% of trials (opiate: 82%, and ex-drug: 79%, controls: 87%) (Ersche et al. 2005a). Although this difference was not statistically significant, the neuroimaging data revealed significant disturbance in the mediation of decision-making by the prefrontal cortex in all three drug user groups. Chronic amphetamine or opiate users, regardless of whether they were currently using drugs, showed over-activation in the orbitofrontal cortex and under-activation in the dorsolateral prefrontal cortex. These findings are consistent with other neuroimaging studies in drug users (e.g., Bolla et al. 2003), showing abnormal brain activation during decision-making, even before impairment becomes behaviorally measurable.

At present, the nature of impaired decision-making in drug users is still unclear. There is some evidence that working-memory deficits adversely affect performance on the IGT (Bechara and Martin 2004). Sub-optimal choices on the CGT and Risk Task have been linked with the duration of amphetamine use (Rogers et al. 1999a) and the previous amount of daily cocaine use (Monterosso et al. 2001) , which might indicate an adverse effect of chronic stimulant use on probability estimations. Risky choices on the Risk task have been associated with low intelligence in poly drug users (Fishbein et al. 2005), while risky reward-seeking on the IGT has been related to abnormalities in anticipatory skin conductance responses, prior to card selections from the 'risky decks' (Bechara et al. 1997). Polydrug users who showed risky card selections on a discounting version of the IGT had abnormal anticipatory skin conductance responses, reflecting a hypersensitivity to reward and a hyposensitivity to punishment (Bechara et al. 2002) . This pattern of abnormal skin conductance responses has been interpreted as an inability to utilize ongoing feedback in guiding future decisions (Bechara et al. 2002).

Leland and Paulus (2005) investigated risky decision-making in young people, who had experiences with illicit stimulants. Volunteers had to quickly decide whether to accept a small but safe bet, or to wait in prospect of a larger reward or penalty. Risky choices in young people,

regardless of whether they were consuming stimulants, were associated with personality traits of sensation seeking and motor impulsivity. They further found that although young people with a history of stimulant use made riskier choices throughout the task than their drug-naïve counterparts, they showed normal responses to negative feedback (Leland and Paulus 2005). The authors suggested that the increased risk-taking behavior in young stimulant users reflects a hypersensitivity to reward but normal sensitivity to punishment. This decision-making strategy stands in sharp contrast to the risky decision-making observed in methadone-maintained opiate users. Although the overall decision-making performance in opiate users was not measurably impaired (Ersche et al. 2005a; Ersche et al. 2005b; Rogers et al. 1999a), methadone-maintained opiate users were significantly more likely to make risky decisions when they had been unsuccessful on the previous trial (Ersche et al. 2005b). In other words, only those opiate users who were maintained on methadone were less inclined to 'play safe' when they had lost on the previous trial; street heroin users, amphetamine users and former drug users all showed normal responses to punishing feedback (see Fig. 4). Since the two opiate groups were matched on other descriptive variables, one possible explanation of this finding may be the type of the opiate used. Several possible explanations for the abnormal responses of methadone users have been proposed, including a down-regulation of noradrenaline, altering the perception of risk and a dysregulation in processing of punishment (Ersche et al. 2005b). Nevertheless, further research is warranted to elucidate the adverse influence of methadone on feedback processing.

In summary, accumulating evidence has shown that chronic consumption of amphetamines and opiates is associated with difficulties in making decisions, which can involve negative consequences. Neuroimaging studies have provided strong evidence for neural network disruptions during decision-making, even in the absence of detectable behavioral impairments on some paradigms (e.g., Bolla et al. 2003; Ersche et al. 2005a, 2006b; Paulus et al. 2005). The quality of decision-making in chronic amphetamine and opiate users may depend upon the cognitive demands that the decisional strategy requires. Cognitive deficits that adversely affect decisional choices have been shown to be associated with chronic amphetamine and opiate use, such as impaired learning of stimulus reward associations, probability judgements, reflection, and feedback processing. There are a variety of moderator variables, such as young age (Deakin et al. 2004), low intelligence quotient (Fishbein et al. 2005), affective instability (Jollant et al. 2005, 2007), low levels of cortisol (van Honk et al. 2003),

