Review

Parallel studies of cocaine-related neural and cognitive impairment in humans and monkeys

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Cocaine users display profound impairments in executive function. Of all the components of executive function, inhibition, or the ability to withhold responding, has been studied the most extensively and may be most impaired. Consistent with these deficits, evidence from imaging studies points to dysregulation in medial and ventromedial prefrontal cortices, areas activated during performance of inhibition tasks. Other aspects of executive function including updating, shifting and decision making are also deficient in cocaine users, and these deficits are paralleled by abnormalities in patterns of prefrontal cortical activation. The extent to which cocaine plays a role in these effects, however, is not certain, and cannot be determined solely on the basis of human studies. Investigations using a non-human primate model of increasing durations of cocaine exposure revealed that initially the effects of cocaine were restricted to ventromedial and orbital prefrontal cortices, but as exposure was extended the intensity and spatial extent of the effects on functional activity also expanded rostrally and laterally. Given the spatial overlap in prefrontal pathology between human and monkey studies, these longitudinal mapping studies in non-human primates provide a unique window of understanding into the dynamic neural changes that are occurring early in human cocaine abuse.

Keywords: cocaine; executive function; imaging; non-human primate; prefrontal cortex; functional activity

1. INTRODUCTION

There is considerable consensus that cocaine users suffer from significant neuropsychological impairments (Cadet & Bolla 1996; Bolla *et al.* 1998; Garavan & Hester 2007). Deficits in cognitive function can hinder the ability of substance abusers to benefit from treatment, especially those based on cognitive therapies, as well as impede the decision to enter treatment. Neuropsychological impairments may also impact the course of substance abuse by interfering with decisions about experimentation and continued drug seeking (Rogers & Robbins 2001).

Characterizing the nature and underlying causes of these deficits, however, has proved to be less than straightforward. For example, there is little standardization of the batteries of neuropsychological and/or individual cognitive tests administered to substance abusers. There are also considerable differences across studies in the characteristics of the stimulant abusers included in terms of the duration of use, the pattern of use, the number of abstinence episodes and the degree of drug use other than stimulants. This is compounded further by similar incongruities in control populations

as well as difficulties in matching user populations to controls on characteristics such as age, IQ, education and socioeconomic status. Finally, the influence of potential premorbid deficits on the cognitive performance of chronic cocaine users remains a significant confound that cannot be easily ruled out. Here, we present a brief non-comprehensive review of the profile of neuropsychological deficits associated with chronic cocaine abuse and the disruptions in functional brain activity associated with these deficits. This is followed by a comparison of these findings to those in a non-human primate model of cocaine self-administration.

2. COGNITIVE DEFICITS EXHIBITED BY COCAINE USERS

Cognitive impairments exhibited by chronic cocaine users are often related to problems in executive function, a group of processes involved in the learning, control and monitoring of complex goal-directed behaviour (Teuber 1972; Stuss & Knight 2002; Garavan & Hester 2007). Executive functioning can be differentiated into three components: (i) updating, or the ability to monitor and update incoming information relevant to the task at hand, while discarding old information, (ii) shifting, or the ability to shift mental sets back and forth between multiple tasks and operations (Miyake *et al.* 2000), and

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(iii) inhibition, or the ability to inhibit prepotent, automatic or impulsive responses. Additionally, the process of decision making has sometimes been identified as a separate component within the organization of executive function (Verdejo-Garcia & Perez-Garcia 2007). There is a growing body of literature describing the neuropsychological impairments of cocaine users on these four components of executive function, often relating the deficits to dysfunction in areas of the prefrontal cortex.

(a) Updating

The executive function component of updating is typically measured by tasks that rely heavily on working memory, fluency and analytic reasoning (cf. Miyake *et al.* 2000; Verdejo-Garcia & Perez-Garcia 2007). More difficult tasks that tax working memory, such as the two- and three-back conditions on a standard *n*-back task, regularly elicit poor performance by substance abusers (Verdejo-Garcia *et al.* 2006; Tomasi *et al.* 2007), while less challenging tasks, such as sustained attention tasks, rarely yield differences between groups (Goldstein *et al.* 2007).

Hester & Garavan (2004) altered a classic Go/No-Go response inhibition task by embedding a working memory component into the presentation of the task. Increasing working memory load by increasing the number of letters to be remembered, from one to three to five in this case, significantly reduced the number of correct inhibitions in both cocaine users and healthy subjects. Controls, however, performed significantly better than cocaine users at all load levels and that advantage was amplified as working memory load increased (Hester & Garavan 2004). Recently, our group has used another measure of working memory function, the delayed match to sample task (figure 1a), to examine the updating component of executive function in current cocaine users. Preliminary data indicate that cocaine users are not significantly impaired compared with age-matched controls at shorter delays, but perform more poorly than controls at longer delays (C. A. Hanlon *et al.* 2007, unpublished observations). These results are consistent with other findings that suggest significant impairments in working memory function, particularly as the load is increased.

These deficits in memory function of cocaine users appear to persist even during periods of abstinence (Di Sclafani *et al.* 2002; Verdejo-Garcia *et al.* 2006). At six weeks of abstinence, for example, crack cocaine users performed more poorly than controls on attention tasks, memory tasks, reaction time tasks and an analytic reasoning task. These results are striking in that the deficits in performance continue to be significant even after six months of abstinence in those subjects who did not relapse before the second test session (Di Sclafani *et al.* 2002; Verdejo-Garcia *et al.* 2006). This lack of recovery could imply that any neuroadaptations consequent to heavy cocaine use may in fact be permanent. An alternate interpretation, however, might suggest that such deficits are symptomatic of differences in performance that predate any drug use. The absence of correlations between duration of use and degree of impairment supports the latter interpretation.

Figure 1. Impaired performance on two tests of executive function by cocaine users ($n=37$) and healthy controls ($n=57$). (a) Per cent correct on the delayed match to sample task (working memory) at three delay intervals for cocaine users (dashed line) and controls (solid line). (b) Total errors on the intra- and extra-dimensional set shifting task (attentional set shifting) in cocaine users (grey bars) and controls (black bars). * $p<0.05$, ** $p<0.005$, *t*-test for independent groups. ID, intra-dimensional; ED, extra-dimensional.

(b) Shifting

Deficits in the shifting component of executive function have been observed in cocaine users on tasks of probabilistic response reversal, which have been used to examine behavioural adaptation to changing reward contingencies (Cools *et al.* 2002; Hornak *et al.* 2004). Chronic cocaine users have problems altering behaviour on such tasks after a change in the reward contingencies and tend to perseverate on previously rewarded responses (Fillmore & Rush 2006; Ersche *et al.* 2008). Others have found that cocaine-dependent individuals perform more poorly than controls on tasks requiring switching within and between the modalities of verbal and visuospatial attention (Kubler *et al.* 2005). Recent data from our group indicate that cocaine users make significantly more errors on the intra/extr-dimensional set-shifting task that is part of the CANTAB battery (Cambridge Cognition Ltd, Cambridge, UK) than healthy control participants (figure 1b). When specific stages of the task are considered, users are most impaired on the extra-dimensional shift stage of the task (C. A. Hanlon *et al.*, unpublished observations; figure 1b).

However, a number of studies have reported that there are, at most, only marginal differences in perseverative responding between cocaine users and healthy controls on the Wisconsin Card Sorting task, another measure of set-shifting behaviour (Bechara *et al.* 2000; Verdejo-Garcia *et al.* 2006). Yet, Bolla *et al.* (1999) did find significant negative correlations among the total dose of cocaine and the duration of use with the three outcome measures of the Wisconsin Card

Sorting task: categories completed; number of correct responses; and number of perseverations. As with the updating component of executive function, it is difficult to rule out the impact of antecedent differences in ability. Furthermore, the inconsistencies across reports may be due to differences in the characteristics of the cocaine user population or to those in the neural processes that are tapped into by Wisconsin Card Sorting and other set-shifting tasks.

(c) *Inhibition*

This aspect of executive function is of particular interest, since poor inhibitory control or an inability to gate inappropriate responses to external influences may increase the likelihood of risky behaviours such as drug seeking. One frequently used task to measure inhibitory control is the Go/No-Go task, in which subjects must respond to some stimuli while withholding responses to others. For example, Kaufman *et al.* (2003) observed that cocaine users made significantly more errors of commission on this task than healthy controls. Furthermore, other reports have shown that not only do cocaine users exhibit impaired inhibitory control, but they are also less aware of their errors than healthy controls. Cocaine users, for example, had significantly more difficulty in adjusting their performance appropriately immediately after failing to inhibit a response (Hester *et al.* 2007).