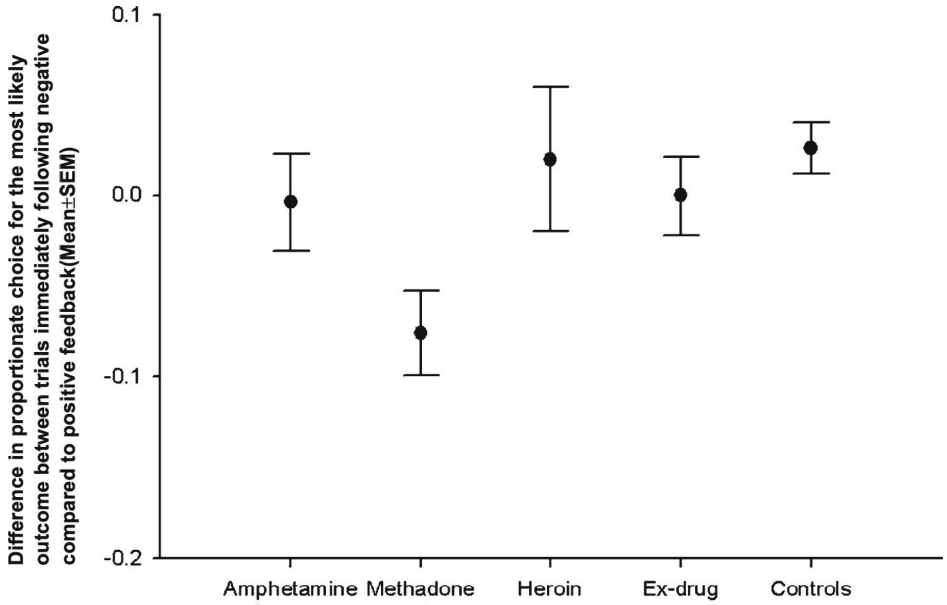

Fig. 4 The graph shows how feedback modulates ongoing decision-making differentially in current and former users of amphetamine and opiates on the Risk Task. Individual difference scores (computed by subtracting likely choices following a win from likely choices following a loss) reflect whether the likely option was chosen preferably following positive or negative feedback. As can be seen in the graph, negative feedback induced greater risk-taking than positive feedback in the methadone group but not in any of the other groups. This differential effect of task feedback on decision-making was significantly greater in methadone maintained opiate users than in controls (p=0.003) and street heroin users (p=0.010); (see Ersche et al. 2005b), printed with permission from the nature publishing group

or sensation seeking (Leland and Paulus 2005), which may exacerbate decision-making problems in individuals with substance use disorders.

Memory and Learning

A substantial body of evidence has shown a wide range of learning and memory impairments in chronic amphetamine and methamphetamine users (Ersche et al. 2006a; Gonzalez et al. 2004; Hoffman et al. 2006; Kalechstein et al. 2003; Moon et al. 2007; Omstein et al. 2000; Rippeth et al. 2004; Simon et al. 2002; Woods et al. 2005). Memory impairment in chronic amphetamine users is related to self-reported severity of drug use (McKetin and Mattick 1998) and correlates with the availability of dopamine transporters in the striatum (Volkow et al. 2001d). There is evidence that verbal memory performance improves following protracted drug abstinence (Wang et al. 2004). Woods et al. (2005) have shown that memory impairment in methamphetamine users is not necessarily due to mnemonic dysfunction but may result from inefficient strategies in encoding, organizing and retrieving information.

Impairment in memory function associated with chronic opiate users is less consistent in the literature: while a number of studies identified various aspects of memory impairment such as word/pattem recognition, learning and recall of words/figures, episodic memory, paired associate learning and retrieval (Amir and Bahri 1994; Darke et al. 2000; Ersche et al. 2006a; Fishbein et al. 2007; Guerra et al. 1987; Omstein et al. 2000; Papageorgiou et al. 2004; Pirastu et al. 2006; Prosser et al. 2006), others do not find memory deficits in opiate users (Davis et al. 2002; Mintzer et al. 2005; Rapeli et al. 2006; Rounsaville et al. 1982). The reasons for these inconsistencies are less clear but may be related to clinical differences between the samples or test sensitivity. Although most studies do not find associations with the amount of opiates consumed or the duration of use (Darke et al. 2000; Ersche et al. 2006a; Prosser et al. 2006; Rounsaville et al. 1982; Verdejo-Garcia et al. 2005), there is some evidence that methadone impairs episodic memory in a dose-dependent manner (Curran et al. 2001). For example, methadone-maintained opiate users showed significantly better episodic memory recall when they received placebo instead of their usual methadone treatment (Curran et al. 2001). It is not clear if the impairments were specific for methadone or reflect opiate-related impairment, in general. By contrast, improved memory function has been reported in a within-subject comparison, following two months of enrollment in methadone-maintenance treatment (Gruber et al. 2006). However, further validation would be welcome because this study lacked a placebo condition and did not control for potential practice effects.