Other groups, however, have reported that these deficits may be due to other factors, including a disruption of sensory information processing. In a Go/No-Go task of visual similarity, Go trials were defined as two identical images, easy No-Go trials were two obviously dissimilar images and hard No-Go trials were two more similar images. Cocaine users were more impaired than controls on the most difficult No-Go trials only, leading to the conclusion that the response inhibition deficits were more likely to be caused by attentional processing deficits rather than an inability to inhibit responding (Lane *et al.* 2007).

The 'stop-signal' paradigm is based on a cognitive model of control which asserts that the ability to inhibit a response is determined by the outcome of competing activating and inhibitory processes elicited by cues to perform or withhold a response (Logan *et al.* 1984; Logan 1994). The task provides a measure of the time required by an individual to inhibit a prepotent motor response (Fillmore & Rush 2002; Chamberlain *et al.* 2006). When tested on this task, cocaine users required more time to make inhibitory responses and had a significantly lower probability of inhibiting their responses than controls (Fillmore & Rush 2002). These data are more consistent with the concept that cocaine users have deficiencies in inhibitory control rather than in sensory processing. Compromised inhibitory control is the one aspect of deficient executive functioning about which there is the greatest degree of consensus; however, the question of whether this is due to cocaine exposure or other factors remains unanswered. Indeed, pre-existing deficits in inhibitory control would be expected to increase the likelihood of drug experimentation and other risky behaviours.

(d) *Decision making*

Although not typically considered an element of executive function, decision-making tasks frequently combine multiple executive function processes. Poor performance on the Iowa Gambling task (Bechara *et al.* 1994) or tasks such as the Cambridge Gambling task (Rogers *et al.* 1999), for example, can result from impairments of inhibitory control, set shifting and/or updating. Cocaine users perform very poorly on the Iowa Gambling task relative to control participants (Bechara *et al.* 2000; Stout *et al.* 2004; Verdejo-Garcia *et al.* 2007). Whereas controls tend to learn to make more advantageous choices over the course of the task, cocaine users continue to make choices that provide immediate gains, regardless of the losses accrued over time. Their poor performance on such tasks suggests that users are unable to process future negative consequences in the presence of an opportunity for immediate gratification. Again, such deficits might lead to increased likelihood of drug experimentation and vulnerability for addiction.

Neuropsychological dysfunction in cocaine abusers, then, is severe and widespread, spanning multiple components of executive function. These cognitive deficits may contribute to onset of use, transition from recreational use to dependence and continuance of drug-seeking behaviours. They also may interfere with treatment programmes that rely heavily on cognitive therapies for successful abstinence. Whether these deficits are the result of cocaine use, however, remains an unanswered question when so many other factors can impact cognitive function. Efforts to understand further the executive functioning deficits of cocaine users have led to examinations of brain function during performance of many cognitive tasks using single photon emission computed tomography, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) neuroimaging techniques.

3. NEUROANATOMICAL SUBSTRATES OF COGNITIVE DEFICITS EXHIBITED BY COCAINE USERS

Much of our understanding of the neurobiological consequences of chronic drug use in humans has come from imaging studies using PET and fMRI to measure cerebral metabolism, blood flow or blood volume. One consistent finding of these studies of the consequences of chronic cocaine use is that of 'hypo-frontality', or decreased function of the prefrontal cortex of cocaine abusers when compared with non-drug using controls. Numerous reports have demonstrated that cocaine users have lower rates of glucose usage as measured with fluorodeoxyglucose and PET (Volkow *et al.* 1991, 1992, 2005; Goldstein & Volkow 2002; Goldstein *et al.* 2004). These depressed rates of functional activity have been reported to persist for up to three months of abstinence (Volkow *et al.* 1993), a finding that has been recently confirmed in our laboratory (Hanlon *et al.* 2006). In addition, disruptions in cerebral perfusion have also been consistently observed in prefrontal brain regions (Tumeh *et al.* 1990; Holman *et al.* 1991; Weber *et al.* 1993; Adinoff

et al. 2003; Tucker *et al.* 2004). The majority of these studies, however, were conducted at rest when the subjects were lying quietly in the scanner.

The importance of the role of the prefrontal cortex in executive function has been demonstrated in innumerable neuroimaging investigations in both healthy adults and populations of patients with pathologies specific to the frontal cortex (Salmon & Collette 2005; Koechlin & Hyafil 2007; Robbins 2007). A number of recent neuroimaging studies of cocaine abusers have specifically addressed the role of prefrontal cortical dysfunction on the components of executive function: response inhibition; updating; set shifting; and decision making.

Perhaps the most well-studied component of executive function in cocaine users is response inhibition (Goldstein *et al.* 2001; Bolla *et al.* 2003; Kaufman *et al.* 2003; Hester & Garavan 2004). In healthy controls, performance on tasks, such as the Go/No-Go task, that require the inhibition of a prepotent response is accompanied by activation in the anterior cingulate (Bush *et al.* 2000; Kaufman *et al.* 2003; Hester & Garavan 2004), dorsolateral prefrontal (Garavan *et al.* 1999; Blasi *et al.* 2006), inferior frontal (Aron *et al.* 2003) and orbitofrontal cortices (Horn *et al.* 2003). Cocaine users, however, have consistently lower levels of activity in the anterior cingulate and medial prefrontal cortices while performing such tasks (Kaufman *et al.* 2003). On other tasks requiring inhibitory control such as the Stroop task, cocaine users perform more poorly and exhibit decreased cerebral glucose metabolism in the orbitofrontal cortex when compared with controls (Goldstein *et al.* 2001). Furthermore, baseline levels of glucose metabolism in the orbitofrontal cortex were positively correlated with task performance (Goldstein *et al.* 2001). This positive correlation between orbitofrontal function and Stroop performance may provide some physiological basis for the recent observation that better performance on this task predicts greater treatment compliance (Streeter *et al.* 2007).

Several studies have reported deficits in the updating component of executive function in chronic cocaine users (O'Malley & Gawin 1990; Dackis & O'Brien 2001; Kubler *et al.* 2003; Goldstein *et al.* 2007; Tomasi *et al.* 2007), which appear to persist into abstinence (Verdejo-Garcia *et al.* 2006). Few studies, however, have addressed the potential deficits in brain activity specifically associated with these tasks. A recent fMRI study by Tomasi *et al.* (2007) investigated the brain activation of cocaine users during *n*-back performance. Cocaine users had greater activation than controls throughout large portions of the medial and cingulate prefrontal cortices, as well as in the superior frontal gyrus. When assessing the impact of working memory load on response inhibition, however, lower activity in the anterior cingulate was seen in cocaine users relative to controls (Hester & Garavan 2004). These investigators demonstrated that as memory load increased, there was a significant decay in response inhibition in cocaine users, which was associated with decreased activity in the anterior cingulate. Considered together, these studies underscore the complex and overlapping nature of anterior cingulate activity involved in the

components of executive function and how disruptions in processing in this brain region may have widespread effects on a broad range of behaviours, not just those related to executive function.

Performance of set-shifting tasks in healthy control populations is generally accompanied by increased functional activity within the anterior cingulate, orbitofrontal and dorsolateral prefrontal cortices (Dias *et al.* 1996; Fellows & Farah 2003; Cools *et al.* 2004; Wager *et al.* 2005). Cocaine users, by contrast, exhibit *reduced* activity in both the anterior cingulate and medial prefrontal regions (Bolla *et al.* 2004; Kubler *et al.* 2005). Activity in the dorsolateral aspects of the prefrontal cortex, however, has not generally been found to differ significantly from that of controls (Kubler *et al.* 2005). The selective impairment of medial and ventral prefrontal regions of cocaine users suggests that, depending upon the processes tested, functional deficits associated with cocaine abuse may have a specific, rather than global, distribution within the prefrontal cortex.

Performance on the Iowa Gambling task by healthy controls is associated with activity in the anterior cingulate cortex as well as the dorsolateral prefrontal areas (Bechara *et al.* 2000, 2001; Adinoff *et al.* 2003; Bolla *et al.* 2003). Cocaine users have reduced functional activation relative to control participants in both dorsolateral and rostral anterior cingulate, as well as greater activation in orbital prefrontal areas during gambling task performance (Bolla *et al.* 2003). Users with the lowest resting cerebral blood flow levels in the dorsolateral prefrontal cortex and anterior cingulate had the poorest task performance (Adinoff *et al.* 2003). The presence of these dorsolateral prefrontal functional abnormalities in cocaine users when performing the gambling task is in contrast to the results from set-shifting studies, where there was little evidence for dorsolateral prefrontal disruption.