Summary and General Comments

Chronic separate and combined use of amphetamines and opiates is associated with a wide a range of cognitive deficits, including the domains of attention, inhibitory control, planning, decision-making, learning and memory. Although both amphetamine users and opiate users show marked impairment in various aspects of cognitive function, substance-specific differences are most pronounced in functions of inhibitory control and feedback processing. For example, while amphetamine users demonstrate profound deficits in suppressing planned actions (behavioral inhibition) and thoughts (cognitive inhibition), impairment in inhibitory control in opiate users appears to be limited to the cognitive domain. Chronic use of amphetamines has also shown to be associated with disturbances in the neural network implicated in feedback processing, which may cause difficulties predicting outcome probabilities. In opiate users, by contrast, the impairment in the processing of feedback seems to be specific to feedback of negative valence, such as errors and punishment. Compromised cognitive function in both substance-user populations is reflected in abnormal patterns of brain activation both at rest and during cognitive performance. Although this review did not discuss gender differences, there is accumulating evidence indicative of differences in brain structure and function between male and female stimulant users (Chang et al. 2005; Ersche et al. 2006a; Kim et al. 2005b; Stout et al. 2005). Gender differences in brain function in chronic opiate users have, to our knowledge, not been reported.

Clinical Implications of Cognitive Deficits in Chronic Drug Users

A substantial body of evidence has identified cognitive dysfunction in chronic drug users, including those using stimulants and opiates. However, despite the increasing knowledge of cognitive dysfunction in this population, cognitive abilities of drug users still play a peripheral role in clinical practice, as reflected in the most recent U.K. Department of Health's Guidelines on Substance Dependence (1999). In light of the growing need for improving treatment efficacy, in particular for psychostimulant users (de Lima et al. 2002; Shearer 2007), addressing cognitive deficits within treatment settings may prove beneficial in three regards.

Cognitive Function Moderates Treatment Retention and Efficacy

Accumulating evidence has documented the moderating role of neurocognitive function on treatment retention and

treatment efficacy, such that drug users with cognitive impairments are more likely to drop out of treatment early and show less engagement in the treatment process (Aharonovich et al. 2003, 2006; FalsStewart and Schafer 1992; FalsStewart and Lucente 1994a; Katz et al. 2005; Morgenstern and Bates 1999; Teichner et al. 2002). Consequently, the adaptation of treatment to meet the drug users' cognitive needs is a necessary prerequisite if individuals with cognitive impairment are to benefit from treatment intervention. By way of example, drug counseling that makes use of mapping techniques, which addresses drug users' problems in planning and problem solving by visualising and organizing information, has been shown to improve treatment outcome significantly (Czuchry and Dansereau 2003b; Dansereau and Dees 2002; Pitre et al. 1996). Various strategies developed previously to remediate cognitive dysfunction in patients with traumatic head injuries, are equally suitable for use in cognitively impaired drug users, and could be implemented in treatment settings without major difficulty (see Weinstein and Shaffer 1993 for extensive review). Adjusting interventions to the cognitive abilities of drug users may not only be beneficial for the achievement of treatment goals, but could also improve communication and relationships between drug users and staff (Weinstein and Shaffer 1993).

Cognitive Assessment on Admission Useful for Clinical Decision-Making

Standardized cognitive status examination on admission to identify the individual's strengths and impairments would provide valuable information for clinical decision-making. Allocation of treatment intervention that meets the drug user's individual profile has received increased attention in recent years (see Gastfriend and McLellan 1997). Most approaches aiming to match patients to treatment intervention have focused on demographic, social and psychiatric variables (e.g., McLellan et al. 1997). However, growing evidence suggests that cognitive dysfunction in drug users interacts with both pharmacotherapy and psychotherapy (Block et al. 2003; Jaffe et al. 1996), and should be taken into consideration during clinical decision-making. For example, alcohol dependent individuals with poor cognitive function and high levels of craving seem to respond particularly well to pharmacological treatment relative to placebo (Jaffe et al. 1996), and benefit more from inpatient than outpatient care (Rychtarik et al. 2000). Low levels of verbal learning appear to impede psychotherapy but do not affect the efficacy of supportive treatment such as coping skill training (Jaffe et al. 1996). Neurocognitive assessment would help with identification of an individuals' strengths and weaknesses, and assist in determining which intervention would be most beneficial (Tapert et al. 1999, 2004).

Objective indicators of cognitive function would also improve drug workers' understanding of drug users' problems in everyday activities (Verdejo-Garcia and Perez-Garcia 2007). In fact, an objective cognitive status examination is more likely to reflect the extent of impairment than a counselors' subjective judgement on drug users' cognitive abilities (FalsStewart 1997). An emphasis on neuropsychological aspects of assessment and treatment would be very useful in the training of staff working in drug services, but at present neuropsychology is still leading only a shadowy existence in current drug addiction training (Boys et al. 1997; Kerwin et al. 2006).