In summary, although cocaine users appear to have impaired processing throughout much of the prefrontal cortex, the most consistent deficits in functional activity are within ventromedial orbital and anterior cingulate cortices, regardless of the task. Although there are also deficiencies in the dorsolateral prefrontal cortex, particularly in the more rostral portions of this region, these are not as consistent despite the critical role of this region in executive function.

4. ADDRESSING THE CONFOUNDS OF HUMAN STUDIES

Many of these investigations into the cognitive and neurobiological consequences of cocaine use often imply or assume that cocaine exposure is the cause of these deficits. However, the influence of factors such as concomitant psychiatric illness, lifestyle differences and the use of multiple licit and illicit substances can be significant confounds in the interpretation of these data. Perhaps most difficult is assessing whether any of these impairments actually occur as a result of drug exposure itself or predate any drug experiences.

Owing to these and many other problems, it is virtually impossible to isolate and address the issue of the consequences of chronic cocaine exposure in human

populations. This is a critical question for treatment and prevention. An alternate approach to pursuing questions about the long-term effects of chronic exposure to drugs is the use of animal models in which carefully controlled experiments can be conducted. Animal models allow systematic evaluation of dose, session length, duration of experience, total lifetime intake, duration of abstinence, etc. Importantly, animal models allow us to assess the role of the drug itself on structure and function by directly examining the temporal course of drug exposure and the accompanying neuroadaptations. Using a non-human primate model of cocaine self-administration, our laboratory has investigated the long-term effects of chronic drug exposure.

Non-human primates have been used in intravenous self-administration studies for close to 60 years and have proved a valid and reliable model of human drug abuse (Thompson & Schuster 1964; Griffiths *et al.* 1980; Johanson & Fischman 1989; Mello & Negus 1996). Monkeys share cytoarchitectural, neurochemical and ultrastructural similarities with humans, particularly with respect to the prefrontal cortex (Carmichael & Price 1994, 1996; Porrino & Lyons 2000; Hardman *et al.* 2002). Given that connectivity patterns of the prefrontal cortex are highly homologous to those of humans (Ongur *et al.* 2003) and monkeys can perform higher order cognitive tasks, they may provide insights into the psychiatric and cognitive deficits observed in human drug users.

Our current model of cocaine exposure makes use of rhesus monkeys initially trained to respond for food reinforcement. Once stable baselines are established, some animals remain on the food reinforcement schedule (controls), whereas others go on to self-administer cocaine on a similar schedule. Animals self-administer high doses of cocaine (9.0 mg kg^{-1}) daily for increasing durations chosen to model stages of the addiction process. With this model, we have been able to document significant dysregulation in neurotransmitter systems including increases in the density of noradrenaline (Beveridge *et al.* 2005) and dopamine transporters (Letchworth *et al.* 2001), increases in dopamine D₁ receptors (Nader *et al.* 2002), as well as decreases in the concentration of dopamine D₂ receptors (Nader *et al.* 2002). Thus, these studies have clearly shown that chronic exposure to cocaine in and of itself can produce substantial neuroadaptations in both brain structure and function over the temporal course of drug exposure.

5. METABOLIC MAPPING OF THE FUNCTIONAL CONSEQUENCES OF CHRONIC COCAINE EXPOSURE IN THE PREFRONTAL CORTEX OF NON-HUMAN PRIMATES

Important questions, then, are how functional activity within the prefrontal cortex has changed over the course of cocaine exposure, and how such changes might account for the cognitive impairments associated with cocaine use in human substance-abusing populations.

To address this question, we have used the 2- $[^{14}\text{C}]$ deoxyglucose method to map the changes in cerebral metabolism after increasing durations of cocaine exposure. By assessing these changes in metabolism

following the final infusion of cocaine at the end of a self-administration session, we are effectively measuring the response of the brain to a cocaine challenge in animals with different drug histories. Using this approach, we have been able to characterize alterations in the pattern and intensity of the changes in functional activity in the prefrontal cortex after increasing the durations of cocaine self-administration experience: (i) initial exposure, designed to model the initial phases of drug exposure, when cocaine use is still considered casual or recreational (5 days of cocaine self-administration), (ii) chronic exposure, designed to model the effects of repeated cocaine self-administration (3.3 months of self-administration), and (iii) prolonged exposure, designed to more closely model investigations of human addicts in which the minimum inclusion criterion is typically at least 1 year of heavy use, and actual duration of use is frequently much longer (1.2 years of cocaine self-administration). We have recently undertaken a detailed re-analysis of the effects of cocaine on functional activity in the prefrontal cortex in order to map more carefully the topography of the initial effects and any potential shifts in this topography with continued exposure.

In the initial stages of drug exposure, cocaine produced a highly restricted pattern of changes in functional activity throughout the brain. Within the prefrontal cortex, significant decreases in cerebral metabolism were focused along the more caudal sectors of the medial wall in the gyrus rectus (area 14), cingulate areas 24 and 25 and caudal portions of area 32 (figure 2a(ii)(iii)). These regions that have been shown to be involved in visceromotor functioning, providing cortical influence over autonomic and endocrine function (Price 1999). Decreases were also found in anterior insula cortex (area Ia), areas believed to be responsible for associations between taste and smell, specifically linking olfactory and gustatory cues to reward (Rolls 1996). These decreases were accompanied by increases in dorsomedial and dorsolateral portions of the prefrontal cortex (areas 45, 46 and 9). In primates as in humans, these regions are essential for working memory function (Baddeley 1986; Fuster 1997). These effects may result from a continuing representation of the drug-associated environment that persists beyond the end of the session. This continued activation at a time when access to cocaine has ceased may constitute the basis for the formation of memories for cues that can elicit cravings, even in abstinence. Thus, it appears that even in the initial stages of drug experience, cocaine may influence higher order processing of converging sensory and visceral information, as well as the formation of associations between various stimuli with the presence of reward.

After chronic self-administration, however, adaptations to repeated cocaine exposure became evident. In these studies, monkeys had total intakes of over 900 mg kg^{-1} of cocaine over more than a three-month period. In contrast to the rather restricted pattern of changes in cerebral metabolism in the initial stages of exposure, the pattern after repeated exposure shifted to encompass larger expanses of the prefrontal cortex. In addition, the magnitude of the changes was more intense than in the earlier stages of cocaine experience.

Figure 2. Time course of the effects on local cerebral glucose metabolism in prefrontal cortex of non-human primate brain. Schematic illustrating the spatial extent of the effects of increasing durations of cocaine self-administration histories on functional activity: (a) initial, 5 days; (b) chronic, 3.3 months and (c) prolonged, 1.2 years ((i) rostral, (ii) middle and (iii) caudal). Areas shaded in grey represent regions exhibiting significant decreases in functional activity. Numbers represent Brodmann areas.

Although there was considerable overlap when comparing the initial and chronic stages along the medial wall of the prefrontal cortex (areas 14, 24, 25 and 32), the decreases extended further rostrally into more anterior portions of the cingulate cortex (figure 2*b*(i)). Furthermore, functional activity was altered in areas not seen previously, in the orbitofrontal cortex (area 13), as well as in the caudal portions of area 12 (figure 2*b*(ii)(iii)). These are areas that are critical for the processing of reward value and salience (Schultz *et al.* 2000; Tremblay & Schultz 2000). Another important difference at this time point was the absence of any increases in cerebral metabolism. In fact, metabolism was decreased in some portions of the dorsal prefrontal regions, suggesting that significant adaptations may be occurring within the dorsolateral prefrontal cortex as a result of the more chronic drug exposure.

Studies of the changes in functional activity associated with cocaine self-administration exposure have recently been extended to include protracted periods of cocaine exposure. The goal of these studies was to include durations of exposure more consistent

with most investigations of human addicts where subjects report extended periods of heavy use. In these studies, animals self-administered high doses of cocaine for a minimum of 300 sessions, receiving on average 2700 mg kg^{-1} cocaine total intake. Although these data are still preliminary, glucose metabolism in the prolonged cocaine exposure group was significantly decreased in the medial and orbital regions of the prefrontal cortex, in a pattern very similar to that observed following chronic cocaine exposure (figure 2*c*(ii)(iii)). The overlap in terms of spatial extent between the two groups was striking. The only difference was an extension of functional changes into more rostral ventromedial and orbital cortices (areas 10, 11 and 12 (figure 2*c*(i))). Furthermore, there was very little change in the magnitude of the effects despite the much longer cocaine histories.