Neurocognitive Training and Remediation to Improve Long-Term Outcome

Improvement in cognitive function through neurocognitive training and remediation, as part of drug rehabilitation, may enhance treatment outcome in the long-term. Cognitive training modules have already shown effectiveness in a variety of clinical groups, including patients with schizophrenia (Bell et al. 2005; Hogarty et al. 2004; Kosten et al. 2006; Wykes et al. 2003), traumatic brain injury (Sarajuuri et al. 2005), and chronic drug users (Czuchry and Dansereau 2003a; FalsStewart and Lucente 1994b). In particular, the training of attention and memory skills, functions that are severely impaired in both amphetamine and opiate users, may prove useful, since these abilities have the greatest predictive value for the employment of drug users (Mackin et al. 2005). Cognitive remediation programs in patients with schizophrenia have shown promising results, since improvement in cognitive function at six-month follow up was not only reflected in successful vocational rehabilitation but was also associated with ameliorated social functioning and quality of life (Bell et al. 2005; Wykes et al. 2003).

Options for Pharmacological Intervention

In light of the severity of cognitive deficits that can occur in chronic drug users, the application of cognitive enhancer drugs to ameliorate these deficits appears useful (Duka et al. 2005; Malcolm et al. 2002). Cognition-enhancing drugs such as modafinil have shown efficacy ameliorating cognitive inhibition on the Stroop task in depressed patients (DeBattista et al. 2004), enhancing cognitive flexibility on the IDED task in patients with schizophrenia (Turner et al. 2004b), and improving motor-inhibition deficits on the Stop-Signal task in adults with attention deficit hyperactivity disorder (ADHD) (Turner et al. 2004a). Neuroimaging research suggests that modafinil has the potential to modulate activation in the ACC during working memory performance (Spence et al. 2005); an intriguing finding in

light of significant under-activation during cognitive performance (Forman et al. 2004; Paulus et al. 2003) and at rest (Galynker et al. 2000; Kim et al. 2005b). Modafinil is an anti-narcoleptic agent with mild stimulant effects through classical (al-receptor) and non-classical (orexin/hypocretin) arousal pathways (Ballon and Feifel 2006; Ferraro et al. 1999). The weak dopaminergic affinity of modafinil and the low abuse liability resulting from it (Deroche-Gamonet et al. 2002; O'Brien et al. 2006) may provide ideal grounds for a supplementary treatment of chronic drug users (Malcolm et al. 2002; Vocci et al. 2005). Clinical trials are now needed to establish modafinil's efficacy in enhancing cognitive function in drug users with diminished cognitive abilities, and to identify those individuals for whom treatment with modafinil may not be suitable, e.g., drug users with co-morbid anxiety disorder (Taneja et al. 2007).

Another potential route for improving cognitive function in chronic drug users is atomoxetine, a selective noradrenaline reuptake inhibitor (Bymaster et al. 2002), which has been found to be effective in the treatment of ADHD (Michelson et al. 2001). Atomoxetine has shown to selectively increase catecholamine levels in frontal lobes via noradrenaline transporters, but compared to psychostimulants, has low abuse liability (Bymaster et al. 2002). In light of atomoxetine's efficacy in improving behavioral inhibition in healthy volunteers as well as in individuals with ADHD (Chamberlain et al. 2007), potential use in chronic drug users awaits investigation.

In summary, growing evidence suggests that addressing cognitive deficits in drug users in treatment settings offers great potential to improve overall treatment efficacy. The variety of options available for managing cognitive dysfunction may allow implementation in different kinds of clinical settings. Most important, all aforementioned ways in addressing cognitive impairments in drug users are not mutually exclusive. It is even conceivable that the most effective means is a combined approach of psychological strategies, remediation training, and cognition-enhancer drugs.

Summary and Outlook

Over recent years, neuropsychology has provided new insights into the neural basis of cognitive and behavioral problems associated with chronic drug use, including amphetamines and opiates. The translation of this knowledge into clinical practice will ideally become increasingly apparent in the coming years. Investigation into the specific components of impairment, such as the processing of feedback in amphetamine and opiate users (Ersche et al. 2005b; Paulus et al. 2002, 2003) would be of great clinical relevance, since it may indicate a need for reconsidering the way feedback is provided in clinical settings. Furthermore, understanding the neurobiological substrates underlying cognitive impairment in drug users may have the potential to guide therapeutic intervention in the future.

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