6. CONCLUSIONS

Cocaine abusers have significant cognitive impairments that encompass all aspects of executive function. These deficits in cognitive performance are coincident with differences in functional activation observed

throughout the prefrontal cortex of cocaine users when compared with healthy controls. It is difficult, however, to attribute these impairments directly to the consequences of chronic cocaine exposure on the basis of these data alone. Cognitive impairments can also derive from concomitant psychiatric conditions, differences in lifestyle or educational experiences, as well as the use of other licit and illicit substances. Furthermore, it is not possible to rule out antecedent differences in function that may have impacted performance above and beyond the influence of cocaine itself. However, the shift in the functional consequences of cocaine within the prefrontal cortex in a non-human primate model of the temporal course of drug exposure described here strongly supports the idea that cocaine is an important contribution to the significant impairments of cognitive performance experienced by drug users.

Our non-human primate studies have shown that the effects of cocaine are initially highly restricted to portions of the ventromedial prefrontal cortex, but with increasing experience and escalated intakes, the effects rapidly spread more rostrally and laterally to encompass the orbital and dorsolateral cortices. The increasing magnitude and the shift in topography of the alterations in functional activation in the prefrontal cortex after greater cocaine exposure parallel the association between cognitive decline and cocaine exposure reported in some studies in human users (Bolla et al. 1999, 2003; Colzato et al. 2007). For example, Colzato et al. (2007) demonstrated a significant correlation between the magnitude of deficits in the performance of a stop-signal task and total lifetime cocaine intake. Because these users were considered recreational, their intakes were within the range of those of the monkeys in the mid or chronic stages (3.3 months) of experience.

After over a year, however, despite the fact that the duration of exposure to cocaine has been increased more than threefold, the alterations in functional activity do not continue to intensify or expand at the same rate as they had between the initial and chronic stages of drug exposure. Although the effects of continued cocaine exposure undoubtedly continue to accumulate, they appear to do so at a much slower rate. This suggests that there may be a plateau after a rapid acceleration early in the course of drug experience, and may help to explain the frequent absence of positive correlations between the duration of use and the degree of cognitive impairment in many studies, where the minimum reported drug use is often longer than 1 year and intakes are beyond those included even in these non-human primate studies.

One interesting aspect of the progression that has been identified is the growing involvement of frontopolar cortex (BA10) in the consequences of cocaine self-administration. Of all the areas of the orbitofrontal cortex, this region has undergone the greatest expansion in humans when compared with monkeys (Ongur et al. 2003). Both neuroimaging studies and lesion data have shown that this region of the prefrontal cortex is involved in prospective or intentional thinking and memory. Patients with lesions tend to have great difficulty remembering and developing intentions to act (Burgess et al. 2007). Other studies have pointed to

this area as critical for exploratory decisions (Daw et al. 2006) where there is uncertainty about the outcomes of the selections. A recent paper has hypothesized that the frontopolar regions of cortex enable the considerations of multiple stimulus sets simultaneously or the so-called multitasking behaviour (Koechlin & Hyafil 2007). The common element in all of these functions is the ability to think about future events and anticipate consequences. It is easy to speculate how disruption of information processing in this brain region could impact decisions about drug use and impair treatment. The inability of substance abusers to consider potential future negative consequences is a hallmark characteristic of this disorder.

Although the imaging modalities and experimental designs vary, there is remarkable consistency in the spatial distribution of prefrontal cortical functional deficits in both the human and monkey literature. The anterior cingulate cortex, the medial prefrontal cortex, the orbital frontal cortex and, to a lesser degree, the dorsolateral prefrontal cortex all appear to be affected after chronic cocaine use. In addition to the other limitations of human research, however, it is extremely difficult to assess the temporal progression of functional brain changes in human users. Instead, most imaging studies are performed on individuals who have been using cocaine for several years, a time point similar to that of our group of monkeys with the most cocaine experience. At this time point, we found that most of the prefrontal cortical brain changes had stabilized. The dynamic periods of functional alterations to chronic cocaine use are probably occurring early in use and before the typical user is enrolled in human imaging investigations. Given the spatial overlap in prefrontal pathology between human and monkey studies, these longitudinal mapping studies in non-human primates provide a unique window of understanding into the dynamic neural changes that occur early in human cocaine abuse, a question that has been elusive but may provide insights into the initial stages of the addiction process in humans.

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